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Impact Of Ivabradine On Orthostatic Intolerance, Quality Of Life And Heart Rate In Post-COVID Postural Orthostatic Tachycardia Syndrome: Results From The RECOVER-Autonomic Trial

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Disclosures

- Consultant to: Amgen, Cleerly, Bayer, Boehringer Ingelheim, HeartFlow Edwards, Esperion, Jazz, Lexicon, Lilly, Novo Nordisk, Novartis, Medtronic, Roche and Corcept.

Research Funding/ Grants:

- NIH R01 DK118278 and 2R01DK118278-06A1: (PI: Taub PR) (NCT0405733)
- Hillblom Network Grant (PI: Taub PR) (NCT05365529)
- Dysautonomia International Grant (PI: Taub PR) (NCT05409651)
- NIH RECOVER OT2HL156812

Executive Steering Committee Member for Clinical Trials:

- VICTORIAN-1P, *Sponsor: Novartis; NCT 05739383*
- TRANSFORM Trial, *Sponsor: Cleerly Health; NCT 06112418*
- SPYRAL GEMINI: Sponsor: *Medtronic; ; NCT06907147*
- EASi-PROTKT Trial, *Sponsor: Boehringer Ingelheim; NCT07064473*

US National Lead/Steering Committee Member:

- VICTORION-2P CVOT, *Sponsor: Novartis; NCT 05030428*
- Ocean(a) Lp(a) lowering CVOT, *Sponsor: Amgen; NCT 05581303*
- Oral PCSK9 Inhibitor CVOT (MK- 0616), *Sponsor: Merck; NCT 06008756*
- ACCLAIM Lp(a) lowering CVOT, *Sponsor: Lilly NCT06292013*

All relevant financial relationships have been mitigated.

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Pam Taub, Cyndya Shibao, Peter Novak, Tae Hwan Chung, Kanecia Zimmerman, Marat Fudim, Sean O'Brien, Hirra Fissler, Orsolya Moy, Yves Rosenberg, Jun Wen, Nikki Freeman, Christopher B. Granger for the RECOVER-AUTONOMIC Clinical Trial Group
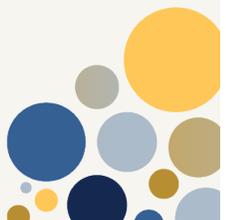
RECOVER
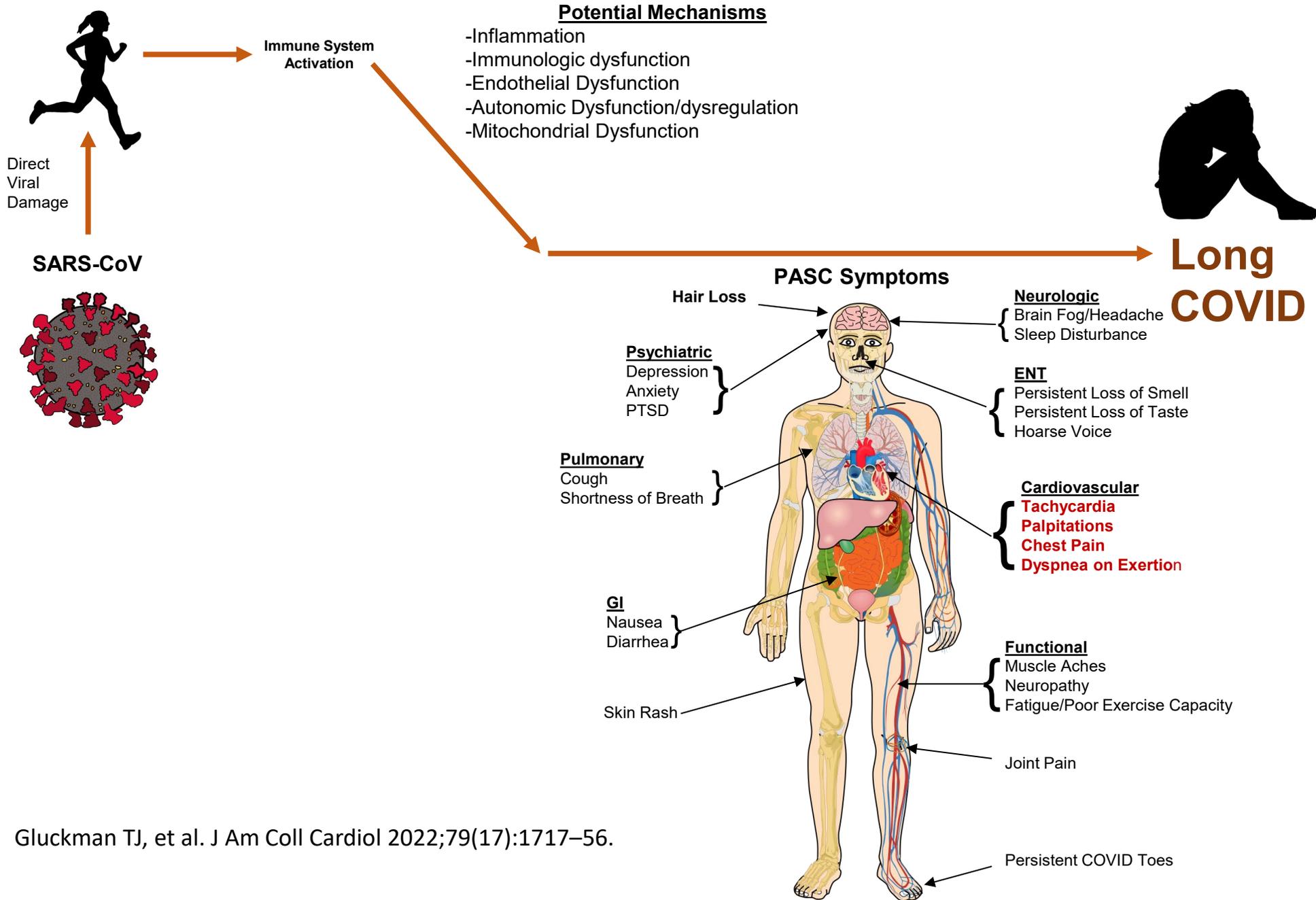Researching COVID to Enhance Recovery

