



# Impact of symptomatic neurogenic orthostatic hypotension (nOH) on symptom burden and daily functioning in patients with alpha synucleinopathies

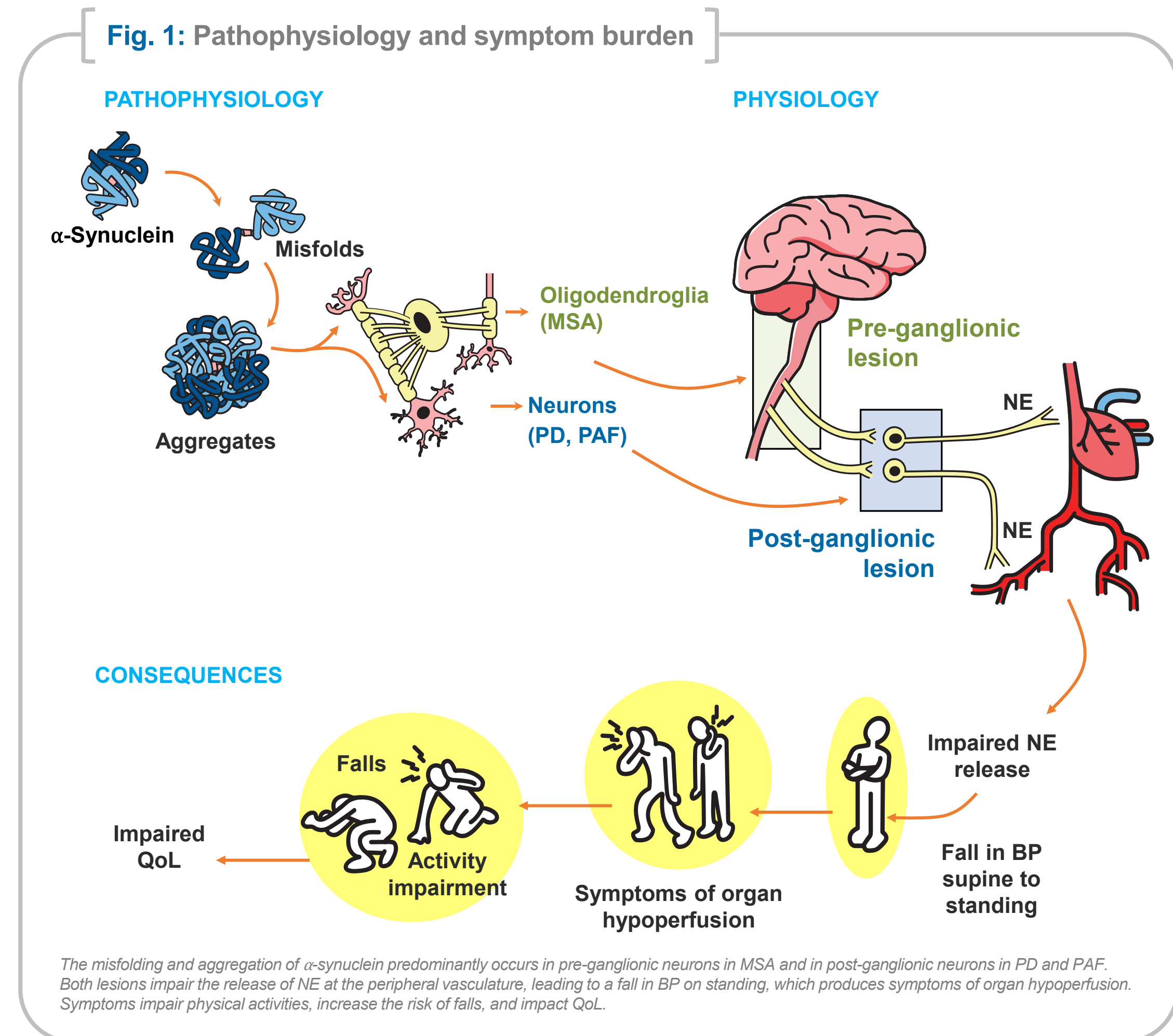
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## INTRODUCTION

