Hiding in Plain Sight: Autonomic Neuropathy in heart failure patients with hATTR

FRIDAY MAY 7, 2021 / 5:00 – 5:50 pm ET

Alnylam® PHARMACEUTICALS

Welcome and Introductions

Moderator: Anil Gupta, MD, FRCPC
Staff Cardiologist, Trillium Health Partners
Lead, Undergraduate Cardiology Education, UTM
Cardiology Lead, Cardiac Diagnostics and Cardiac Rehabilitation
Lecturer, University of Toronto
Investigator, Institute for Better Health, Trillium Health Partners
Research Director, One Heart Care Ventures
Toronto, ON

Chair: Nowell M. Fine MD, SM, FRCPC, FACC, FCCS, FASE, FHFSA
Clinical Assistant Professor of Cardiac Sciences, Medicine and Community Health Sciences
Clinical Director, Libin Cardiovascular Institute
Director of Echocardiography, Heart Failure Cardiologist
Cumming School of Medicine, University of Calgary
Calgary, AB

Planning Committee & Faculty

Chair: NOWELL M. FINE MD, SM, FRCPC, FACC, FCCS, FASE, FHFSA
Clinical Assistant Professor of Cardiac Sciences, Medicine and Community Health Sciences
Clinical Director, Libin Cardiovascular Institute
Director of Echocardiography, Heart Failure Cardiologist
Cumming School of Medicine, University of Calgary
Calgary, AB

Moderator: ANIL GUPTA, MD, FRCPC
Staff Cardiologist, Trillium Health Partners
Lead, Undergraduate Cardiology Education, UTM
Cardiology Lead, Cardiac Diagnostics and Cardiac Rehabilitation Lecturer, University of Toronto
Investigator, Institute for Better Health, Trillium Health Partners
Research Director, One Heart Care Ventures
Toronto, ON

ANIQUE DUCHARME, MD, MSc, FRCP
President – Canadian Heart Failure Society
Director, Heart Failure clinic, Montreal Heart Institute,
Professor of medicine, University of Montreal, (Canada)
University of Montreal Chair holder: Fondation Marcelle et Jean Coutu,Cal et Janine Moisan for better practices in advanced heart failure

ZAEEM A. SIDDIQI, MD, PhD
Professor, Division of Neurology
Director Neuromuscular & Autonomic Diseases Programs
University of Alberta
Edmonton, AB

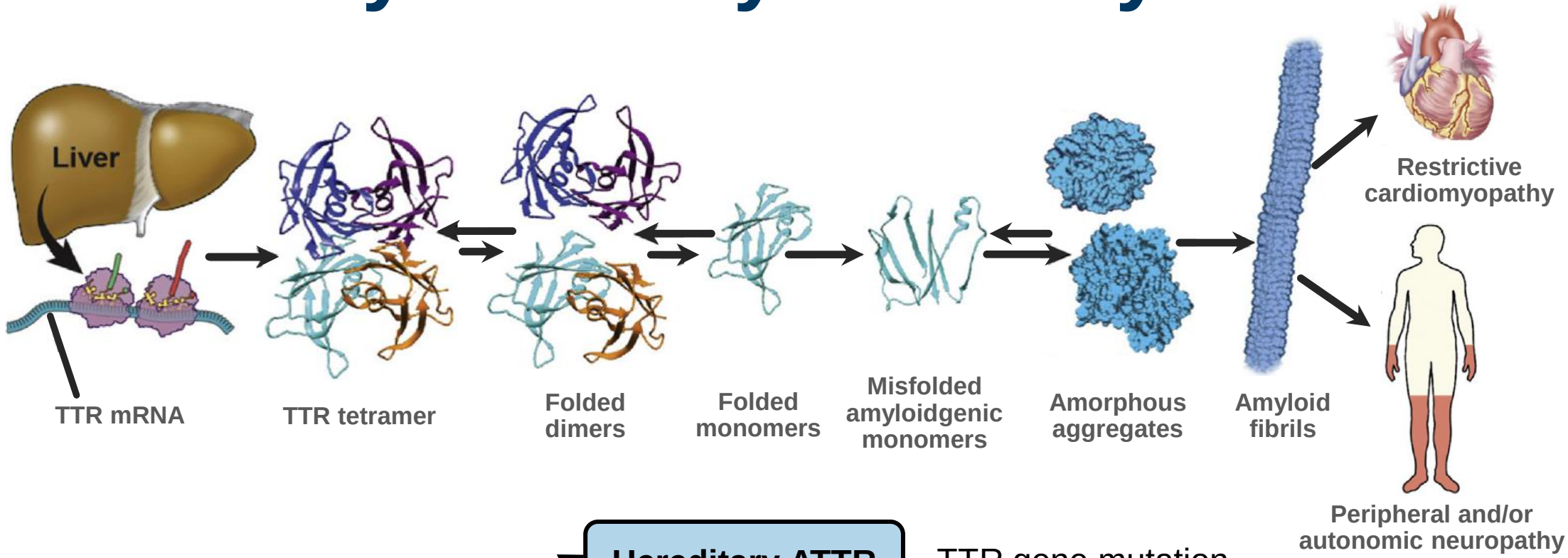
Disclosure of Commercial Support

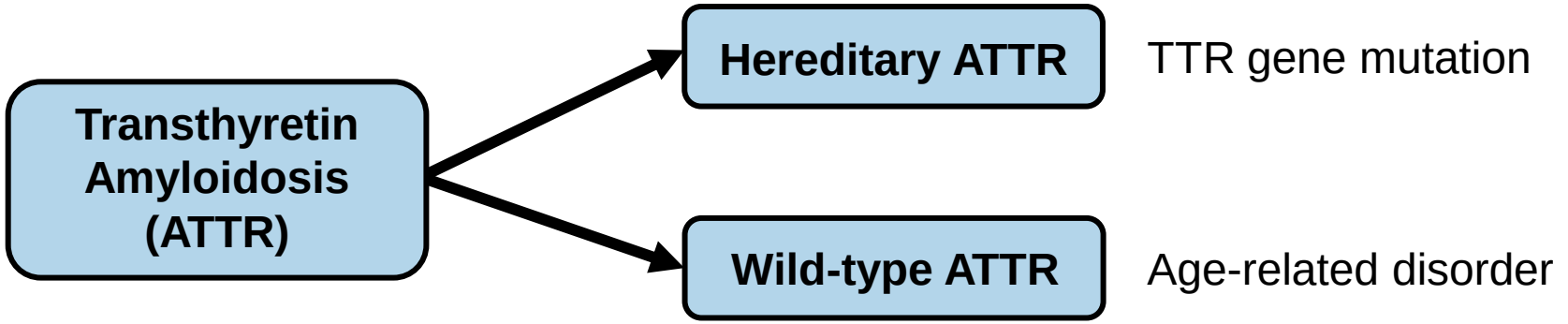
This program has received financial support from Alnylam

Learning Objectives

- Recognize that autonomic neuropathy is a hallmark feature of hATTR amyloidosis and an important symptom for early diagnosis and treatment
- Define the clinical presentation of autonomic neuropathy in heart failure patients with hATTR amyloidosis
- Assess autonomic function in patients with suspected or diagnosed hATTR amyloidosis within a cardiology practice
- Efficiently treat mixed CM/PN patients with autonomic impairment caused by hATTR amyloidosis

Hereditary Transthyretin Amyloidosis





Ruberg et al. JACC 2019;73:2872

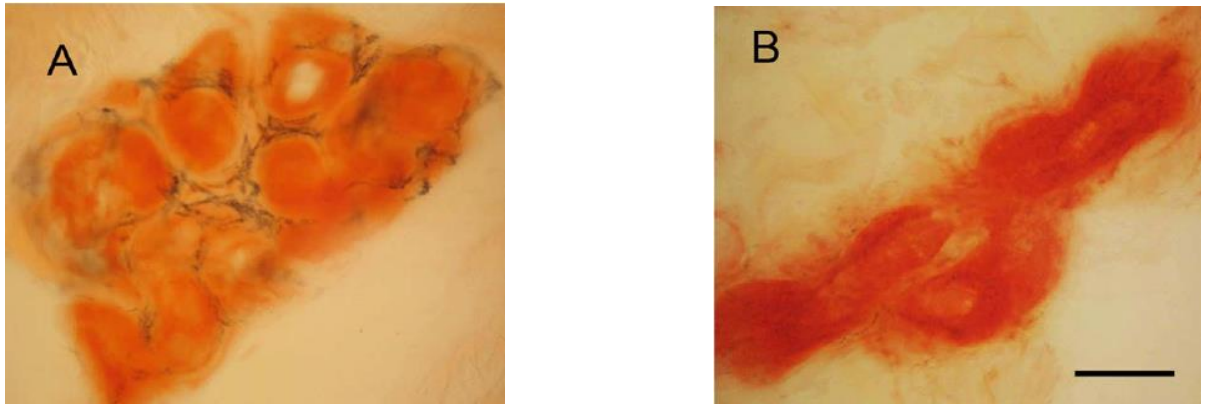
Autonomic Neuropathy: A major feature of hATTR amyloidosis

Zaeem A. Siddiqi, MD, PhD
Professor, Division of Neurology
Director Neuromuscular & Autonomic Diseases Programs
University of Alberta
Edmonton, AB

Neuropathy in hATTR Amyloidosis

- Results from deposition of insoluble, aggregated TTR amyloid fibrils in various nerves and other tissues causing progressive damage and dysfunction[1–3]
- Infiltration of the small myelinated or unmyelinated autonomic nerve fibres is correlated with increased autonomic dysfunction[4]