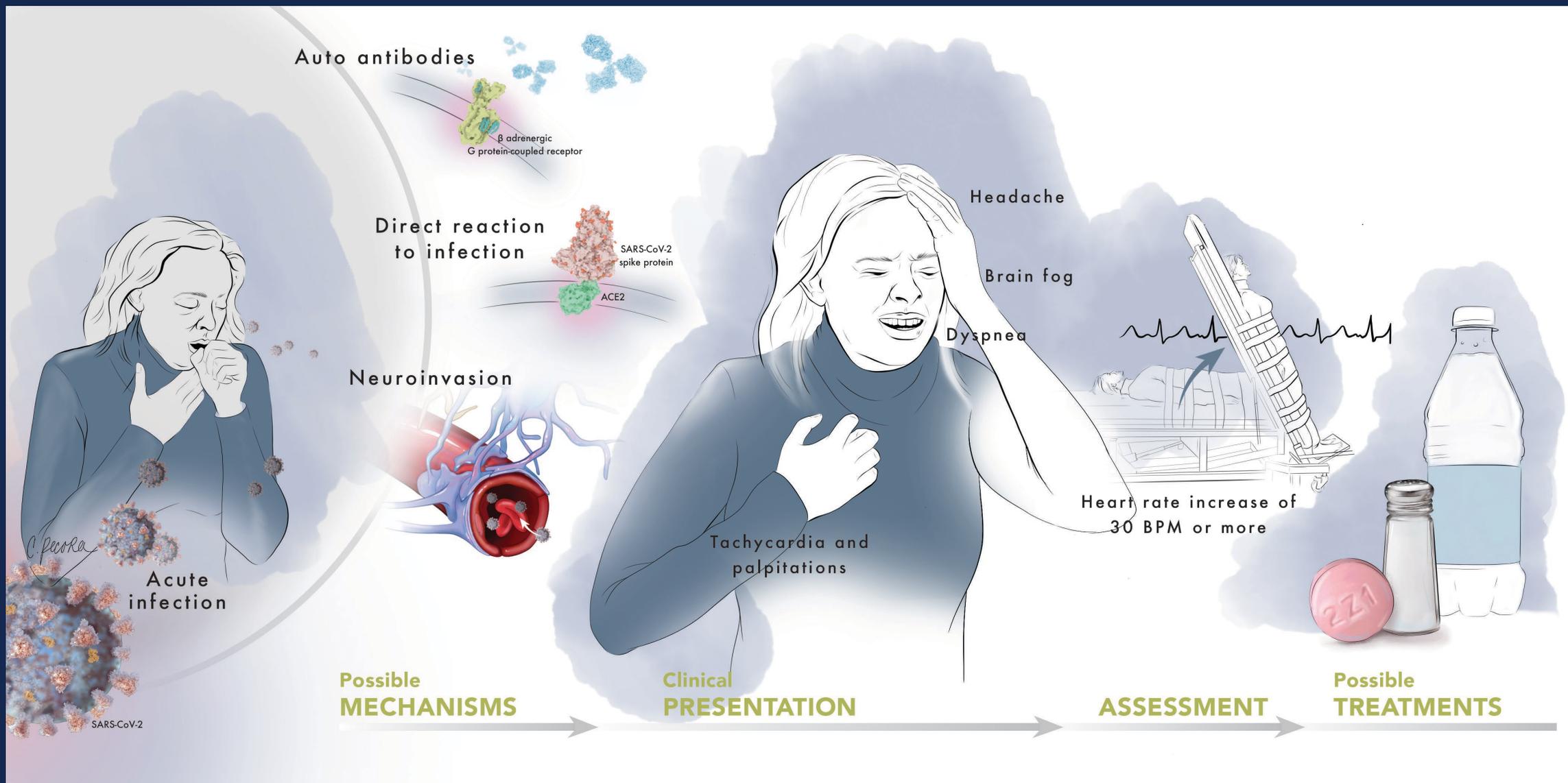*An Initiative Funded by the National Institutes of Health*

