Musculoskeletal Manifestations in Patients with ATTR Amyloidosis: Evidence from Real-World Analyses and Clinical Trials

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Methods and Overview of Studies Included in the Analysis

Objective: To identify the prevalence of MSK manifestations reported in the medical and surgical histories of patients with ATTR amyloidosis

- Data sources included: Retrospective pooled analysis of MSK manifestation prevalence in patients with ATTR amyloidosis in Alnylam-sponsored studies, and data from the patisiran-CM EAP and a patient survey in patients with ATTRwt or ATTRv amyloidosis
  - MSK manifestations included: Carpal tunnel syndrome | spinal stenosis | biceps tendon rupture | trigger finger | osteoarthritis
- Medical and surgical history captured in the enrollment/baseline assessment from each study in the pooled analysis were analyzed for the prevalence of MSK manifestations

Studies included in pooled analysis

Study	Total Number of Patients N=1010 (%)	Study Description
Patisiran Ph2 OLE[1]	27 (2.7)	Safety and tolerability of long-term patisiran: ATTRv amyloidosis with mild-to-moderate neuropathy
APOLLO (Ph3)[2]	225 (22.3)	Safety and efficacy of patisiran: ATTRv amyloidosis with PN
Patisiran-PN EAP[3]	154 (15.2)	Expanded access study of patisiran: ATTRv amyloidosis with PN
Post-OLT (Ph3b)[4]	23 (2.3)	Safety, efficacy, and PK of patisiran: ATTRv amyloidosis with PN progression after orthotopic liver transplant
APOLLO-B (Ph3)[5]	359 (35.5)	Safety and efficacy of patisiran: ATTR amyloidosis with CM
US observational study (Ph4)[6]	58 (5.7)	Effectiveness of patisiran: ATTRv amyloidosis with PN with a V122I or T60A variant (US)
HELIOS-A (Ph3)[7]	164 (16.2)	Safety and efficacy of vutrisiran: ATTRv amyloidosis with PN

ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; CM, cardiomyopathy; EAP, expanded access program; MSK, musculoskeletal; OLE, open-label extension; OLT, orthotopic liver transplant; Ph, Phase; PK, pharmacokinetics; PN, polyneuropathy

