Postural Orthostatic Tachycardia Syndrome

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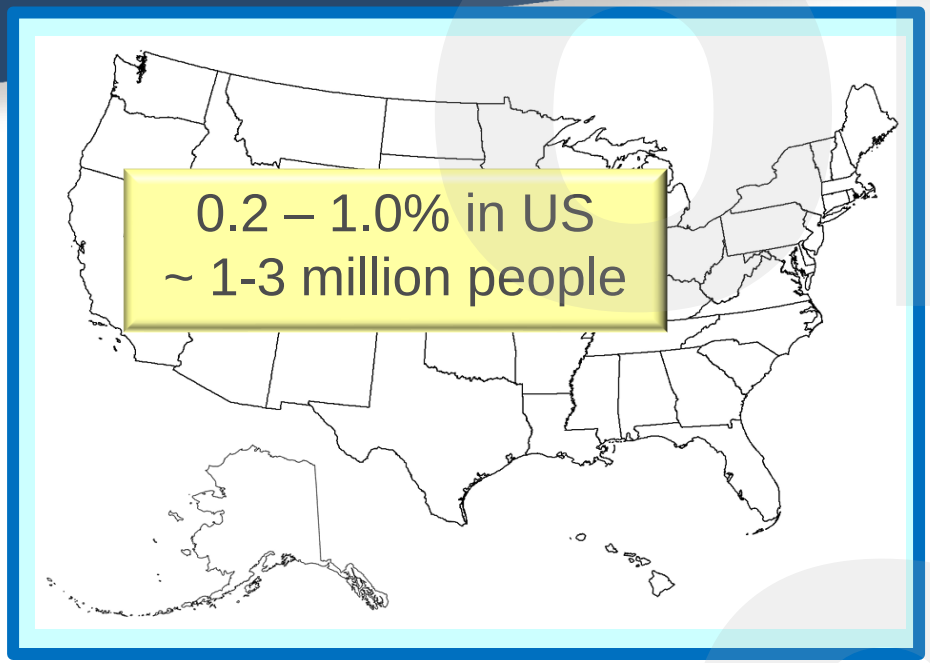
Disclosures

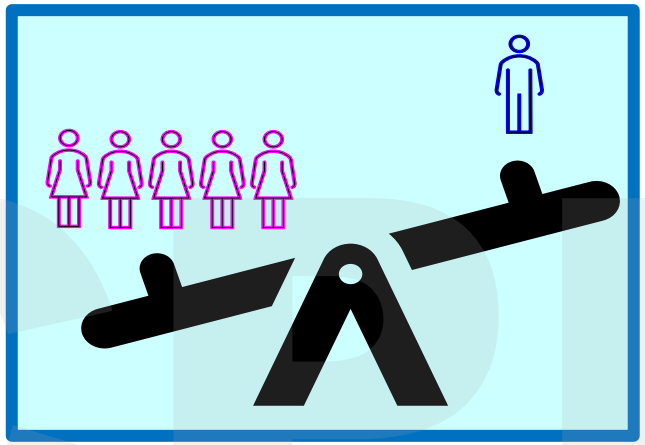
- No actual or potential conflicts of interest in relation to this program or presentation to disclose.
- There are **NO** FDA-approved medications for POTS
- All medications discussed are for off-label use but have been studied in clinical trials.
- The contents do not represent the views of the U.S. Department of Veterans Affairs or the U.S. government.

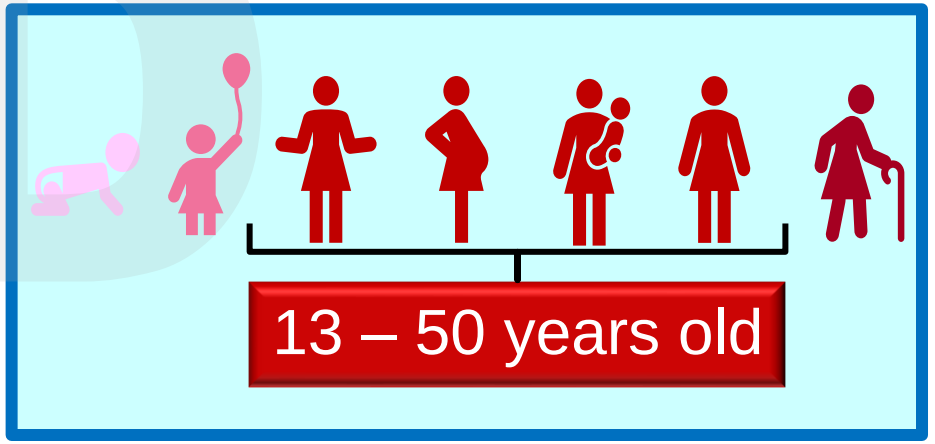
Objectives

- Recognize the criteria to diagnose postural orthostatic tachycardia syndrome (POTS)
- Select the appropriate nonpharmacologic and pharmacologic treatment for POTS