Background and Rationale

- Postural orthostatic tachycardia syndrome (POTS) is a complex, multisystem disorder characterized by orthostatic intolerance and excessive tachycardia.

- 31% of individuals with post-acute sequelae of SARS-CoV-2 infection (PASC), commonly referred to as Long Covid, develop POTS, often resulting in substantial functional impairment, reduced quality of life, and impaired ability to work.

- There are very few randomized clinical trials in POTS and Long COVID POTS.
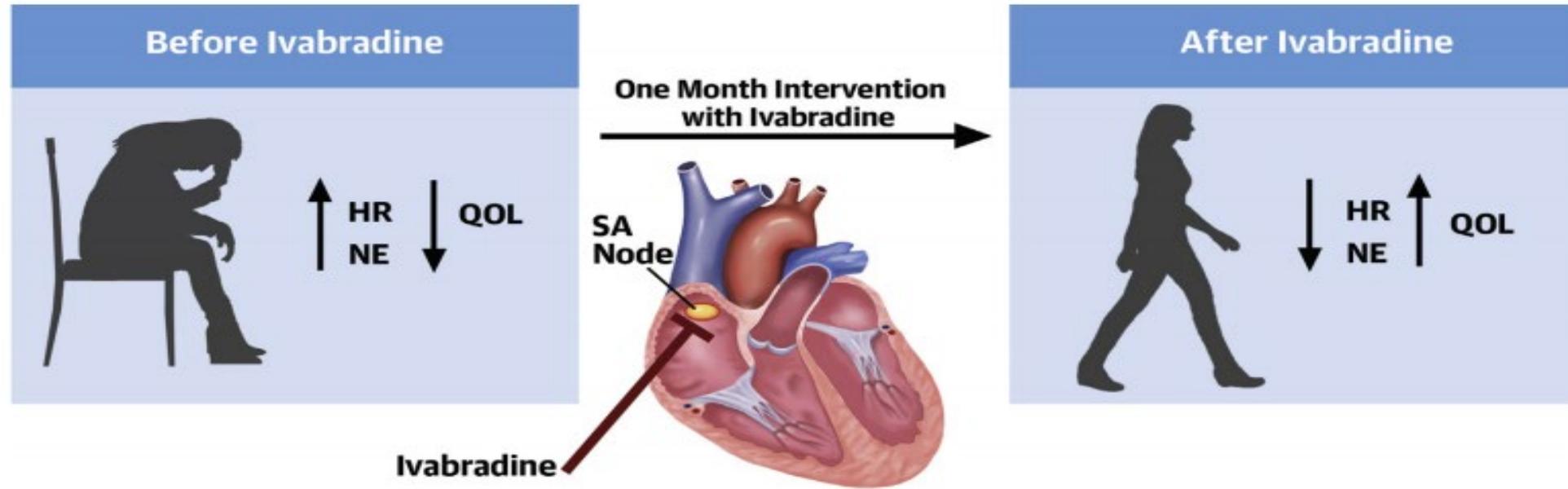
Long COVID Is a Complex, Heterogeneous Multisystem Disease With Diverse Clinical Manifestations
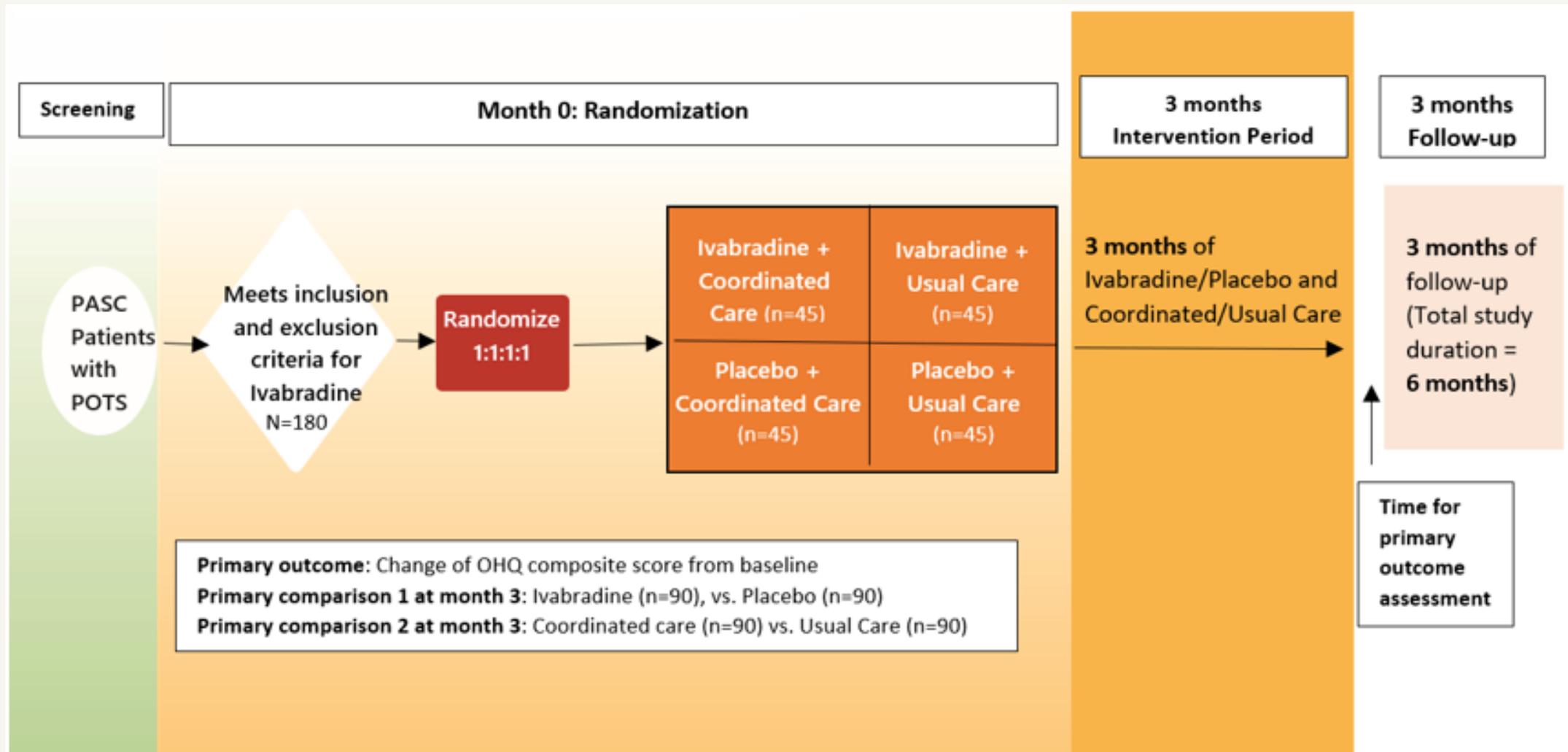

Potential Mechanisms
-Inflammation
-Immunologic dysfunction
-Endothelial Dysfunction
-Autonomic Dysfunction/dysregulation
-Mitochondrial Dysfunction

Immune System Activation

Direct Viral Damage

SARS-CoV

Long COVID

PASC Symptoms

Hair Loss

Neurologic
Brain Fog/Headache
Sleep Disturbance

Psychiatric
Depression
Anxiety
PTSD

ENT
Persistent Loss of Smell
Persistent Loss of Taste
Hoarse Voice

Pulmonary
Cough
Shortness of Breath

Cardiovascular
Tachycardia
Palpitations
Chest Pain
Dyspnea on Exertion

GI
Nausea
Diarrhea

Functional
Muscle Aches
Neuropathy
Fatigue/Poor Exercise Capacity

Skin Rash

Joint Pain

Persistent COVID Toes

Gluckman TJ, et al. J Am Coll Cardiol 2022;79(17):1717–56.