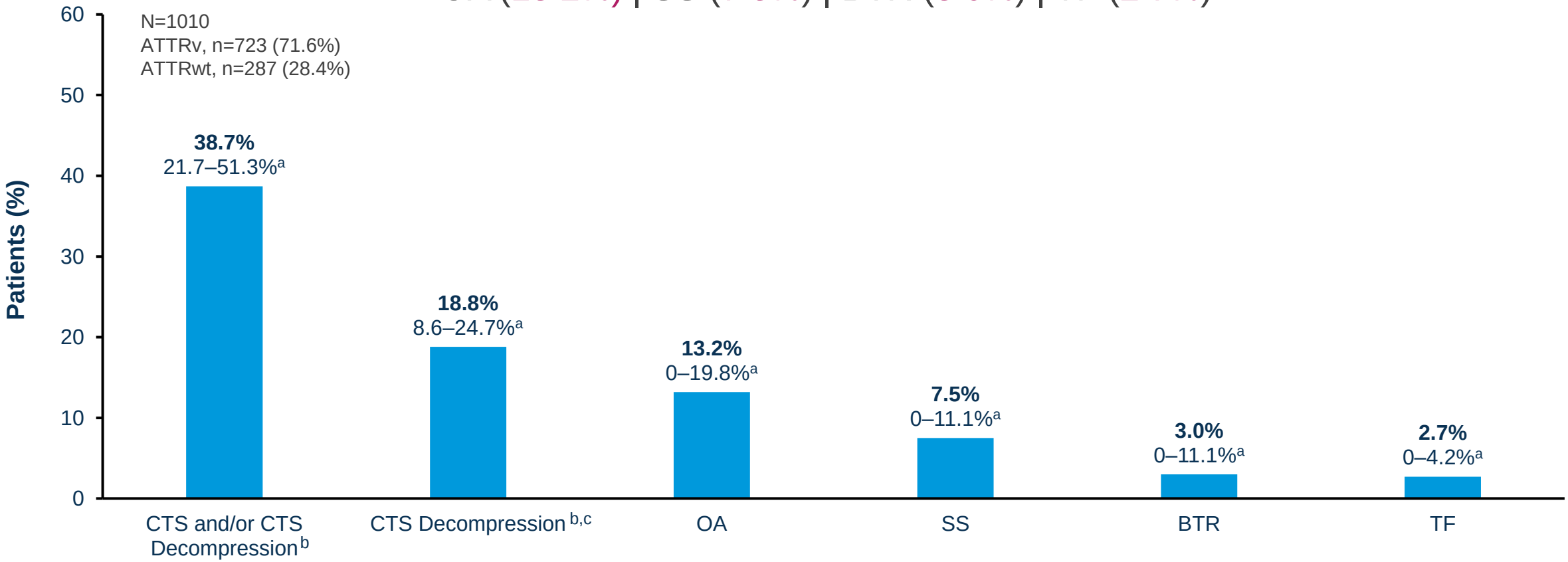
1. Coelho T et al. *Orphan J Rare Dis* 2020;15:179; 2. Adams D et al. *N Engl J Med* 2018;379:11–21; 3. ClinicalTrials.gov: NCT02939820. Available at: https://clinicaltrials.gov/ct2/show/NCT02939820;
4. Schmidt HH et al. *Am J Transplant* 2022;22:1646–57; 5. Maurer MS et al. *New Engl J Med* 2023;389:1553–65;
6. ClinicalTrials.gov: NCT04201418. Available at: https://clinicaltrials.gov/ct2/show/NCT04201418; 7. Adams D et al. *Amyloid* 2023;30:18–26.

Prevalence of Musculoskeletal Manifestations

Pooled Data Analysis

- CTS and/or CTS decompression (38.7%) was the most prevalent MSK manifestation/MSK-related procedure in the overall population followed by:

OA (13.2%) | SS (7.5%) | BTR (3.0%) | TF (2.7%)



[a]Range for the prevalence of MSK manifestations in the individual studies. [b]CTS and CTS decompression surgery are not mutually exclusive
[c]Includes patients who had undergone CTS decompression surgery, with or without reporting a diagnosis of CTS
ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; BTR, biceps tendon rupture; CTS, carpal tunnel syndrome; MSK, musculoskeletal; OA, osteoarthritis; SS, spinal stenosis; TF, trigger finger

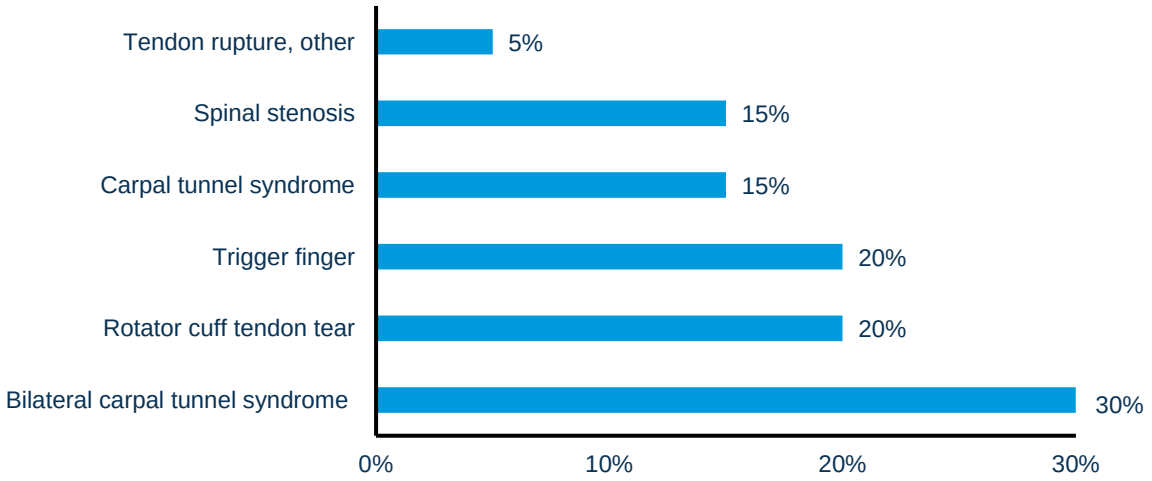
Musculoskeletal Manifestations in ATTR Amyloidosis