- nOH is common in  $\alpha$ -synucleinopathies, which are a group of neurodegenerative diseases that impact the autonomic nervous system (Fig. 1).<sup>1</sup>
- nOH leads to a fall in BP on standing that can impair perfusion to organs, producing symptoms of ischemia.<sup>1</sup>
- In most patients with nOH, adequate symptom relief is not achieved with available pressor agents.<sup>1</sup>

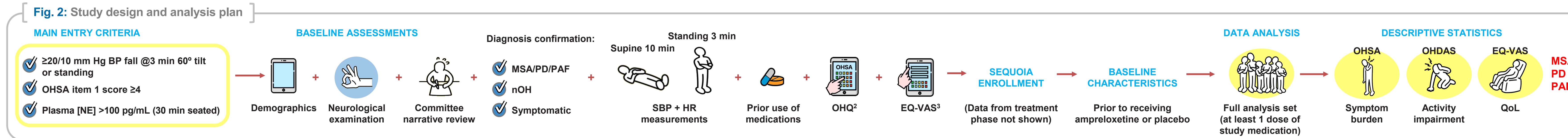


## OBJECTIVE

- To explore the relationship between standing BP and the symptomatic burden of nOH at baseline in patients with  $\alpha$ -synucleinopathies enrolled in the 4-week, Phase 3 SEQUOIA study (NCT03750552).

## STUDY DESIGN

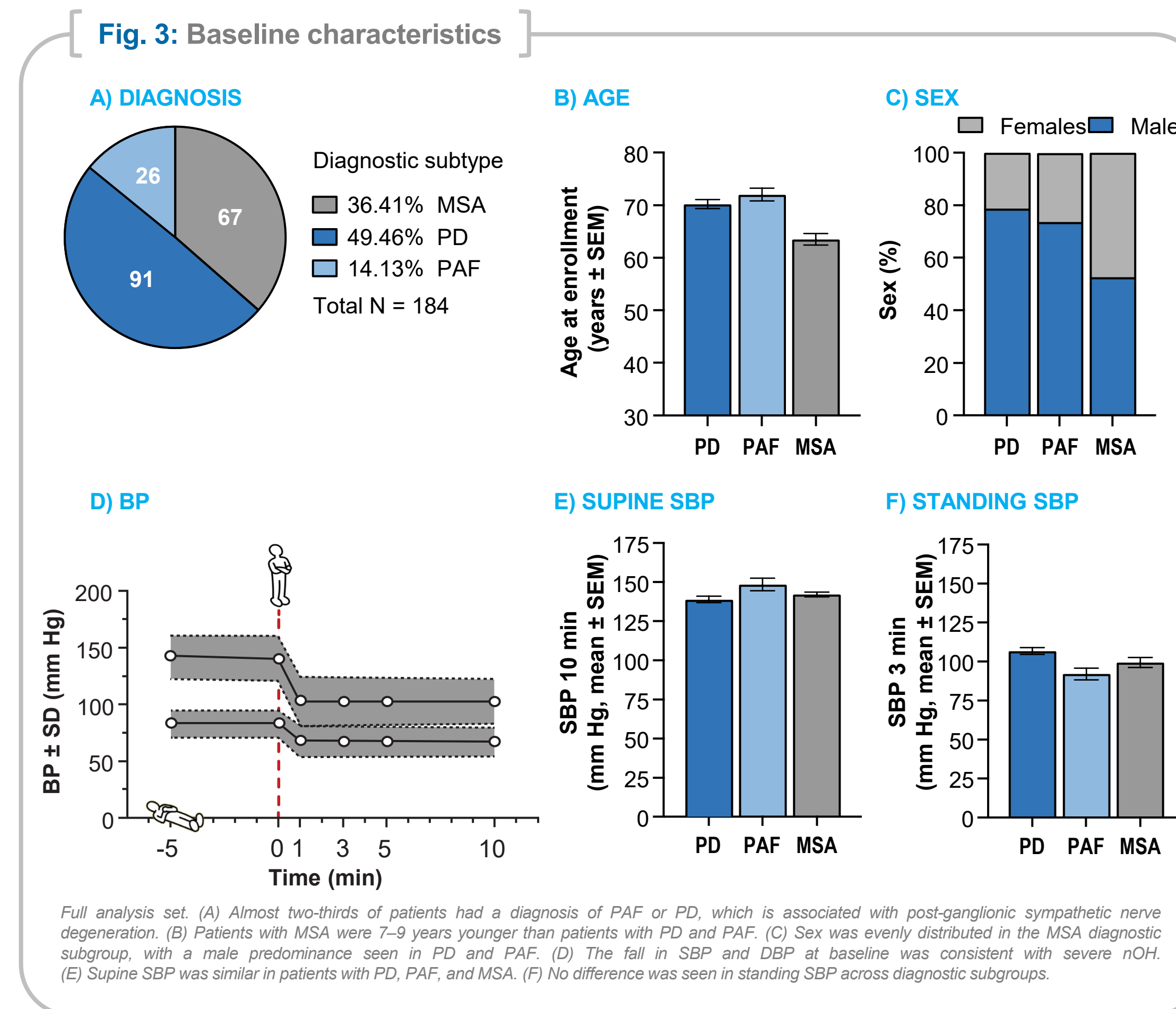
- In this analysis, clinical characteristics and baseline (pretreatment) assessments of autonomic function, symptom burden, and QoL scales were assessed (Fig. 2).