Auto antibodies

β adrenergic
G protein-coupled receptor

Direct reaction
to infection

SARS-CoV-2
spike protein

ACE2

Neuroinvasion

Acute
infection

SARS-CoV-2

Headache

Brain fog

Dyspnea

Tachycardia and
palpitations

Heart rate increase of
30 BPM or more

Possible
MECHANISMS

Clinical
PRESENTATION

ASSESSMENT

Possible
TREATMENTS

Ormiston CK, Świątkiewicz I, Taub PR. *Heart Rhythm.* 2022;19(11):1880-1889

CENTRAL ILLUSTRATION Ivabradine Improves Heart Rate, Quality of Life, and Norepinephrine Levels in Hyperadrenergic Postural Orthostatic Tachycardia Syndrome

Ivabradine Study Design

| Screening | Month 0: Randomization | 3 months Intervention Period | 3 months Follow-up |

PASC Patients with POTS → Meets inclusion and exclusion criteria for Ivabradine N=180 → Randomize 1:1:1:1 →

| Ivabradine + Coordinated Care (n=45) | Ivabradine + Usual Care (n=45) |
| Placebo + Coordinated Care (n=45) | Placebo + Usual Care (n=45) |

3 months of Ivabradine/Placebo and Coordinated/Usual Care

3 months of follow-up (Total study duration = 6 months)

Time for primary outcome assessment

Primary outcome: Change of OHQ composite score from baseline
Primary comparison 1 at month 3: Ivabradine (n=90), vs. Placebo (n=90)
Primary comparison 2 at month 3: Coordinated care (n=90) vs. Usual Care (n=90)

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Coordinated Care

Check their heart rate and blood pressure once a week

Eat a high-salt diet and drink a recommended amount of fluids per day

Wear a compression belt around their stomach while doing upright activities

Complete recommended physical activities

Keep a weekly log of their study activities

Receive weekly phone calls from the care coordinator

Fudim M et al.. Design and rationale of RECOVER-AUTONOMIC: A randomized platform trial evaluating interventions for Long COVID postural orthostatic tachycardia syndrome. Am Heart J. 2026;296:107384.

Protocol Overview

Hypotheses being addressed:

Ivabradine (vs placebo) will improve symptoms and QOL at 3 months

Non-pharmacologic *coordinated care* intervention with assistance from a care coordinator (versus usual care) will improve symptoms and QOL at 3 months

Inclusion/Exclusion Criteria

Inclusion

- Autonomic dysfunction symptoms persisting ≥12 weeks post–acute Covid-19
- COMPASS-31 score >20
- OHQ/OIQ item 1 score >2
- POTS criteria: heart rate increase ≥30 bpm on active stand or tilt table test (without orthostatic hypotension)

Exclusion

- Severe cardiac disease or atrial fibrillation/uncontrolled arrhythmia
- History of POTS prior to Covid-19
- HR increase <30 bpm on active stand test

Primary End Point: Change in Orthostatic Hypotension Questionnaire (OHQ)

OHSA — OH Symptom Assessment — Over the past week, rate severity of each symptom from low blood pressure | 0 = None 10 = Worst possible

Symptom	0	1	2	3	4	5	6	7	8	9	10	SCORE
1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out	0	1	2	3	4	5	6	7	8	9	10	
2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)	0	1	2	3	4	5	6	7	8	9	10	
3. Weakness	0	1	2	3	4	5	6	7	8	9	10	
4. Fatigue	0	1	2	3	4	5	6	7	8	9	10	
5. Trouble concentrating	0	1	2	3	4	5	6	7	8	9	10	
6. Head and neck discomfort	0	1	2	3	4	5	6	7	8	9	10	

OHDAS — OH Daily Activity Scale — Rate how much low BP symptoms have interfered with each activity | 0 = No interference 10 = Total interference