Co-localization of amyloid and sweat gland nerve fibres shows markedly reduced sweat gland innervation & increased disruption of tissue organization : (A) Controls (B) hATTR amyloidosis[5]



Amyloid infiltration of ANS continues throughout the disease course and can lead to intractable damage[5]

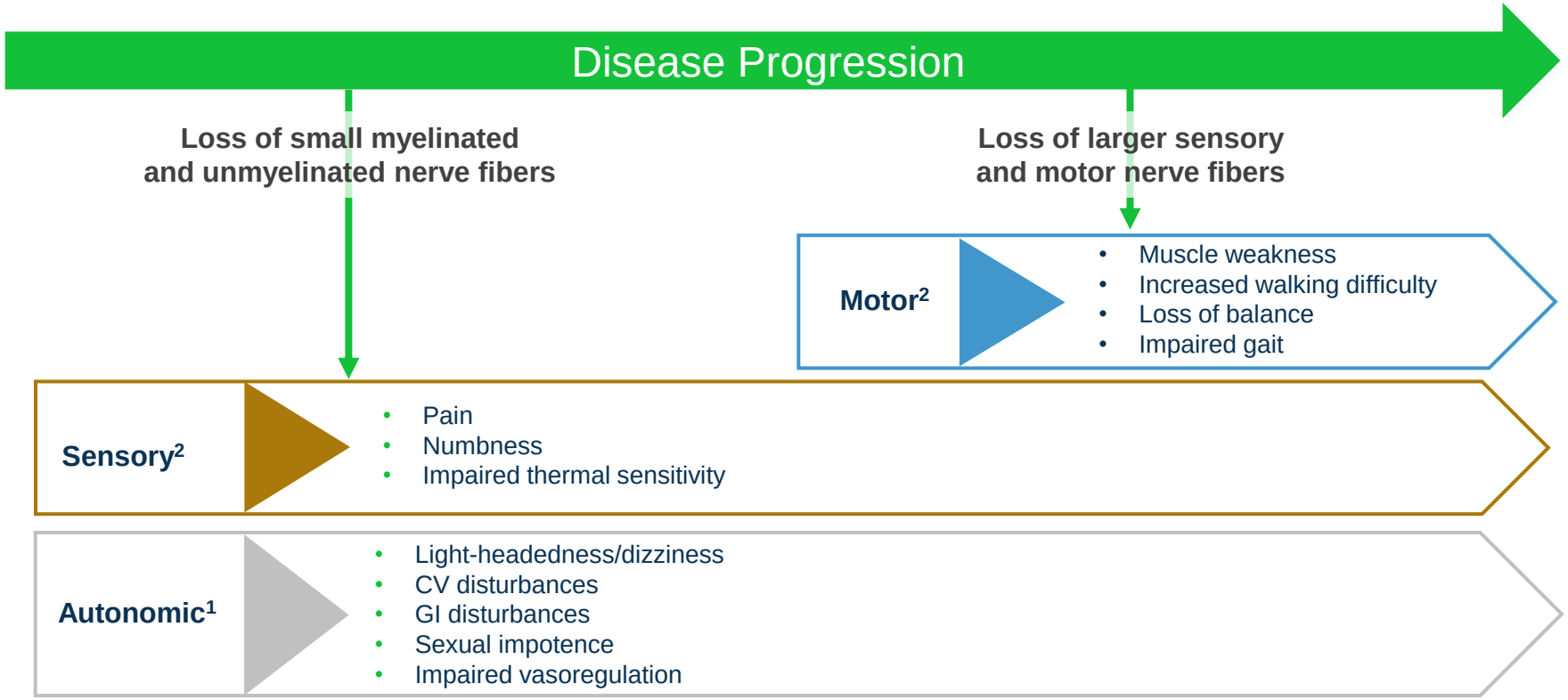
hATTR: a Heterogeneous Disease

Four Main Phenotypes[5]

	Initial Signs and Symptoms						
Phenotype	**Positive Neuropathic**	**Negative Neuropathic**	**Bil. CTS**	**Autonomic**	**GI**	**Conduction Disturbances**	**Cardiomyopathy**
V30M early onset <40 years	+++	++	±	**+++**	++ +	++	±
V30M late onset >50 years	++	+++	+	**+**	±	++	++
Non-V30M cardiac phenotype 35-55 years	±	±	+	**+**	±	++	+++
Non-V30M mixed phenotype 30-55 years	++	++	+	**+**	+	++	+++

Autonomic Dysfunction Can Be One of the Earliest Manifestations of hATTR Amyloidosis

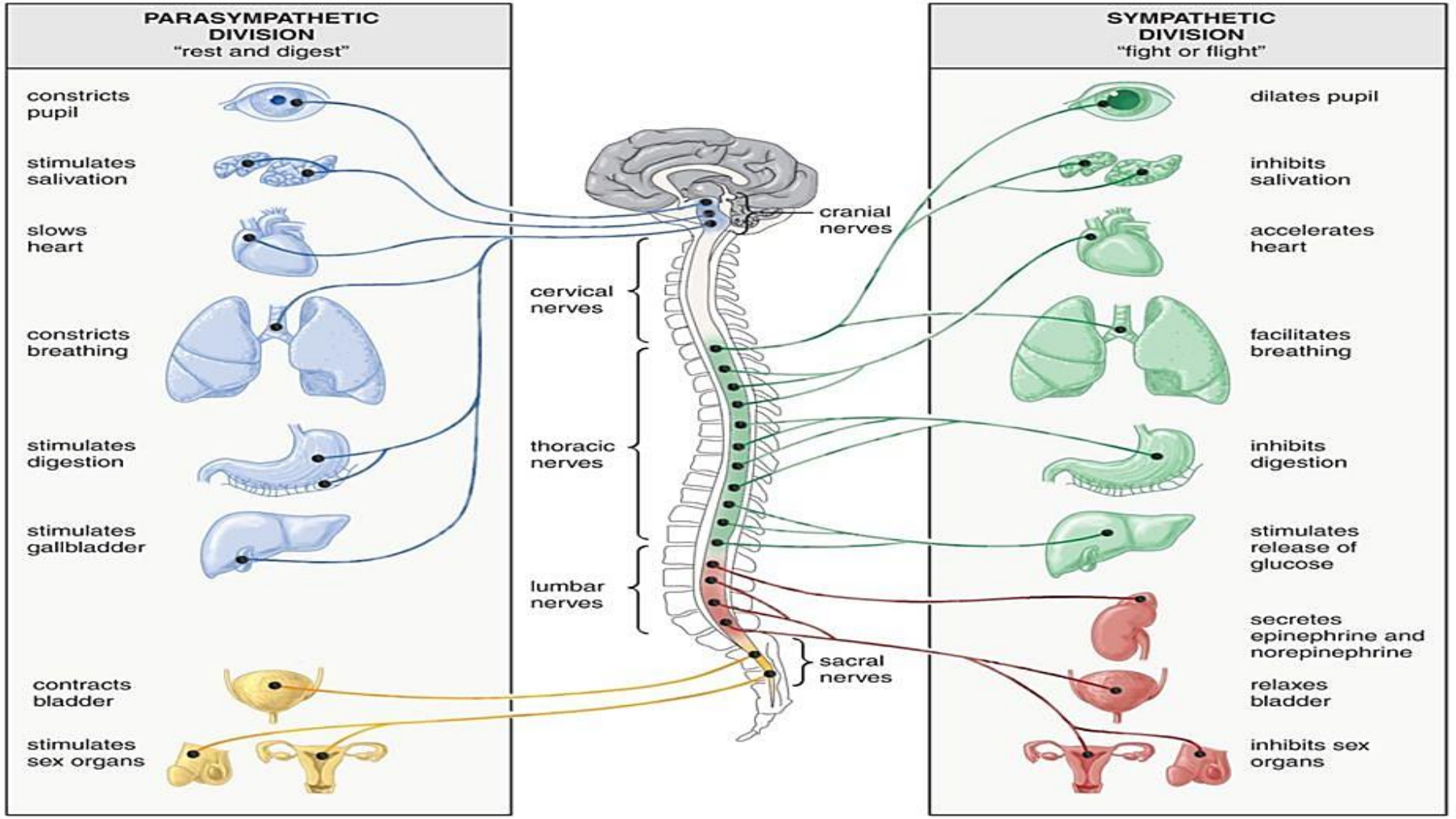
In hATTR amyloidosis, peripheral autonomic nerves are often affected early in the disease course, accompanying sensory deficits, before motor nerve impairment is evident[1]



Early autonomic symptoms may support a diagnosis of hATTR amyloidosis when differentiating from other progressive neuropathies[1]

1. Gonzalez-Duarte. *Clin Auton Res* 2018 Mar 6. [Epub ahead of print]. 2. Ando et al. *Orphanet J Rare Dis* 2013;8:31

THE AUTONOMIC NERVOUS SYSTEM[6]