Patient Survey[1]

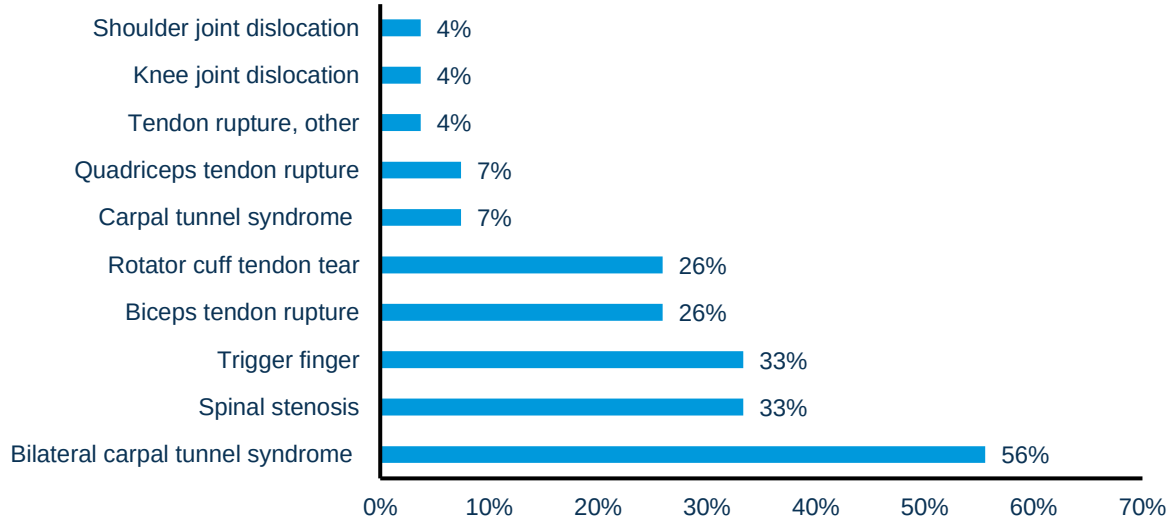
- Members of the Amyloidosis Support Group who were aged ≥18 at the time of their ATTR amyloidosis diagnosis self-reported their signs and symptoms in an online survey
- Symptoms were classified post hoc as neuropathy-, CV-, or orthopedic-related in consultation with expert physician advisors

Orthopedic-related diagnoses

ATTRv amyloidosis (n=20)



ATTRwt amyloidosis (n=27)