## RESULTS

### Demographics and diagnostic subgroups

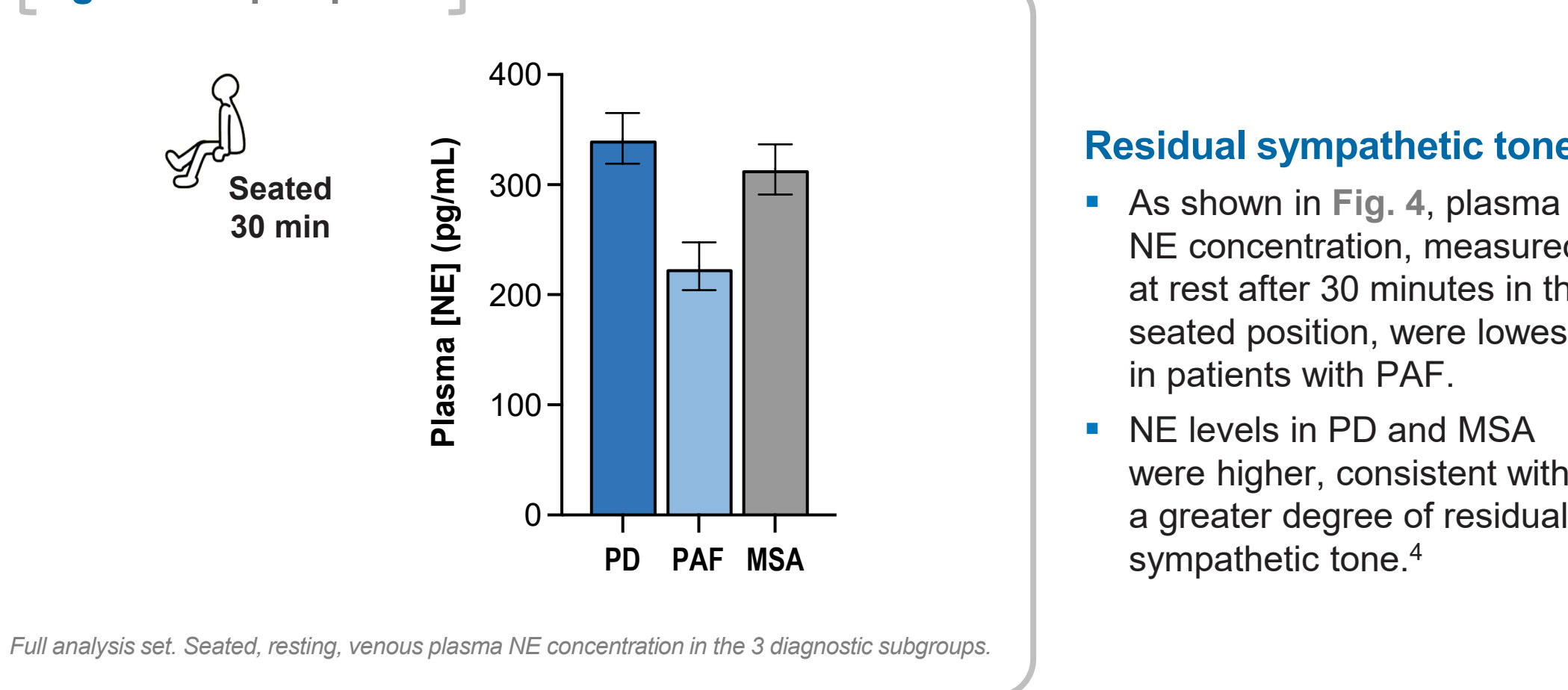
- 195 patients were enrolled; 186 were included in the safety analysis set, 184 in the full analysis set.
- The majority of patients had a diagnosis consistent with peripheral lesions in the post-ganglionic sympathetic neurons (Fig. 3A).<sup>1</sup>
- Patients with MSA were younger at study entry (Fig. 3B), consistent with early age of onset.
- Race, ethnicity, height, weight, and BMI were similar across diagnostic subtypes.
- There was a male predominance in PD and PAF groups, but not in MSA group (Fig. 3C).



