Midodrine Equivalents (ME) Metric for Quantifying Medication Burden in Orthostatic Hypotension

Introduction and Rationale

In the STANDUP study, we aim to evaluate the impact of supracardiac venous angioplasty and stenting on orthostatic intolerance and orthostatic hypotension (OH). A key secondary outcome is the reduction in pharmacological dependence post-intervention, as current treatments (e.g., midodrine, fludrocortisone [Florinef], droxidopa, and pyridostigmine [Mestinon]) are often suboptimal due to limited efficacy and side effects such as supine hypertension. To objectively compare medication usage before and after the procedure, we propose a standardized metric called "Midodrine Equivalents" (ME).

The ME metric normalizes the daily doses of common OH medications to a common scale, allowing for quantification of total medication burden. Midodrine is used as the reference drug because it is a widely accepted first-line therapy for OH, with direct vasoconstrictive effects. In this metric, the maximum recommended daily dose of each medication is assigned 100 ME, representing the "full therapeutic load" for that drug. This normalization facilitates apples-to-apples comparisons across drugs with differing mechanisms, potencies, and dosing ranges, while accounting for their approximate relative efficacy in improving OH symptoms (e.g., standing blood pressure [BP] elevation and symptom relief).

This approach assumes linear proportionality between dose and effect within the therapeutic range, which simplifies calculations but may not capture non-linear pharmacodynamics. The metric is derived from clinical guidelines, pharmacological literature, and practical dosing patterns (e.g., Kaufmann et al., 2014; Biaggioni et al., 2015; Raj et al., 2005; Kulkarni et al., 2024). It will be used to compute pre- and post-intervention totals, with statistical analysis via paired t-tests to assess reductions in ME (as outlined in the study's statistical plan). A sample size of 100 participants provides 80% power to detect clinically meaningful differences in ME, assuming a 30–50% reduction post-intervention based on preliminary venous outflow data.

Calculation of Midodrine Equivalents

The total daily ME for a patient is the sum of ME contributions from each medication, calculated as:

$$\text{Total ME} = (\text{Dose}_{\text{mid}} \times \text{CF}_{\text{mid}}) + (\text{Dose}_{\text{flor}} \times \text{CF}_{\text{flor}}) + (\text{Dose}_{\text{drox}} \times \text{CF}_{\text{drox}}) + (\text{Dose}_{\text{mest}} \times \text{CF}_{\text{mest}})$$

Where:

- Dose_{mid} = Daily dose of midodrine (mg/day)
- CF_{mid} = Conversion factor for midodrine = 100 ME / 30 mg = 3.3333 ME/mg
- $\text{Dose}_{\text{flor}}$ = Daily dose of Florinef (fludrocortisone; mg/day)
- CF_{flor} = Conversion factor for Florinef = 100 ME / 0.3 mg = 333.3333 ME/mg
- $\text{Dose}_{\text{drox}}$ = Daily dose of droxidopa (mg/day)
- CF_{drox} = Conversion factor for droxidopa = 100 ME / 1800 mg = 0.055556 ME/mg

- $\text{Dose}_{\text{mest}}$ = Daily dose of Mestinon (pyridostigmine; mg/day)
- CF_{mest} = Conversion factor for Mestinon = 100 ME / 180 mg = 0.55556 ME/mg

Doses are based on the patient's actual regimen (e.g., from electronic health records or self-report). If a patient is not on a specific medication, its contribution is 0 ME. The maximum possible total ME per patient is 400 (if on maximum doses of all four drugs), though in practice, combinations are typically limited to 2–3 drugs.

Assumptions and Derivation of Conversion Factors

Conversion factors are calculated by dividing 100 ME by each drug's maximum recommended daily dose for OH, as per clinical guidelines:

- **Midodrine (30 mg/day)**: Maximum of 10 mg three times daily (TID); direct alpha-1 agonist increasing standing BP by ∼15–20 mmHg.
- **Florinef (0.3 mg/day)**: Maximum for OH to avoid hypokalemia or excessive volume expansion; mineralocorticoid that increases plasma volume, with sustained but less acute effects than midodrine.
- **Droxidopa (1800 mg/day)**: Maximum of 600 mg TID; norepinephrine precursor with vasoconstrictive effects similar to midodrine.
- **Mestinon (180 mg/day)**: Maximum of 60 mg TID for OH; cholinesterase inhibitor enhancing autonomic transmission, often adjunctive with milder BP effects (∼5–10 mmHg).