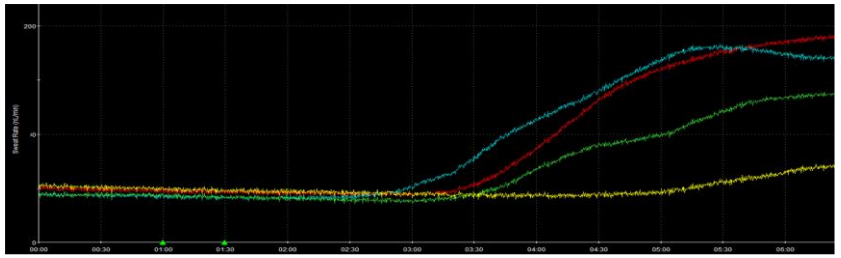


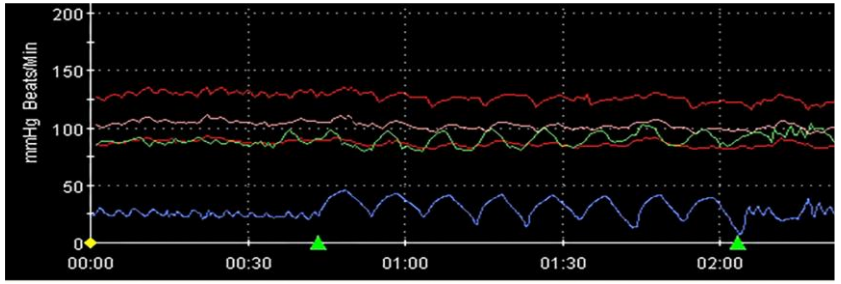
AUTONOMIC NEUROPATHY

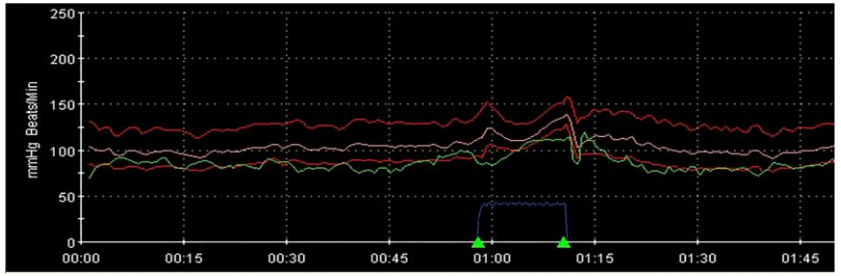
ORGAN	SIGN/SYMPTOMS	
CARDIOVASCULAR	• Tachycardia at rest • Exercise Intolerance • Reduced HR variability	• Orthostatic Hypotension • Silent Myocardial Infarction
SUDOMOTOR/ VASOREGULATORY	• Dry Skin/Anhidrosis • Postprandial Hyperhidrosis	• Intolerance to warm temperature • Abnormally cold hands/feet, discoloration
PUPILS	• Impaired adaptation to lowered light	
GASTROINTESTINAL	• Esophageal Dysmotility • Gastroparesis/Early satiety • Unintentional weight loss	• Diarrhea • Fecal Incontinence • Constipation
GENITOURINARY	• Neurogenic Bladder • *Erectile Dysfunction*	• Retrograde Ejaculation • Female Sexual dysfunction

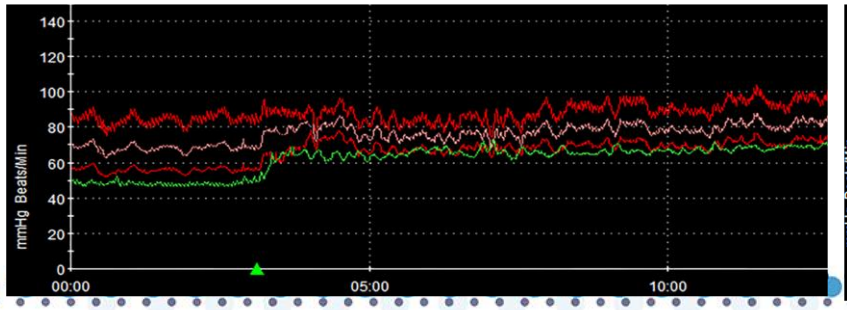
AUTONMIC NEUROPTHY IN AMYLOIDOSIS

Normal

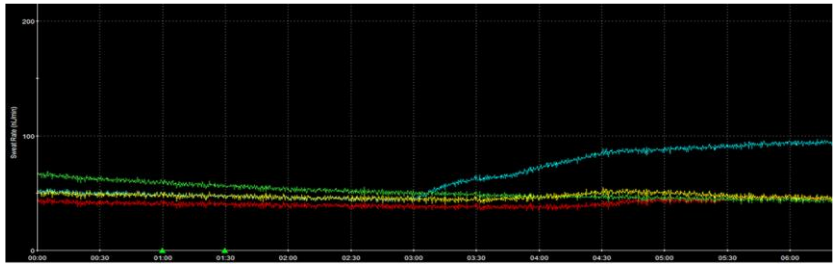


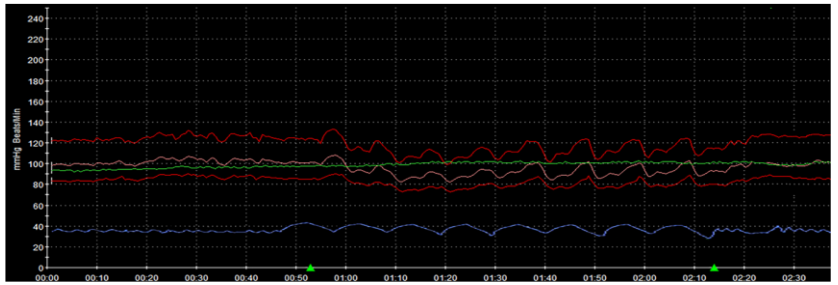


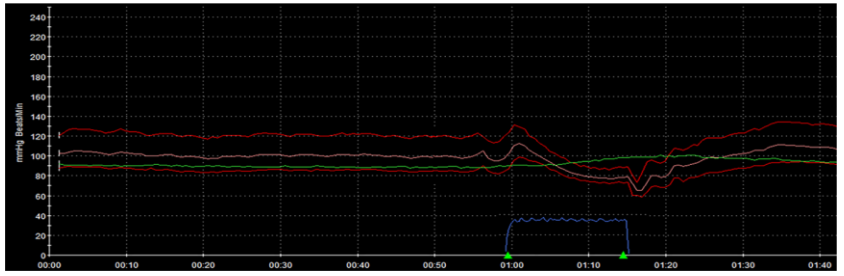


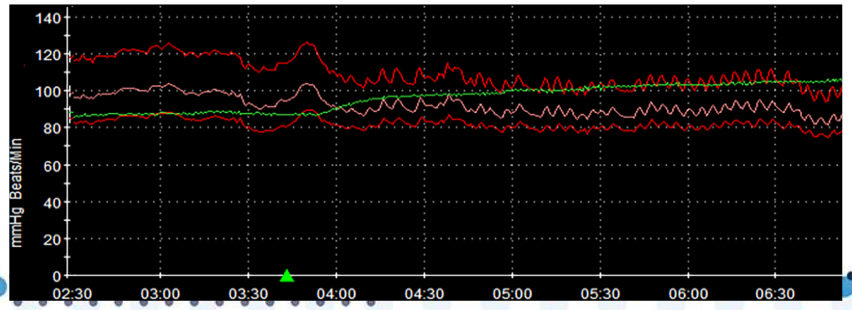


Early Amyloidosis

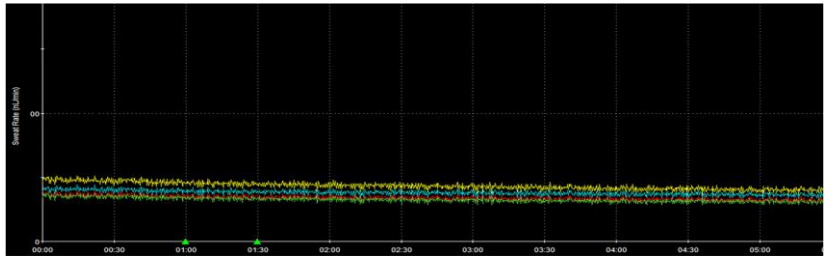


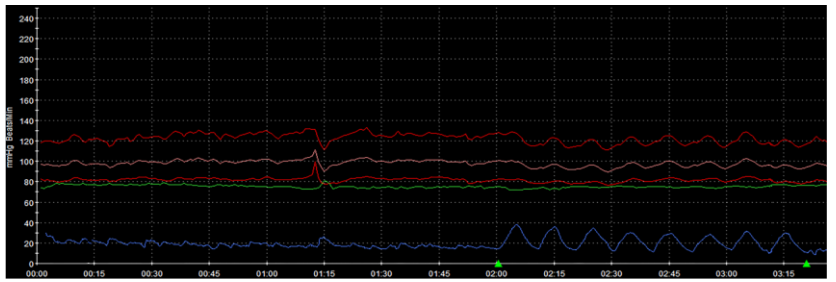


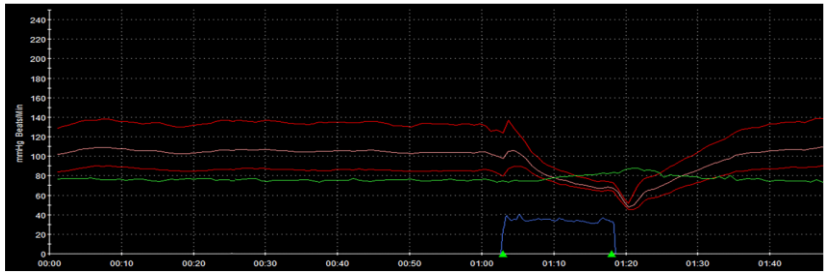


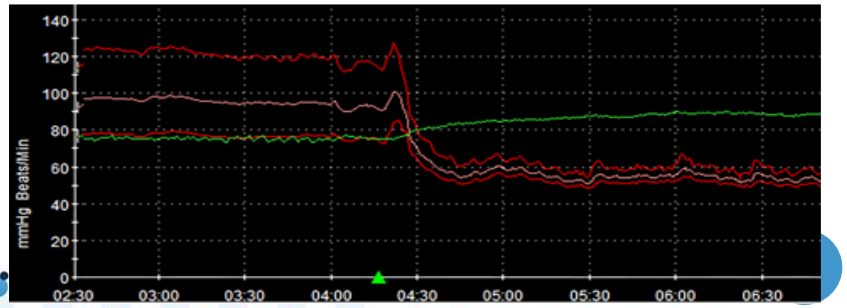


Late Amyloidosis









Conclusions

- Autonomic neuropathy is a common, debilitating aspect of hATTR amyloidosis
- Manifests early in the disease course and has diverse manifestations
- Careful history with appropriate testing can lead to early diagnosis