Activity	0	1	2	3	4	5	6	7	8	9	10	CANNOT DO*
1. Activities requiring standing for a short time	0	1	2	3	4	5	6	7	8	9	10	☐
2. Activities requiring standing for a long time	0	1	2	3	4	5	6	7	8	9	10	☐
3. Activities requiring walking for a short time	0	1	2	3	4	5	6	7	8	9	10	☐
4. Activities requiring walking for a long time	0	1	2	3	4	5	6	7	8	9	10	☐

*Check if activity cannot be performed for reasons other than low blood pressure | Circle 0 if symptom is absent

Baseline Characteristics of the Participants

Characteristic	Ivabradine (N=86)	Placebo (N=95)
Age Median (IQR)	39 (29–52)	36 (27–49)
Female sex – no. (%)	70 (81.4)	83 (87.4)
Race – no. (%)		
White	63 (73.3)	67 (70.5)
Black or African American	9 (10.5)	11 (11.6)
Asian	4 (4.7)	7 (7.4)
Multiple races	7 (8.1)	3 (3.2)
Other or unknown*	3 (3.5)	7 (7.3)
Ethnicity – no. (%)		
Hispanic or Latino	6 (7.0)	11 (11.6)
Body-mass index (kg/m²)Mean ± SD	28.2 ± 7.5	28.6 ± 7.9
OHQ composite score mean ± SD	5.9 ± 1.6	6.1 ± 1.7
COMPASS-31 score mean ± SD	42.1 ± 12.0	42.9 ± 11.4
Malmo POTS score mean ± SD	64.6 ± 24.0	69.0 ± 21.7
Vital Signs During Active Stand Test		
Lowest supine heart rate (beats/min) mean ± SD	71.7 ± 13.4	72.0 ± 12.8
Highest standing heart rate (beats/min) mean ± SD	106.9 ± 14.6	110.3 ± 18.7
Heart-rate change (standing –supine)mean ± SD	35.2 ± 8.4	38.3 ± 14.2
Supine systolic BP (mm Hg) mean ± SD	116.8 ± 12.6	114.9 ± 13.3
Standing systolic BP (mm Hg) mean ± SD	131.5 ± 17.6	130.0 ± 16.1

Primary and Secondary Endpoints

Outcome	Ivabradine (N=86)	Placebo (N=95)	Adjusted Between-Group Difference (95% CI)*	P value
Primary Endpoint				
Change in OHQ composite score	−1.4 ± 1.8	−1.1 ± 1.9	−0.14 (−0.72 to 0.43)	0.63
Secondary Endpoints				
Heart-rate change during active stand test (beats/min)	−13.6 ± 10.4	−11.0 ± 10.6	−3.95 (−6.78 to −1.12)	0.007
Malmo POTS Symptom Score (MAPS)	−14.4 ± 19.6	−11.6 ± 19.5	−3.02 (−9.13 to 3.08)	
COMPASS-31 score	−9.0 ± 14.8	−8.1 ± 14.3	−0.82 (−5.26 to 3.61)	
6-minute walk distance (meters)	+12.1 ± 75.0	+7.0 ± 78.3	1.79 (−20.54 to 24.13)	
PROMIS Physical Function T-score¶	+2.24 ± 4.72	+1.86 ± 4.12	0.46 (−0.95 to 1.87)	