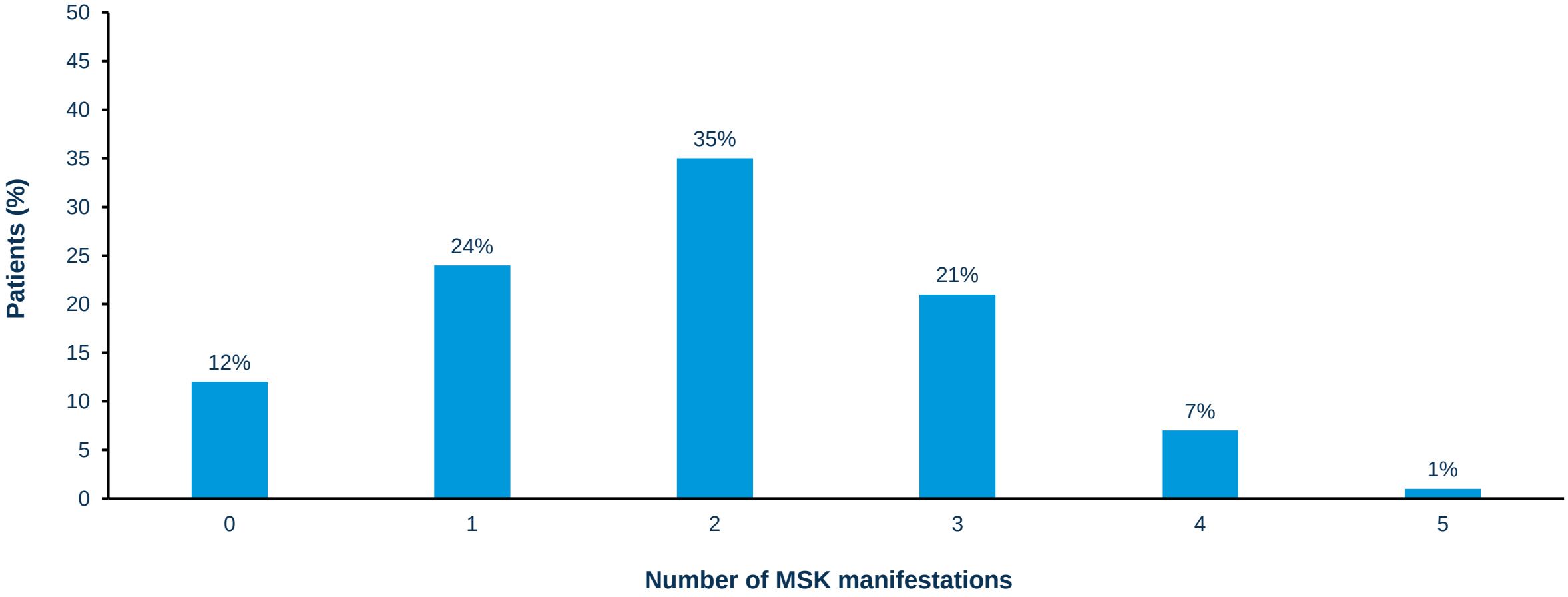
ATTR, transthyretin; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin; CV, cardiovascular