### Severity of nOH at baseline

- All patients met the AAS diagnostic criteria for orthostatic hypotension on entry (Fig. 3D).
- Mean supine SBP was similar across groups (Fig. 3E).
- Mean heart rate for all patients after 10 minutes supine was 68 bpm (range, 43–97 bpm) and increased to only 80 bpm (range, 40–120 bpm) after 3 minutes of standing, indicative of a neurogenic cause for their orthostatic hypotension.<sup>4</sup>
- Despite differing degrees of resting sympathetic tone, standing SBP was similar across diagnostic subtypes (Fig. 3F), with most patients falling into the hypotensive range ( $<100$  mm Hg) after 3 minutes of standing.

Fig. 4: Norepinephrine



### Residual sympathetic tone

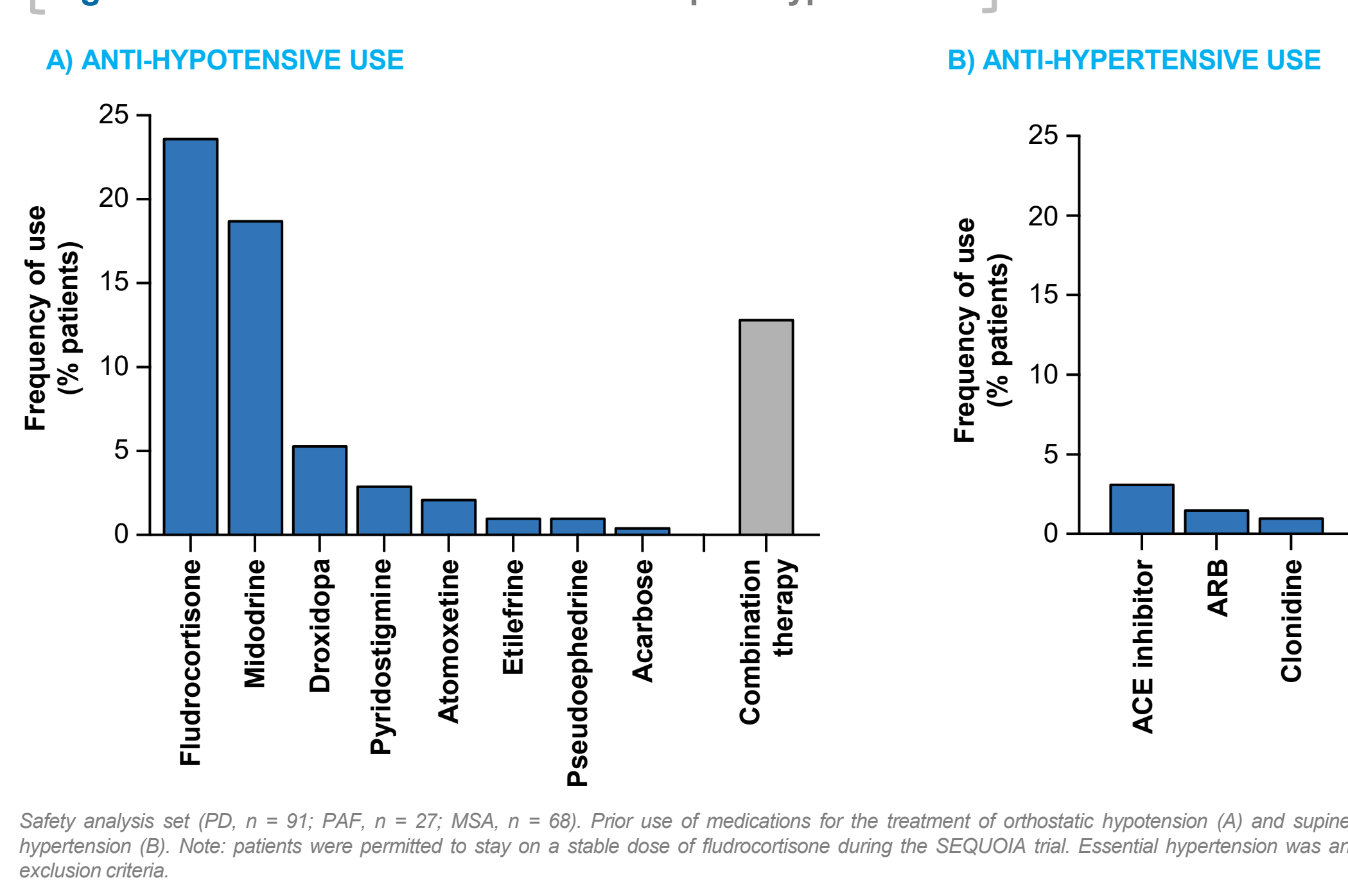
- As shown in Fig. 4, plasma NE concentration, measured at rest after 30 minutes in the seated position, were lowest in patients with PAF.
- NE levels in PD and MSA were higher, consistent with a greater degree of residual sympathetic tone.<sup>4</sup>

Full analysis set. Seated, resting, venous plasma NE concentration in the 3 diagnostic subgroups.