References

1. Ando et al. *Orphanet J Rare Dis* 2013;8:31;
2. Hanna. *Curr Heart Fail Rep* 2014;11:50–7;
3. Hawkins et al. *Ann Med* 2015;47:625–38;
4. Ebenezer et al. *Ann Neurol* 2017;82:44−56; 5. Chao et al. *Ann Neurol* 2015;78:272–83
5. Conceicao *et. al.,* Amyloid, 26:1, 3-9
6. Figure adapted from slide presentation. Available at https://slideplayer.com/slide/6366557/ and Bankenahally & Krovvidi. *BJA Education* 2016;16:381–87

How Does AN Present in hATTR?

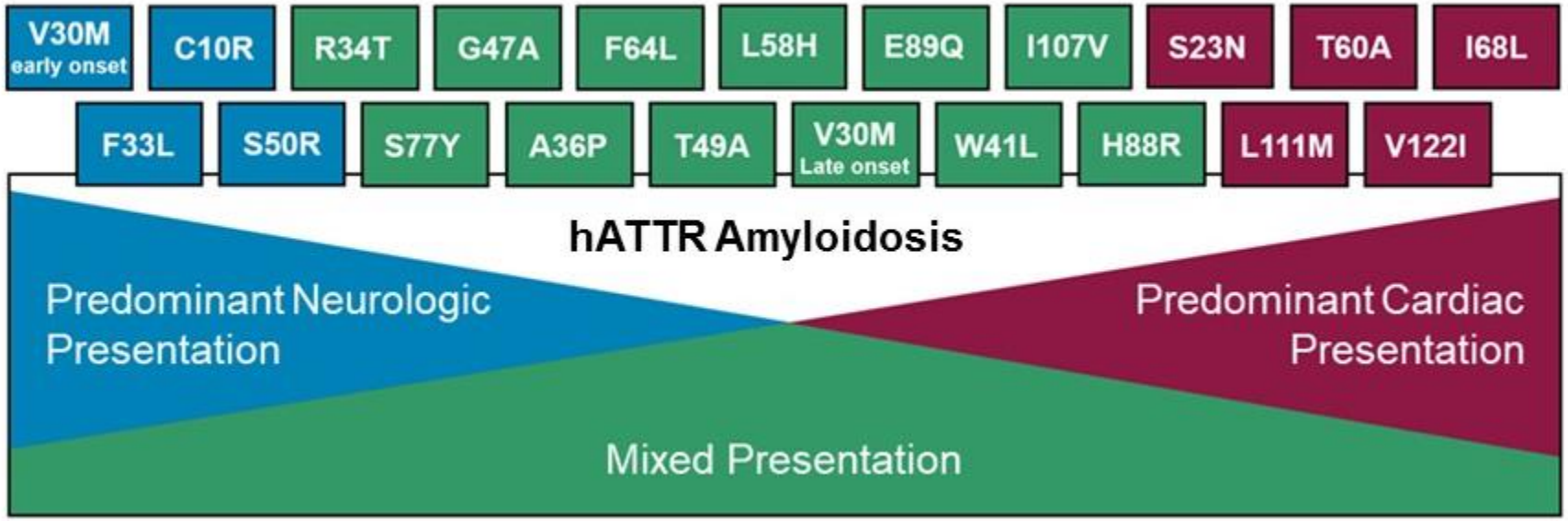
Anique Ducharme, MD, MSc, FRCP
President – Canadian Heart Failure Society
Director, Heart Failure clinic, Montreal Heart Institute,
Professor of medicine, University of Montreal, (Canada)
University of Montreal Chair holder: Fondation Marcelle et Jean Coutu, Cal et Janine Moisan for better practices in advanced heart failure

Diagnosis of amyloid neuropathy

Mahima Kapoor,[1] Alexander M Rossor,[1] Zane Jaunmuktane,[2]
Michael P T Lunn,[1,3] Mary M Reilly[1]

Kapoor M, et al. Pract Neurol 2019;**19**:250–258

hATTR Amyloidosis: Broad spectrum of presentation with different TTR mutations



Select representative mutations shown

- Hereditary amyloidosis is caused by many gene variants, but *TTR* mutations account for the majority[1]
- Transmitted in an autosomal dominant manner with variable penetrance[2,3]
- More than 120 *TTR* mutations have been discovered[1]
- The most common mutation worldwide is Val30Met[4]

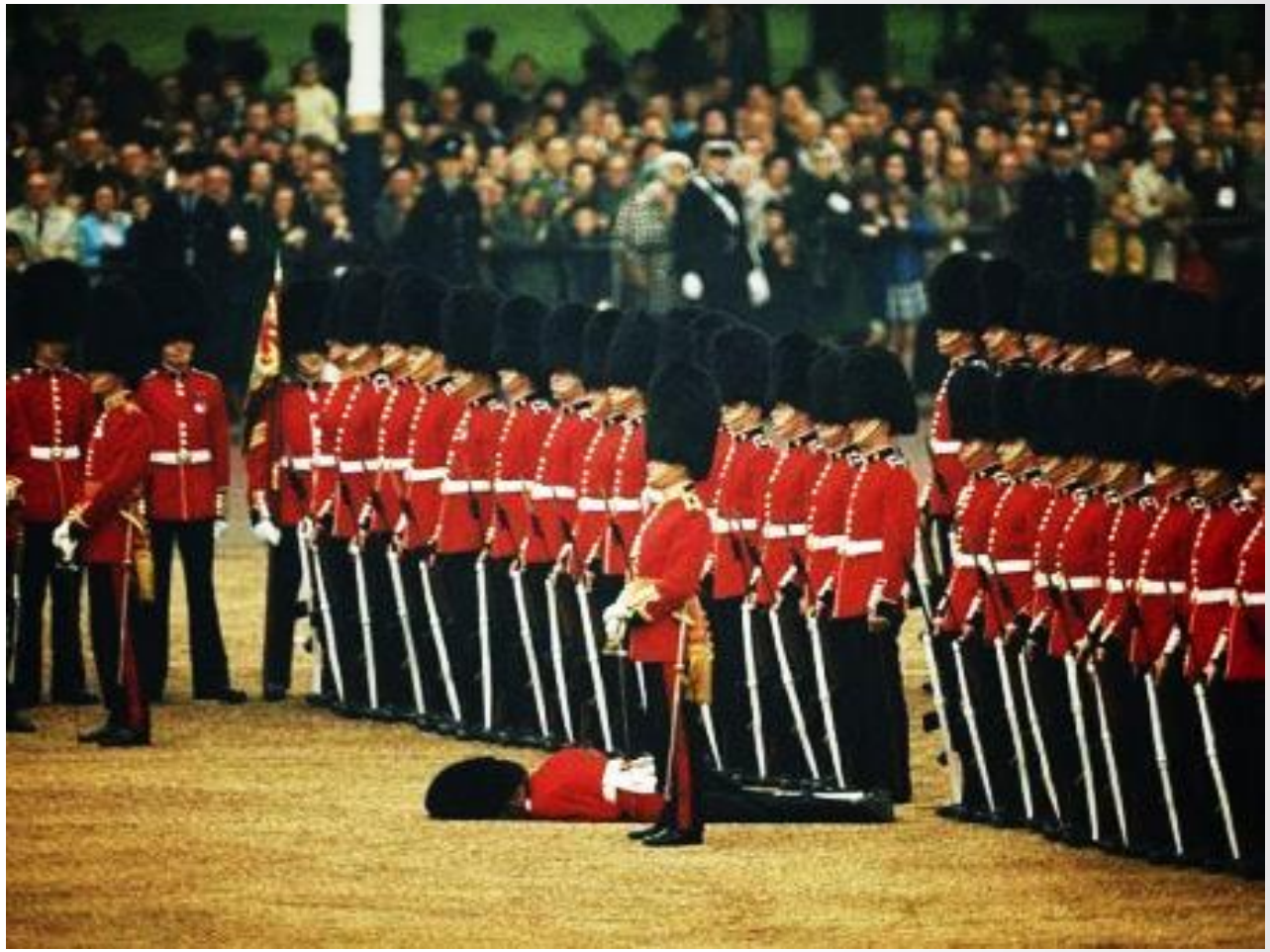
hATTR = hereditary amyloid transthyretin; TTR = transthyretin

1. Rowczenio D et al. *Human Mutation Database in Brief*. 2014;35:E2403–E2412; 2. Coelho T, Maurer M, and Suhr O. *CMRO*. 2013; 29:63-76; 3. Ando et al. Orphanet Journal of Rare Diseases 2013, 8:31; 4. Gertz. Am J Manag Care. 2017;23:S107-S112. Figure sources: Benson. *Am J Pathol*. 1996 Feb;148:351-354; Rapezzi et al. *Eur Heart J*. 2013 Feb;34:520-528; Connors et al. Amyloid. 2003 Sep;10(3):160-84.