1. Karam C et al. *HFSA* 2022. Poster 384

Musculoskeletal Manifestations

Patisiran-CM EAP

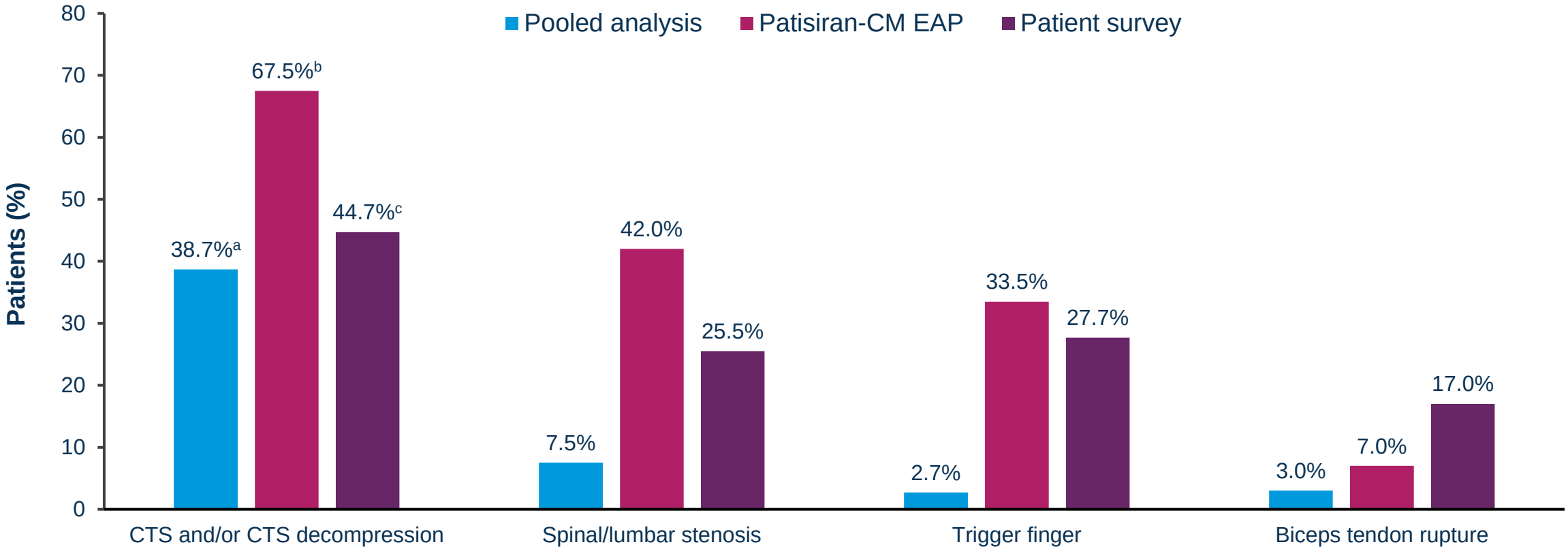
- >1 MSK manifestation: 128/200 (64.0%) patients



CM, cardiomyopathy; EAP, expanded access program; MSK, musculoskeletal

Prevalence of Musculoskeletal Manifestations

- Prevalence of MSK manifestations was higher in the patisiran-CM EAP and patient survey studies
  - This may reflect proactive questioning regarding MSK symptoms and procedures in these studies



[a]CTS and/or CTS decompression. [b]Bilateral CTS. [c]CTS

CM, cardiomyopathy; CTS, carpal tunnel syndrome; EAP, expanded access program; MSK, musculoskeletal

Summary

- These data represent the first comprehensive analysis exploring prevalence of MSK manifestations in patients with ATTR amyloidosis across randomized clinical trials and expanded-access programs

- Understanding the epidemiology and characteristics of MSK manifestations associated with ATTR amyloidosis may support the awareness and recognition of these symptoms among surgeons and other healthcare professionals, allowing for early diagnosis and improved disease management

- Surgeons should consider partnering with cardiology and neurology colleagues to identify patients where biopsies during routine surgical procedures and Congo Red staining may detect amyloid deposition, especially in patients over 60 years undergoing carpal tunnel release

ATTR, transthyretin-mediated; MSK, musculoskeletal.

Back-Up Slides

Baseline Characteristics

Patisiran-CM EAP

Characteristic	Patisiran (n=200)
Mean age at diagnosis, years	73.8
Age at diagnosis, %	
<60 years	2.0
60–75 years	49.5
>75 years	48.5
Mean age at enrollment, years	75.4
Male, %	94.5
White, %	89.5
Genotype, %	
ATTRwt	93.5
ATTRv	6.5
National Amyloidosis Centre ATTR Stage, %	
1	64.5
2	26.0
3	9.5

- Almost all patients were ≥60 years of age
  - Mean age 73.8 years
- Mostly male (94.5%) and White (89.5%)
- Most patients had wild-type ATTR cardiac amyloidosis and Stage 1 disease
  - V122I most common variant (n=10)
  - Others include 1 each for T60A, D18N, and T80I
- ~2/3 diagnosed within a year of symptom onset
  - 27% experienced a 1–10-year diagnostic delay

ATTR, transthyretin; ATTRv, hereditary transthyretin (v for variant); ATTRwt, wild-type transthyretin.