### Prior medication use in the 60 days prior to study entry

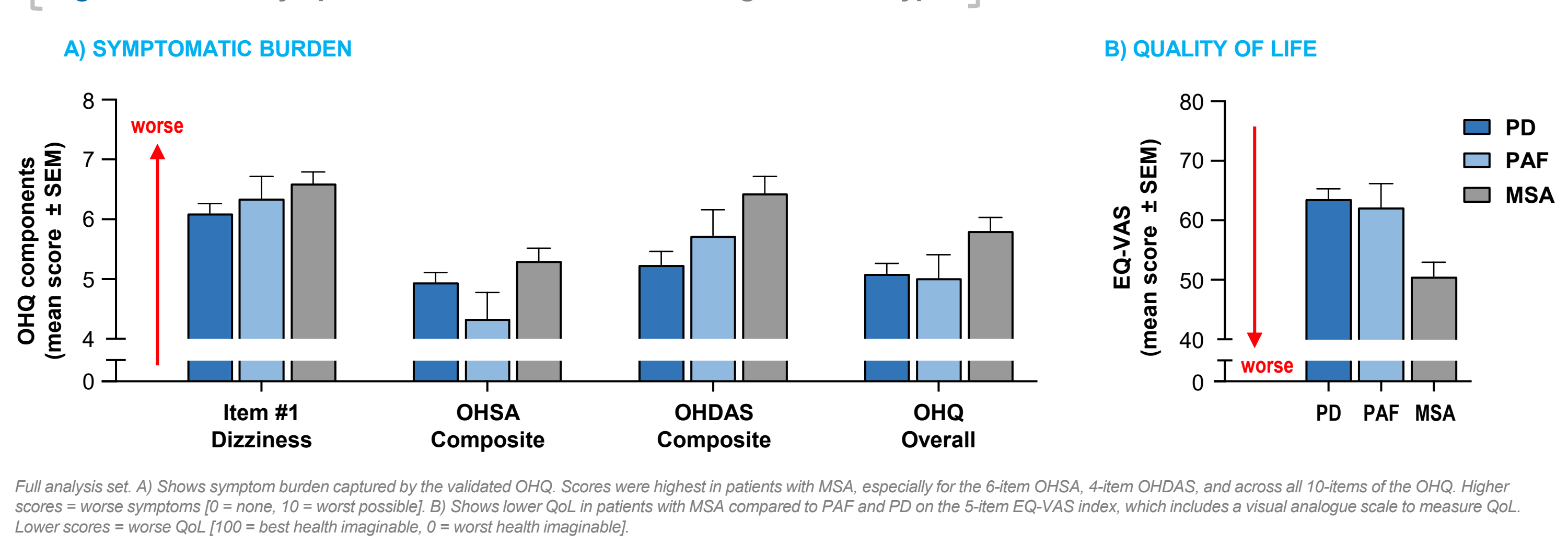
- Overall, 98.9% of patients had taken at least 1 prior medication.
- The most commonly used anti-parkinsonian medications were dopamine precursors (68.3%), dopamine agonists (21.5%), and MAO-B inhibitors (12.4%).
- As shown in Fig. 5A, the most frequently used anti-hypertensive medications were furocortisone (n = 44, 23.7%), midodrine (n = 35, 18.8%), and droxidopa (n = 10, 5.4%).
- In total, 24 patients (12.9%) were receiving combination treatment for nOH with more than 1 anti-hypertensive medication.
- Only a small number of patients were receiving treatment with anti-hypertensives (Fig. 5B).

Fig. 5: Prior medications for nOH and supine hypertension



Safety analysis set (PD, n = 91; PAF, n = 27; MSA, n = 68). Prior use of medications for the treatment of orthostatic hypotension (A) and supine hypertension (B). Note: patients were permitted to stay on a stable dose of furocortisone during the SEQUOIA trial. Essential hypertension was an exclusion criteria.