Relative potencies are approximated as equivalent at maximum doses (hence 100 ME each), based on indirect comparisons:

- Midodrine and droxidopa show similar efficacy in neurogenic OH trials (e.g., ∼10–20 mmHg BP increase).
- Florinef's volume effect is complementary but often requires lower doses for equivalent symptom control.
- Mestinon's weaker, adjunctive role aligns with its lower typical impact.

This normalization prioritizes simplicity over precise pharmacological equivalence, as direct head-to-head trials are lacking. Sensitivity analyses will test alternative potency weights (e.g., Florinef at 75 ME relative to midodrine) to ensure robustness.

Limitations

- **Non-Linear Effects**: Assumes dose proportionality; actual responses may plateau at higher doses.
- **Mechanism Differences**: Drugs vary in onset, duration, and side effects (e.g., midodrine's rapid action vs. Florinef's delayed volume expansion).
- **Patient Variability**: Efficacy depends on OH etiology (e.g., neurogenic vs. non-neurogenic), comorbidities, and compliance.

- **Validation**: The metric will be validated against symptom scores (e.g., Orthostatic Hypotension Questionnaire) and quality-of-life measures in the study.

Dosage Chart for Midodrine Equivalents

The following chart provides ME values for common daily doses of each medication, calculated using the conversion factors above. It serves as a quick reference for study personnel. Exact values are shown, with rounded whole numbers in parentheses for practical use; statistical analyses will use exact values.

WarmGray!15 Medication	Daily Dose (mg)	Conversion Factor (ME/mg)	Midodrine Equivalents (ME)
Midodrine	2.5	3.3333	8.3333 ($\approx$ 8)
	5	3.3333	16.6665 ($\approx$ 17)
	10	3.3333	33.333 ($\approx$ 33)
	15	3.3333	49.9995 ($\approx$ 50)
	20	3.3333	66.666 ($\approx$ 67)
	30 (max)	3.3333	99.999 ($\approx$ 100)
Florinef	0.05	333.3333	16.6667 ($\approx$ 17)
	0.1	333.3333	33.3333 ($\approx$ 33)
	0.15	333.3333	50.0 ($\approx$ 50)
	0.2	333.3333	66.6667 ($\approx$ 67)
	0.25	333.3333	83.3333 ($\approx$ 83)
	0.3 (max)	333.3333	100.0 ($\approx$ 100)
Droxidopa	100	0.055556	5.5556 ($\approx$ 6)
	300	0.055556	16.6668 ($\approx$ 17)
	600	0.055556	33.3336 ($\approx$ 33)
	900	0.055556	50.0004 ($\approx$ 50)
	1200	0.055556	66.6672 ($\approx$ 67)
	1800 (max)	0.055556	100.0008 ($\approx$ 100)
Mestinon	30	0.55556	16.6668 ($\approx$ 17)
	60	0.55556	33.3336 ($\approx$ 33)
	90	0.55556	50.0004 ($\approx$ 50)
	120	0.55556	66.6672 ($\approx$ 67)
	150	0.55556	83.334 ($\approx$ 83)
	180 (max)	0.55556	100.0008 ($\approx$ 100)

Table 1: Dosage Chart for Midodrine Equivalents

Example Application

For a patient on midodrine 15 mg/day, Florinef 0.2 mg/day, and droxidopa 600 mg/day pre-intervention:

$$\text{Total ME} = (15 \times 3.3333) + (0.2 \times 333.3333) + (600 \times 0.055556) \approx 50 + 67 + 33 = 150 \text{ ME}$$

Post-intervention, if reduced to Florinef 0.1 mg/day:

$$\text{Total ME} \approx 33 \text{ ME (reduction of 117 ME, indicating decreased burden).}$$

This metric will be computed as frequently as medication dosage data are available (e.g., at baseline, during follow-up visits, or via patient-reported adjustments throughout the study period). All ME data will be de-identified and stored securely, per the study's protection protocols.