Overall, study completion was high (87.8%) and similar across groups

Distribution of OHQ/OIQ Change Scores by Treatment Group: Patient-Reported Orthostatic Intolerance Primary Endpoint Analysis — Intention-to-Treat Population
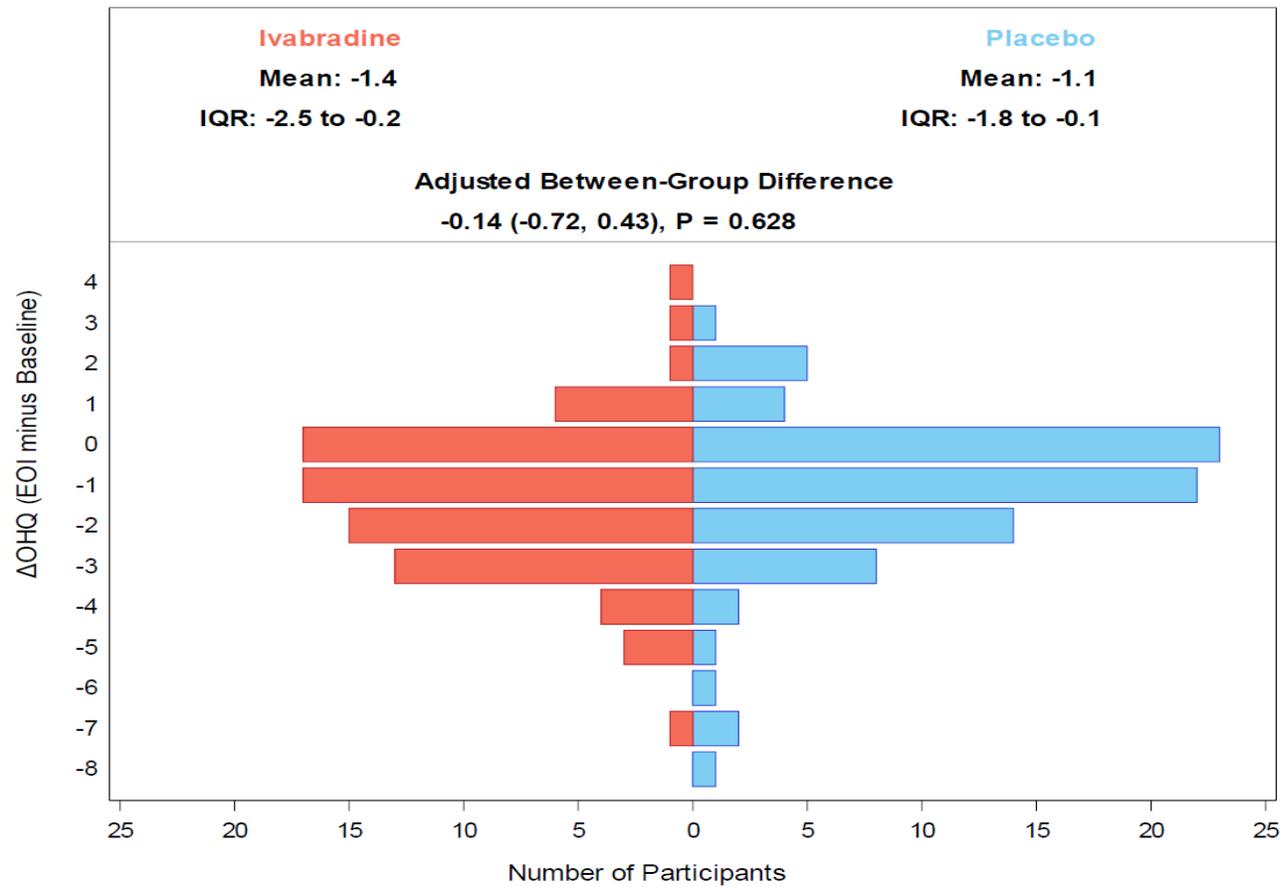
Interaction with Nonpharmacologic Care

In prespecified factorial analyses, the effect of ivabradine on OHQ differed according to assignment to coordinated vs. usual nonpharmacologic care (P value for interaction = 0.004).

Compared with placebo, ivabradine was associated with a lower OHQ/OIQ score among participants assigned to coordinated nonpharmacologic care (adjusted between-group difference in OHQ/OIQ change, -1.03; 95% CI, -1.83 to -0.23) and a higher OHQ/OIQ score among those assigned to usual care (0.72; 95% CI, -0.09 to 1.52).

Summary

- Treatment with ivabradine alone did not significantly improve patient-reported orthostatic intolerance (OHQ) in adults with Long COVID POTS.

- Ivabradine produced a significant reduction in heart rate change (supine to standing) compared to placebo

- Lowering of heart rate alone did not improve patient-reported outcomes

- In prespecified factorial analysis, patients who were randomized to ivabradine coordinated care had improvement in OHQ compared to patients on ivabradine and usual care.

Clinical Implications

- Ivabradine lowers heart rate, but in patients with Long-COVID POTS, heart rate lowering alone may be insufficient to improve symptoms in this multisystemic condition.

- Ivabradine, along with coordinated care, may have clinical benefit.

- There may be certain phenotypes of patients (e.g. patients with elevated norepinephrine levels) who would benefit from ivabradine.

- The natural history of Long Covid POTS is poorly understood, characterized by symptom fluctuation, and better clinical endpoints are needed to assess the impacts of intervention.