Fig. 6: Baseline symptom scores and QoL across diagnostic subtypes

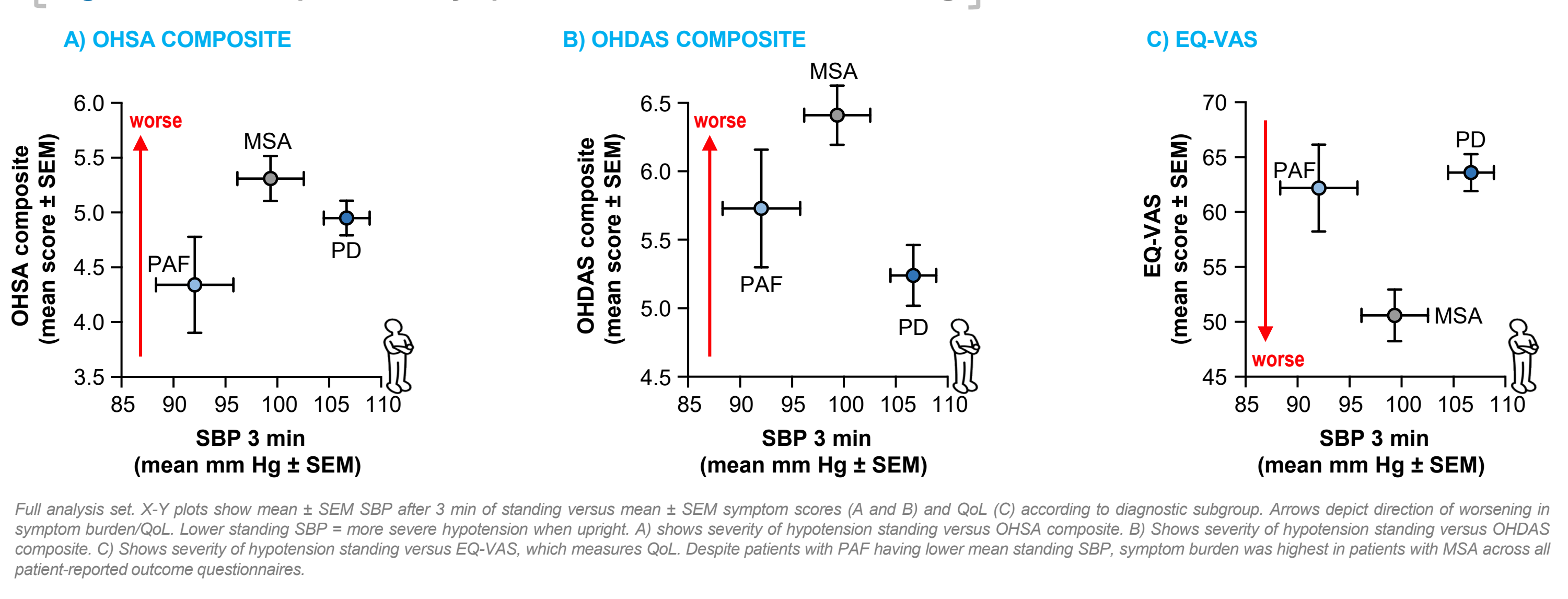


Full analysis set. A) Shows symptom burden captured by the validated OHQ. Scores were highest in patients with MSA, especially for the 6-item OHSAS, 4-item OHDAS, and across all 10-items of the OHQ. Higher scores = worse symptoms [0 = none, 10 = worst possible]. B) Shows lower QoL in patients with MSA compared to PAF and PD on the 5-item EQ-VAS index, which includes a visual analogue scale to measure QoL. Lower scores = worse QoL [100 = best health imaginable, 0 = worst health imaginable].

### Symptomatic burden and quality of life

- nOH symptom burden was consistently higher in patients with MSA across all domains of the OHQ.<sup>2</sup>
- Patients with MSA had the highest scores on the OHSAS composite score, which captures 6 classic features of nOH (dizziness/lightheadedness, visual problems, fatigue, weakness, difficulty concentrating, and "coat-hanger" pain in the upright position; Fig. 6A).
- MSA was also associated with a higher degree of interference from nOH on the OHDAS, which captures 4 activities of daily living (standing for a short time, walking for a short time, standing for a long time, and walking for a long time; Fig. 6A).
- EQ-VAS scores were lowest in the MSA diagnostic subgroup, indicating worse QoL (Fig. 6B).<sup>3</sup>