Meet Harry

- 73 YO man
- HFpEF with one previous hospital admission (2019)
- Af on apixaban and bisoprolol 1.25
- NYHA 2 with no congestion
- Multiple symptoms, including:
  - Dizziness, mostly orthostatic and low SBP 95ish
  - Vague Gi symptoms with usually constipation (2nd furosemide?), but sometimes diarrheas and bloating
  - Lost 5 pounds
  - Erectile dysfunction for which he stopped his BB
  - Had a recent syncope (vagal?)

SYNCOPE



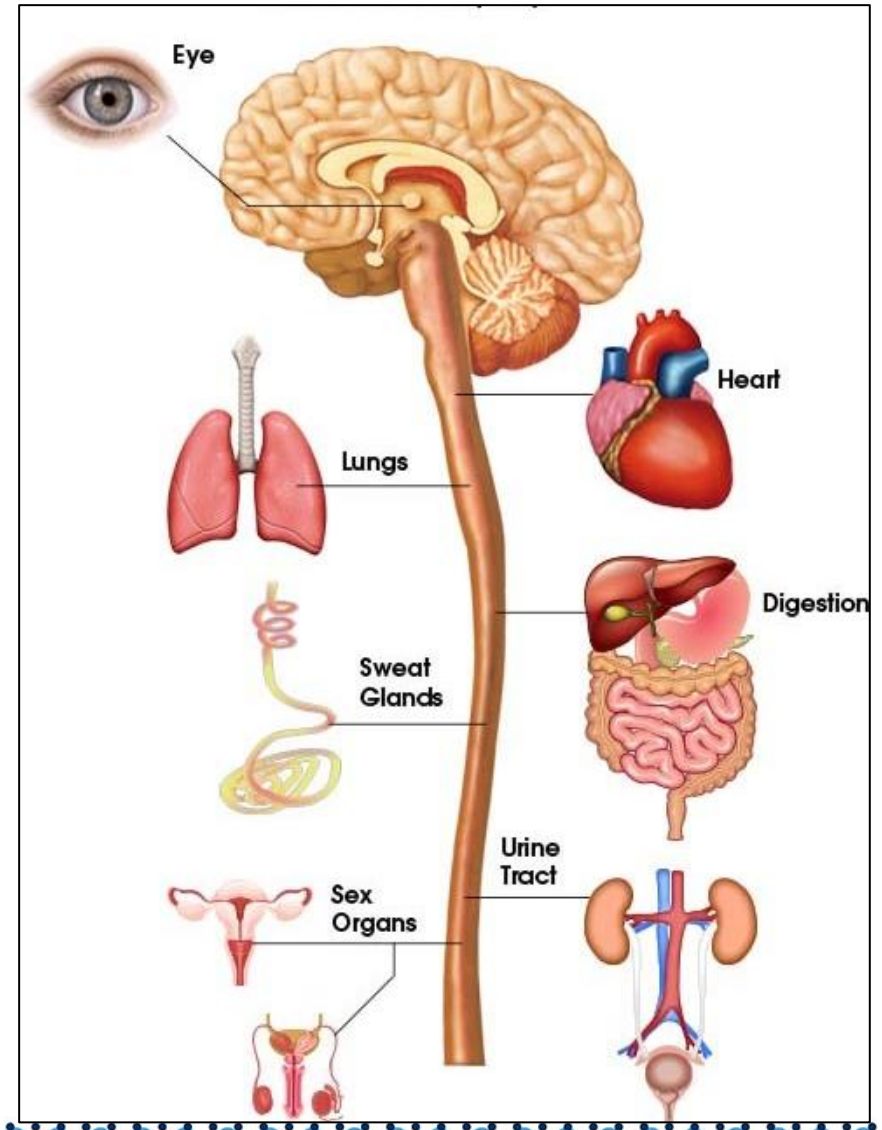
https://www.reddit.com/r/funny/comments/1jhtdq/guard_faints_during_ceremony_other_guards_remain/

Do I really know what's going on ?

https://www.toonpool.com/cartoons/Whats%20Going%20On_158521

https://rantz72.wordpress.com/2012/02/14/things-are-not-always-what-they-appear-to-be/

Autonomic neuropathy



- Refers to an affection of those nerves which control the automatic processes of our body, such as
  - digestion,
  - blood circulation,
  - urination, and
  - sexual functions.
- Autonomic dysfunction can occur early in the disease.

How Does AN Present in hATTR

Cardiovascular AN

- Heart rate changes
  - Postural tachycardia
  - Resting tachycardia
  - Fixed heart rate
- Orthostatic hypotension
- Silent Ischemia
- Loss of Circadian patterns
- Exercise intolerance

Gastrointestinal AN

- Esophageal dysmotility
- Gastroparesis diabeticorum
- Constipation
- Diarrhea
- Fecal incontinence

Genitourinary AN

- Bladder dysfunction
  - Suprapubic fullness
  - Frequency
  - Nocturia
  - Urgency
  - Incontinence
- Erectile dysfunction

Autonomic neuropathy

- Up to 75% of patients with hATTR (65% with AL) -amyloidosis develop symptoms of an autonomic neuropathy.
- Diarrhea and postural hypotension are among the most disabling symptoms.
  - Orthostatic hypotension can be asymptomatic, or can cause persistent fatigue, light-headedness on standing or syncope.
  - Gastrointestinal manifestations include gastroparesis, weight loss from early satiety and unexpected diarrhoea that may be socially prohibitive, often nocturnal especially initially, and may cause incontinence.
- Erectile dysfunction may be an early feature in men, and there may also be urinary frequency and retention.
- Pupillary and sweating abnormalities occasionally occur.

Heart Failure Management

- ✓ Avoid Beta blockers/Calcium Channel Blockers/Digoxin
- ✓ Intolerance of ACE inhibitors
- ✓ Torsemide
- ✓ Spironolactone
- ✓ Salt restriction
- ✓ Midodrine

- ✓ CRT-D

- X Heart transplant/LVAD (?)

Key Point

Remember the nerves!

- *Numbness, pain in feet*
- *Unsteadiness*
- *Carpal tunnel syndrome*
- Orthostatic hypotension
- Syncope
- GI symptoms
- Erectile dysfunction (not always 2nd to βB)

How Do We Assess Autonomic Function?

Nowell M. Fine MD, SM, FRCPC, FACC, FCCS, FASE, FHFSA
Clinical Assistant Professor of Cardiac Sciences, Medicine and Community Health Sciences
Clinical Director, Libin Cardiovascular Institute
Director of Echocardiography, Heart Failure Cardiologist
Cumming School of Medicine, University of Calgary
Calgary, AB

History – Autonomic Neuropathy

- Cardiovascular
  - **Orthostatic hypotension**
    - **Pre/syncope**
  - Post-prandial hypotension
  - **Exercise intolerance**
- Gastrointestinal
  - Esophageal dysmotility
  - **Gastroparesis**
  - **Constipation**
  - **Diarrhea**
  - Fecal incontinence
- Genito-urinary
  - Bladder dysfunction
    - Suprapubic fullness
    - Frequency
    - Nocturia
    - Urgency
    - Incontinence
  - **Erectile/sexual dysfunction**

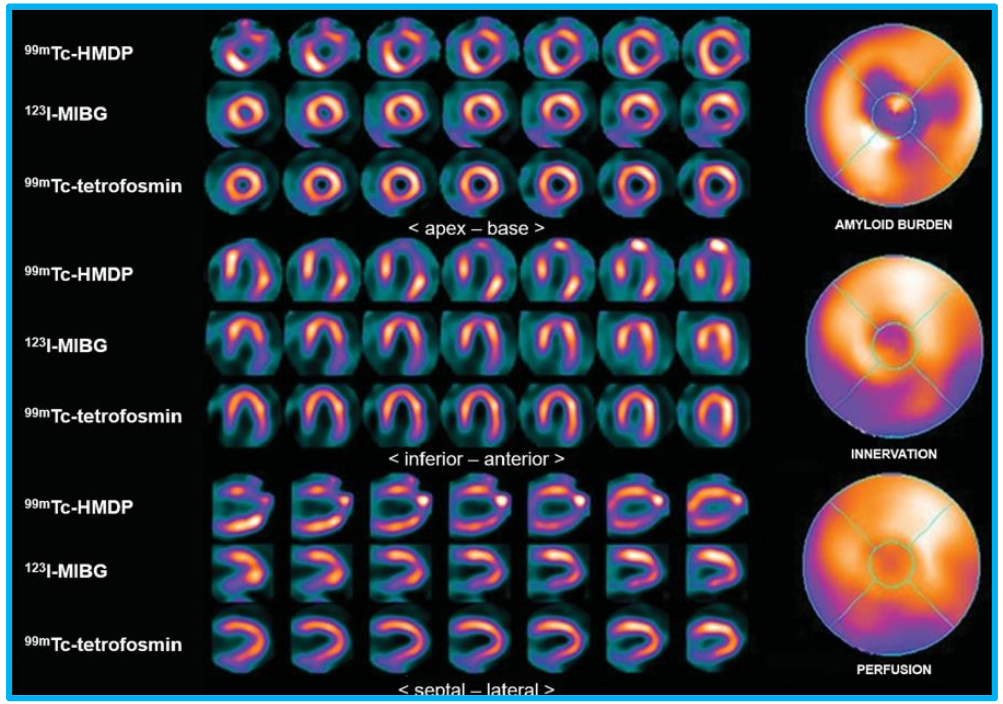
Physical Exam – Autonomic Neuropathy

- Resting tachycardia
- **Fixed heart rate**
- **Orthostatic hypotension**
  - ↓ SBP ≥20 or DBP ≥10 mmHg within 2-5 minutes of standing (after sitting for ≥5 minutes)