Thanks to all our Contributors

DCRI Operations Team

Hirra Z. Fissler; Orsolya V. Moy; Jennifer Hervey; Sean O'Brien; Jun Wen; Nikki L. B. Freeman; Megan Callaghan; Ann Schutte; Jessica Smith; Elizabeth Waddell; Ayowunmi Mabinuori; Carol Pereira; Loren Lytle; Allegra Stone; David Jensen

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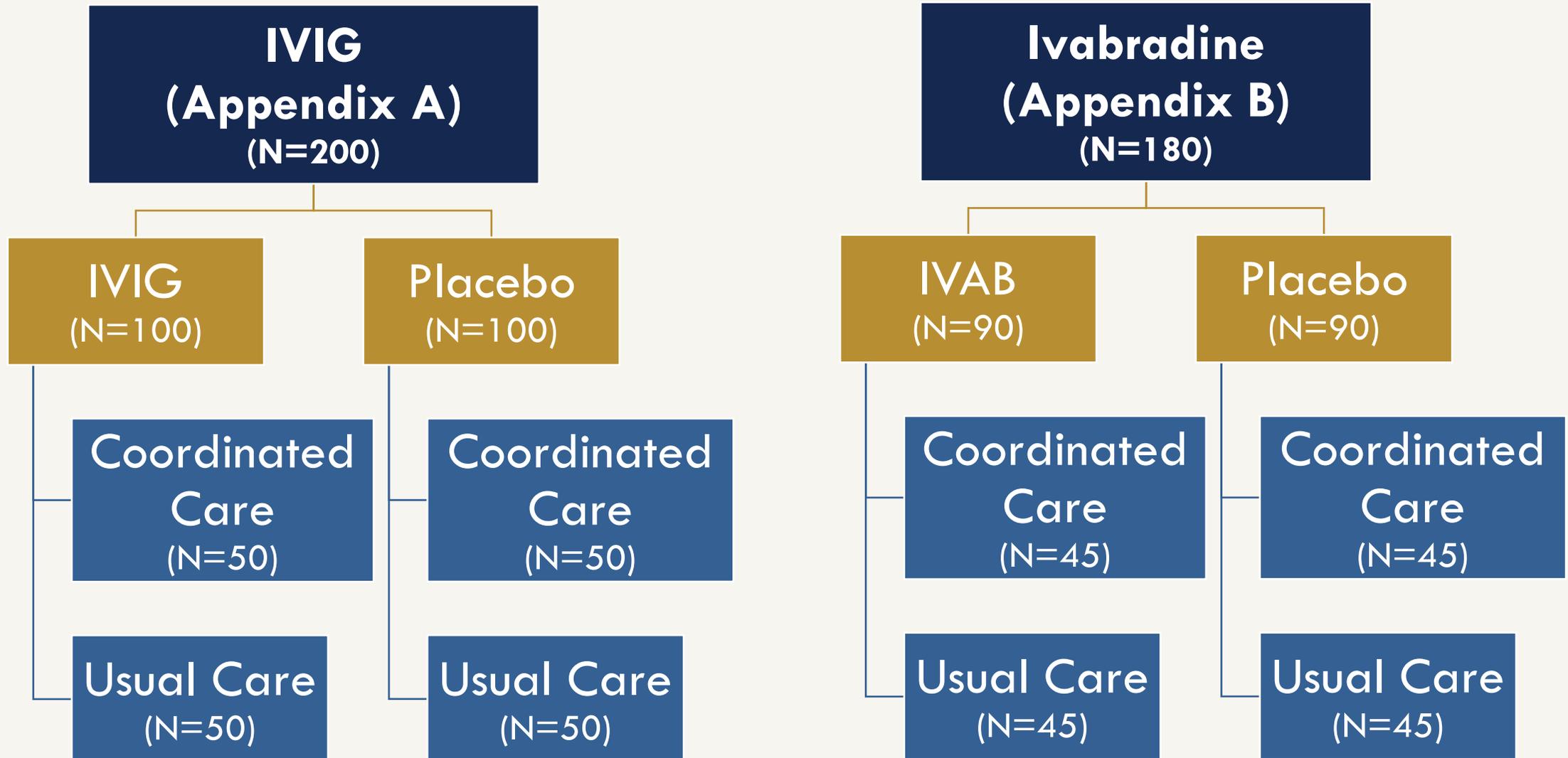
Protocol Overview

Ivabradine Appendix Updates

- Number of sites activated for Ivabradine: 48
- Number of sites enrolled participant(s): 40
- Total number of participants enrolled: 181
- First Patient enrolled: 4/26/24
- Last Patient Last Visit: 12/15/25
- Database lock: 1/5/26