- Fig. 7 depicts the relationship between standing SBP and patient-reported severity scores in the 3 diagnostic groups. For the degree of hypotension when standing, patients with MSA reported a higher symptom burden (Fig. 7A), more interference with activities of daily living (Fig. 7B), and worse QoL (Fig. 7C).

Fig. 7: Relationship between symptom burden, QoL, and BP standing



Full analysis set. X-Y plots show mean  $\pm$  SEM SBP after 3 min of standing versus mean  $\pm$  SEM symptom scores (A and B) and QoL (C) according to diagnostic subgroup. Arrows depict direction of worsening in symptom burden/QoL. Lower standing SBP = more severe hypotension when upright. A) Shows severity of hypotension standing versus OHSAS composite. B) Shows severity of hypotension standing versus OHDAS composite. C) Shows severity of hypotension standing versus EQ-VAS, which measures QoL. Despite patients with PAF having lower mean standing SBP, symptom burden was highest in patients with MSA across all patient-reported outcome questionnaires.

## CONCLUSIONS

- Despite treatment with available pressor agents, a large proportion of patients with nOH remain highly symptomatic.
- A higher degree of residual sympathetic tone in patients with MSA was not associated with a lower symptom burden.
- Despite a similar degree of hypotension when standing, patients with MSA have the highest symptom burden, most severe interference with activities of daily living, and worst QoL.
- There remains a significant unmet need for better nOH treatments, especially for patients with MSA.