- Postural tachycardia (POTS)
  - ↑ HR ≥30 BPM without change in BP upon standing
  - **Uncommon in hATTR**

Investigations – Autonomic Neuropathy

- Treadmill stress test
  - Chronotropic incompetence
- Autonomic function testing
  - Tilt table testing
  - Serum norepi levels – supine, standing
  - HR variability to deep breathing
  - HR response to standing
  - HR and BP response to Valsalva maneuver
  - MIBG – (123-I-metaiodobenzylguanidine)
    - Cardiac autonomic scintigraphy imaging



Gimelli et al. Amyloid 2020;27:237

Investigations – Autonomic Neuropathy

- **Neurology consultation**
  - NCS-EMG
  - Peripheral / vasomotor
    - Quantitative sudomotor axon reflex testing (QSART) – peripheral sympathetic denervation
    - Skin biopsy – small fibre neuropathy, sweat gland
    - Thermoregulatory sweat testing
    - Sympathetic skin response
- Gastrointestinal
  - Gastric emptying scintigraphy
  - Isotope-based breath test
  - Esophageal manometry
  - **Nutritional status** – mBMI (alb x BMI)
- Urologic
  - Post-void residual
  - Urodynamic studies

Summary - Autonomic Neuropathy Assessment

- Assessment for AN is an important component of the evaluation for patients with known or suspected hATTR
- **History and physical exam** are the mainstays of AN assessment
  - Orthostatic hypotension
  - Gastrointestinal
  - Genito-urinary
- Dedicated cardiovascular autonomic function testing (AFTs) can be helpful but have variable availability
- **Neurology consultation** is strongly recommended for all patients with known or suspected hATTR

Application and Implications in Real Life: Case Studies

Nowell M. Fine MD, SM, FRCPC, FACC, FCCS, FASE, FHFSA
Clinical Assistant Professor of Cardiac Sciences, Medicine and Community Health Sciences
Clinical Director, Libin Cardiovascular Institute
Director of Echocardiography, Heart Failure Cardiologist
Cumming School of Medicine, University of Calgary
Calgary, AB

Case

- 64 yo M, Southeast Asian descent, previously healthy on no medications,
- Initially presents to Family Physician 4-years prior with symptoms of **diarrhea**, **numbness and tingling** in all extremities and **exercise intolerance**
  - Stool testing unremarkable
- Referred to Neurologist
  - NCS-EMG and neuropathy labs (thyroid, B12, diabetes, renal, liver, S/UPEP) all **unremarkable**
- Diarrhea progressed, began **losing weight**, referred to Gastroenterologist
  - Endoscopy/colonoscopy, random biopsies taken and were unremarkable, staining for amyloidosis (Congo red) not performed
  - Lomotil recommended

Case

- After 2 years, patient developed **dyspnea on exertion**, **mild peripheral edema**, and **orthostatic lightheadedness**
- Referred to Internal Medicine
  - Laboratory testing repeated and CT chest/abdo performed that was unremarkable, stool tests repeated
- Referred to Cardiology
  - ECG shows nonspecific T-wave changes
  - Holter monitor shows only rare atrial and ventricular ectopy
  - Echo shows **mild increased LV wall thickness** with **normal biventricular function**
  - Troponin and NTproBNP **mildly elevated**
  - Coronary angiography deferred, prescribed low dose diuretic

Case

- Developed new **urinary urgency** and **erectile dysfunction**
- Referred to Urology
  - Prostrate ultrasound and PSA normal, prescribed Tadalafil
- Peripheral neuropathy progressed, developed weakness in extremities
- Re-referred to Neurologist
  - Repeat laboratory testing demonstrated **low albumin, normocytic anemia**, otherwise unremarkable
  - Examination showed **atrophy and weakness** of hand muscles, **bilateral foot drop** and **sensory loss** to pinprick extending to his shoulders and mid thighs
  - Repeat NCS-EMG demonstrated a **severe motor greater than sensory axonal polyneuropathy**

Case

- Referred to Hematology due to progressive anemia
  - Bone marrow biopsy unremarkable, AL excluded
  - Amyloidosis considered, **GI biopsies** previously sampled **re-reviewed** for amyloidosis and **Congo red staining positive**
  - Samples sent to Mayo Clinic for **mass spec**, findings consistent with ATTR, **Val30Met** (pV50M) mutation, confirmed by genetic testing
- Referred to specialized Cardiology and Neurology clinics with focused interest in amyloidosis (Amyloidosis Program of Calgary)
  - **PYP scan positive** for cardiac involvement
  - Initiated on **patisiran**
  - Tolerating well after 3-4 months, symptoms stable, low dose midodrine
  - Referral for **Genetic Counselling**

Case Summary

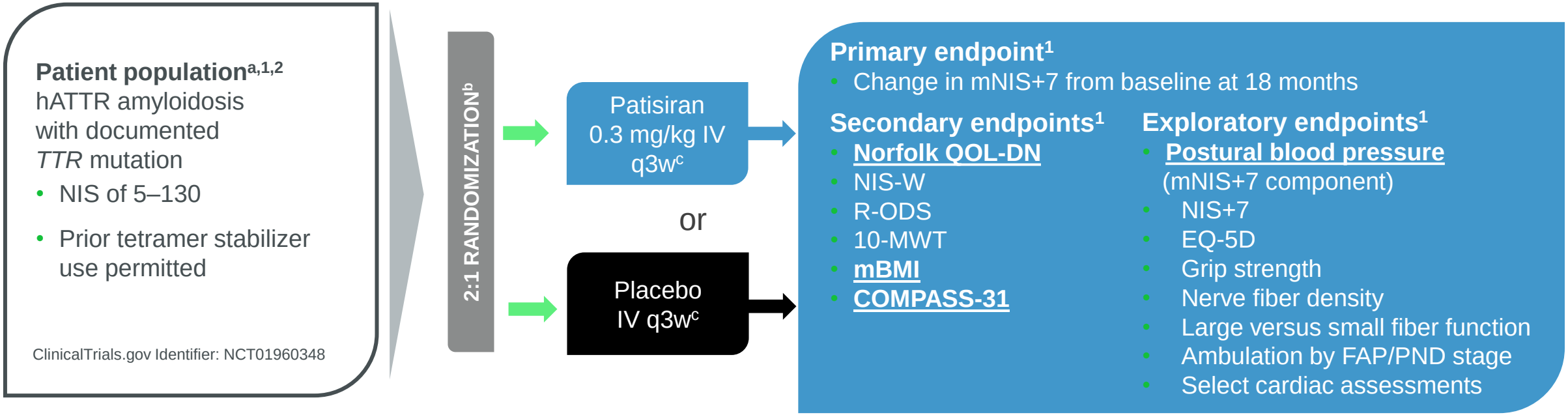
- >4 years
- Numerous Family Physician visits
- 6 specialists
- ‘Red flags’
  - Autonomic neuropathy with multiple manifestations, orthostatic, GI, GU
  - Progressive peripheral neuropathy
  - Cardiovascular abnormalities with mild heart failure
  - Southeast Asian descent
- Summary
  - **Awareness and index of suspicion** are critical for earlier diagnosis and treatment initiation to **attenuate disease progression**

APOLLO: Efficacy in Neuropathic Impairment

Zaeem A. Siddiqi, MD, PhD
Professor, Division of Neurology
Director Neuromuscular & Autonomic Diseases Programs
University of Alberta
Edmonton, AB

Patisiran Phase 3 APOLLO Study Design

- APOLLO (NCT01960348) was a multicenter, international, randomized, double-blind, placebo-controlled, phase III study
  - A total of 225 patients were enrolled at 44 sites across 19 countries between December 2013 and January 2016



10-MWT, 10-meter walk test; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; EQ-5D, EuroQoL 5-dimensions questionnaire; FAP, familial amyloid polyneuropathy; IV, intravenous; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; NIS-W, Neuropathy Impairment Score-Weakness; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; PND, polyneuropathy disability; q3w, once every 3 weeks; R-ODS, Rasch-built Overall Disability Scale

Baseline Autonomic Measurements[a,1]

- Baseline demographics were well balanced, as previously described[2]
- Autonomic measures were well balanced between groups and indicate the autonomic impairment present at baseline in patients in APOLLO

Disease Characteristics of Autonomic Endpoints at Baseline

Characteristic	Placebo (n=77)	Patisiran (n=148)	Total (n=225)
COMPASS-31 total score (range: 0–100), mean (±SD)	**30.3 (16.4)**	**30.6 (17.6)**	**30.5 (17.1)**
Orthostatic intolerance (range: 0–40), mean (±SD)	13.2 (11.2)	14.2 (10.8)	13.8 (10.9)
Vasomotor (range: 0–5), mean (±SD)	1.0 (1.4)	0.9 (1.44)	1.0 (1.4)
Secretomotor (range: 0–15), mean (±SD)	4.9 (3.7)	4.2 (3.7)	4.4 (3.7)
GI (range: 0–25), mean (±SD)	8.1 (3.5)	8.2 (4.3)	8.1 (4.1)
Bladder (range: 0–10), mean (±SD)	1.9 (2.7)	2.0 (2.5)	2.0 (2.5)
Pupillomotor (range: 0–5), mean (±SD)	1.1 (1.1)	1.2 (1.2)	1.2 (1.2)
mBMI ($kg/m^2 \times g/L$), mean (±SD)	**989.9 (214.2)**	**969.7 (210.5)**	**976.6 (211.5)**
BMI (kg/m^2), mean (±SD)	23.6 (4.3)	23.0 (4.4)	23.2 (4.4)
Albumin (g/L), mean (±SD)	41.8 (3.4)	42.1 (3.5)	42.0 (3.5)
Weight (kg), mean (±SD)	67.5 (15.7)	67.3 (16.6)	67.4 (16.3)
mNIS+7 total score (range: 0–304), mean (±SD)	**74.6 (37.0)**	**80.9 (41.5)**	**78.8 (40.1)**
Postural BP (range: 0–2), mean (±SD)	0.6 (0.7)	0.7 (0.8)	0.6 (0.8)
Norfolk QOL-DN total score (range: −4–136), mean (±SD)	**55.5 (24.3)**	**59.6 (28.2)**	**58.3 (27.0)**
Autonomic neuropathy domain (range: 0–12), mean (±SD)	2.9 (2.9)	3.0 (2.8)	3.0 (2.8)

- SD, standard deviation

- [a]Across all study endpoints, there was a lower percentage of missing data in the patisiran group than the placebo group due to a lower rate of treatment discontinuation (7.4% versus 37.7%, respectively; reasons include: death, withdrawal, receipt of alternative therapy due to rapid disease progression, or random missingness)

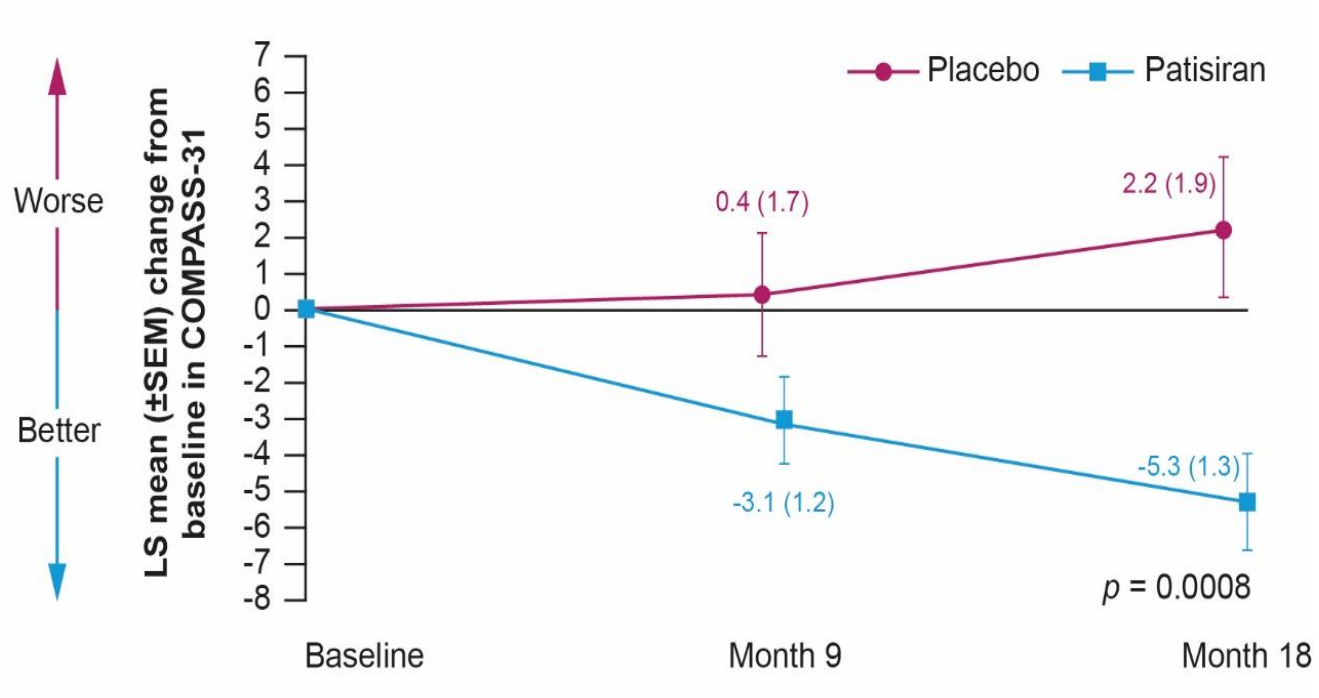
1. González-Duarte et al. *J Neurol* 2019. Epub ahead of print; 2. Adams et al. *N Engl J Med* 2018;379:11–21

Measures of Autonomic Symptoms

COMPASS-31

- Total COMPASS-31 score improved in patisiran- versus placebo-treated patients at 9 months, and reached statistical significance at 18 months, with an LS mean difference of −7.5 (95% CI: −11.9, −3.2; *p*=0.0008)
- Total COMPASS-31 score improved from baseline in patients who received patisiran at 9 and 18 months (LS mean change of −3.1 points [95% CI: −5.5, −0.7] and −5.3 points [95% CI: −7.9, −2.7], respectively) and worsened by 18 months in patients who received placebo (2.2-point worsening [95% CI: −1.6, 6.1])

LS mean change in COMPASS-31 score from baseline to 18 months in patients receiving patisiran or placebo in the APOLLO study



Patisiran improved autonomic neuropathy symptoms compared with placebo as assessed by COMPASS-31

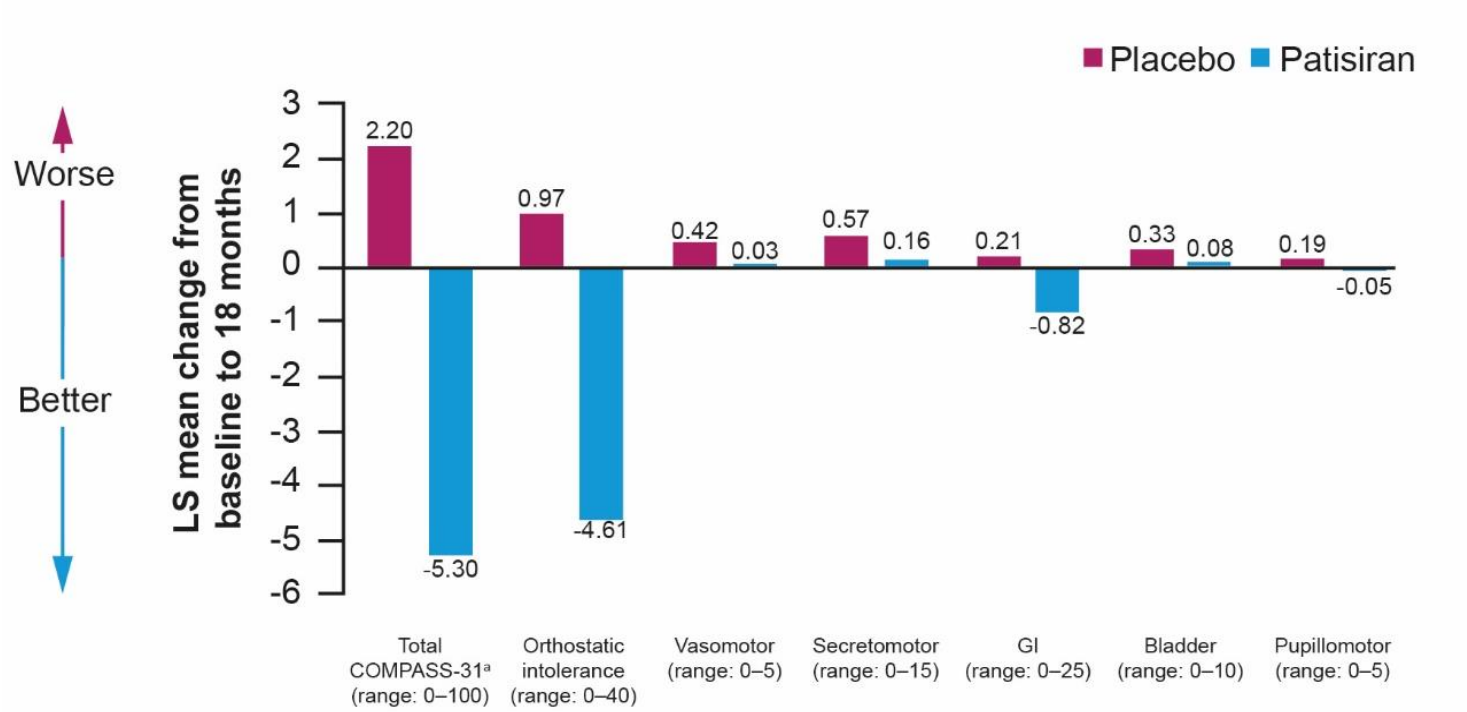
Patisiran treatment also led to improvement from baseline at 18 months for COMPASS-31

Measures of Autonomic Symptoms

COMPASS-31: Individual Domain Scores at Month 18

- An improvement was observed across each of the six autonomic domains of COMPASS-31 compared with placebo
- Orthostatic intolerance and GI domain scores were improved in patisiran-treated patients compared with placebo at 18 months and relative to baseline
  - Orthostatic intolerance domain: LS mean change from baseline −4.6 [95% CI: −6.3, −2.9]
  - GI symptoms domain: LS mean change from baseline −0.8 [95% CI: −1.5, −0.2]

LS mean change in individual COMPASS-31 domains from baseline to 18 months in the patisiran and placebo groups

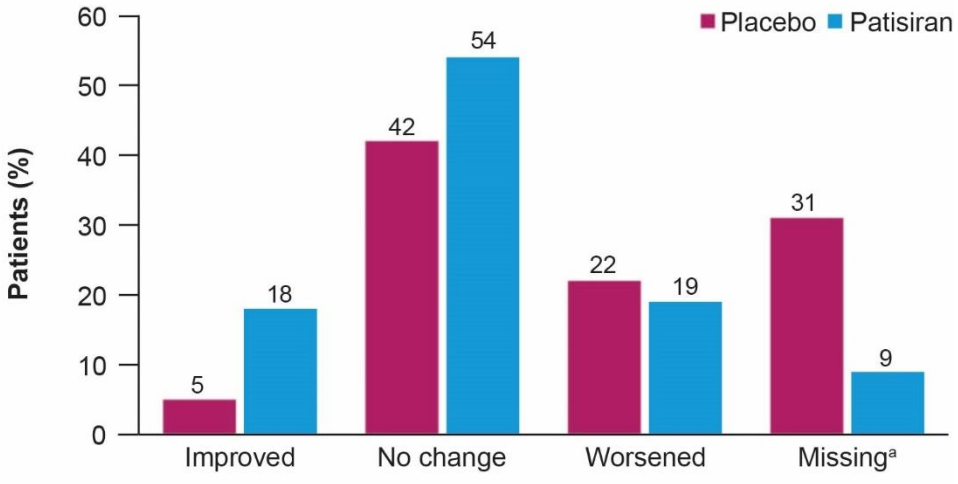


Patisiran treatment led to improvement from baseline at 18 months for COMPASS-31 individual domains, orthostatic intolerance and GI symptoms

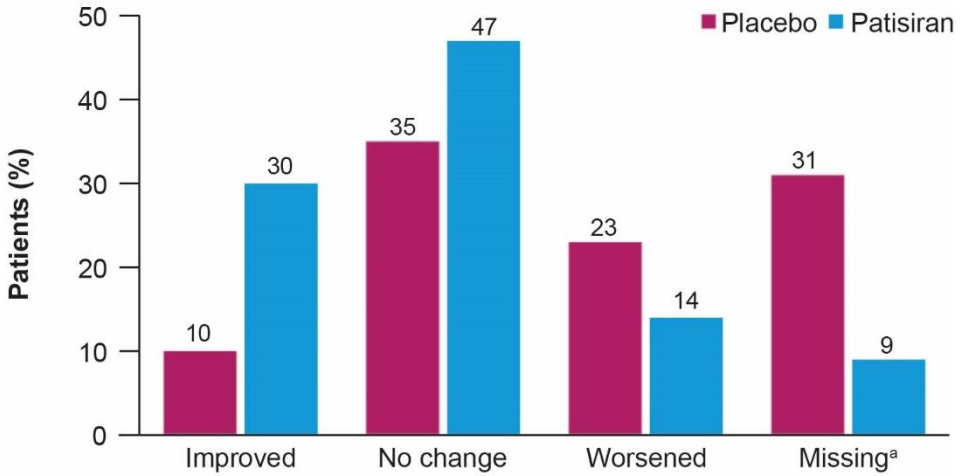
Measures of Autonomic Symptoms

Question-Level Analysis of Domains in COMPASS-31

GI domain: change from baseline in diarrhea presence and severity at Month 18



Orthostatic intolerance domain: change from baseline in orthostatic intolerance presence and severity at Month 18



- After 18 months of treatment, the patisiran group was 3.5-fold more likely to report improvement in diarrhea severity than the placebo group (18% versus 5%, respectively), and 3-fold more likely to report improvement in severity of orthostatic intolerance than the placebo group (30% versus 10%, respectively)
- The patisiran group was less likely to report worsening of orthostatic intolerance symptoms than the placebo group after 18 months (14% versus 23% respectively)

Measures of Autonomic Symptoms

Norfolk QOL-DN: Autonomic Neuropathy Domain

- At 18 months, a significant improvement was observed in Norfolk QOL-DN total score for patisiran-treated patients compared with the placebo group
  - Difference in LS mean change from baseline: −21.1 points (95% CI: −27.2, −15.0; $p=1.10\times10^{-10}$)
- Autonomic neuropathy domain scores also favored patisiran treatment
  - LS mean (SEM) change from baseline at 18 months: −0.6 (0.2) for patisiran and +0.5 (0.3) for placebo
  - LS mean difference −1.1 (95% CI: −1.8, −0.5; $p=0.001$) for patisiran versus placebo
- The consistent effects in favor of patisiran treatment compared with placebo were observed in all Norfolk QOL-DN domains in the overall population
- Question-level analysis at 18 months demonstrated:
  - More placebo-treated patients reported moderate or severe diarrhea and/or loss of bowel control in the past 4 weeks compared with baseline (43% vs 33%, respectively)
  - Fewer patisiran-treated patients reported moderate or severe symptoms in the past 4 weeks compared with baseline (27% vs 34%, respectively)

Question-Level Analysis of Diarrhea Question within the Autonomic Neuropathy Domain of Norfolk QOL-DN (Supplementary Table)

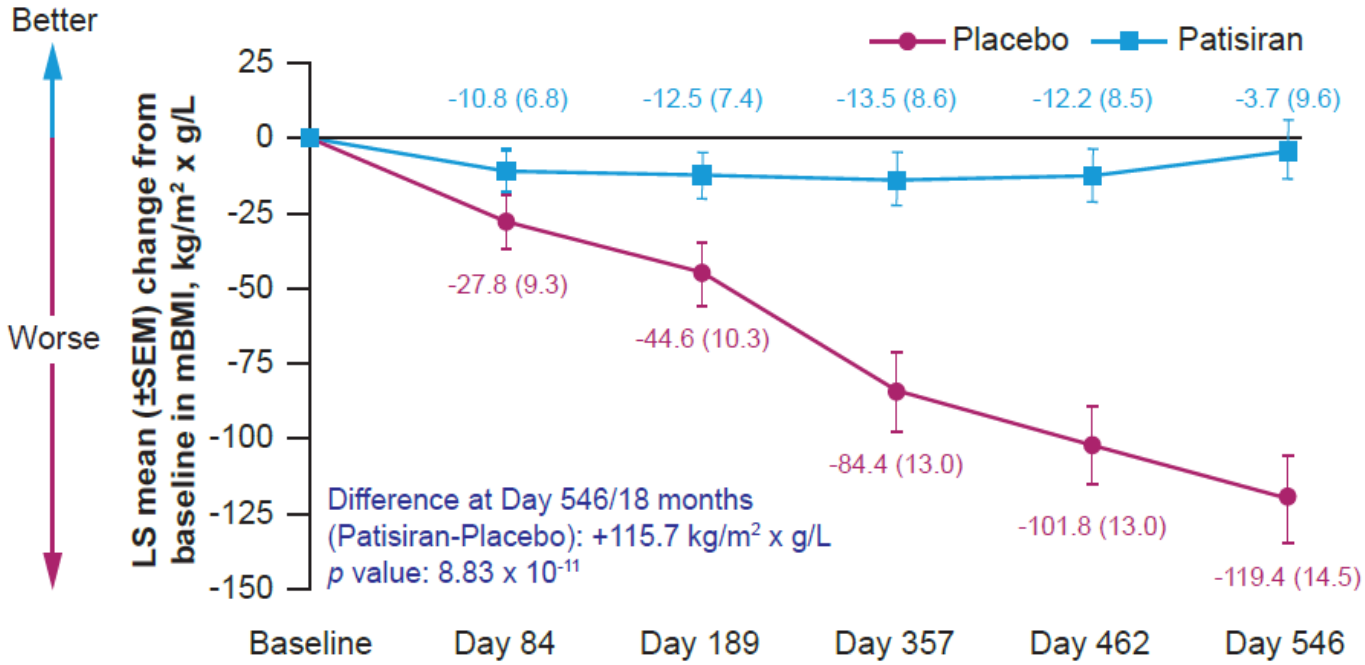
Treatment group	Problem with diarrhea and/or loss of bowel control	Baseline		Month 18		Missing data at Month 18
		n	%	n	%	n
Placebo	Total	76[a]	100	49	100	28[b]
	Moderate or severe problem	25	33	21	43	
	Moderate problem	10	13	12	25	
	Severe problem	15	20	9	18	
Patisiran	Total	147[a]	100	136	100	12[b]
	Moderate or severe problem	50	34	37	27	
	Moderate problem	26	18	21	15	
	Severe problem	24	16	16	12	

Measures of Nutritional Status Affected by GI Autonomic Symptoms

mBMI

- At 18 months, mBMI was significantly improved in patisiran-treated patients compared with placebo-treated patients, with an LS mean difference of +115.7 (95% CI: −82.4, 149.0; p=8.83 × 10^{-11})
- The favorable effect of patisiran on mBMI relative to placebo was observed at the first assessment (3 months) with nominal significance achieved by Day 189
- At 18 months, 41.2% of the patisiran group demonstrated improvement in mBMI (defined as >0 kg/m^2 × g/L increase from baseline) compared with 6.5% of the placebo group
- Improvement with patisiran compared with placebo treatment also observed with BMI (next slide)

Change in LS mean total mBMI score from baseline in patisiran and placebo groups over time (mITT population)



At 18 months, patisiran improved nutritional status (mBMI) compared with placebo

Conclusion

The APOLLO study demonstrated that in patients with hATTR amyloidosis with polyneuropathy, patisiran improved autonomic dysfunction in addition to measures of sensorimotor neuropathy and QOL, supporting its benefit for these patients