Demographics







Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.
Aboseit DO et al. Cleveland Clinic J Med. 2023;90:439-477.
Map by WaterproofPaper.com

In the News…..

The Washington Post

Breaking News

Trending Now — 5 minutes ago

A mysterious condition is striking young, highly trained athletes

First described more than 150 years ago, POTS has proliferated since the coronavirus pandemic. The syndrome tends to strike suddenly, leaving previously healthy people unable to function, with no clear cause. In recent years, doctors have noticed a curious and disproportionate subset of patients: female athletes at peak fitness.

They're young and athletic. They're also ill with a condition called POTS.

Since covid-19, diagnoses have increased, researchers and doctors report

By Ariana Eunjung Cha

April 10, 2024 at 5:00 a.m. EDT

TODAY ON THE SHOW SHOP OLYMPICS WELLNESS PARENTS FOOD LIFE TODAY PLAZA TODAY all day

Katie Ledecky opens up about POTS diagnosis and how she manages it when competing

The swimmer opened up about her diagnosis in her recent memoir, "Just Add Water."

[Katie Ledecky POTS: What to Know About Her Symptoms and Treatment (today.com)]

Prevalence – Long COVID

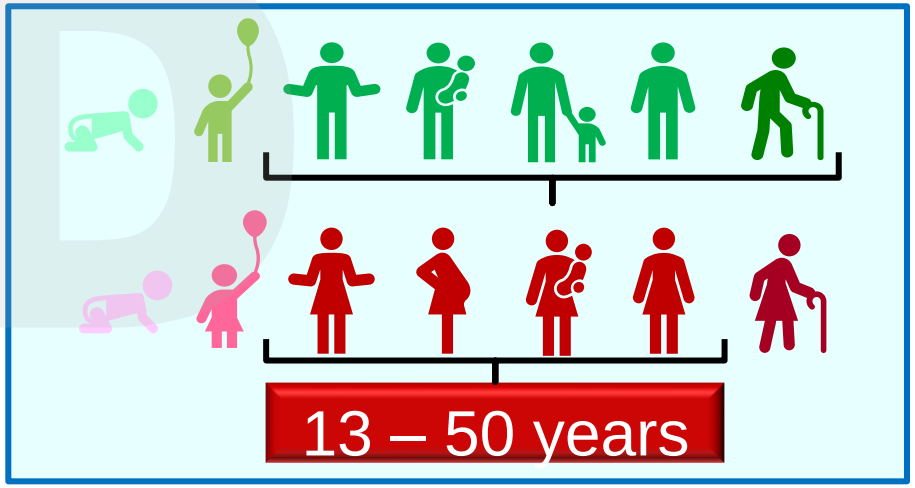
11/2024

- > 776.8 million cases
- 7.1 million deaths
- ~ 47 million long COVID (6%)

12/2024

- ~ 103 million cases
- ~ 1.12 million deaths
- ~ 15.7 million Long COVID (14-18%)

- 2-14% of survivors developed POTs
- 9-61% experienced POTS-like symptoms within 6-8 months
- POTS rate 5-fold higher with infection than with vaccination
- Women > Men
- Whites + Hispanics > Blacks and Asians
- Lower prevalence in higher educated and higher income groups



WHO; CDC
Narasimhan B et al. Vascular Health and Risk Management 2023;19:303-316.
Ormiston CK et al. Heart Rhythm 2022;19:1180-1889.
Kwan AC et al. Nature Cardiovasc Res 2022;1:1187-1194

Why is This Topic Important?

- Difficult to diagnose
- Under- or misdiagnosed
- Affects predominantly young, healthy women
- Attributed to chronic anxiety or panic disorders
- Can be debilitating and negatively affect quality of life
- Challenging diagnosis but can be helpful if confirmed
- Cases may increase because of long COVID

Raj SR et al. Canadian J Cardiol. 2020;36:357-372.

Why is POTS a challenging diagnosis?

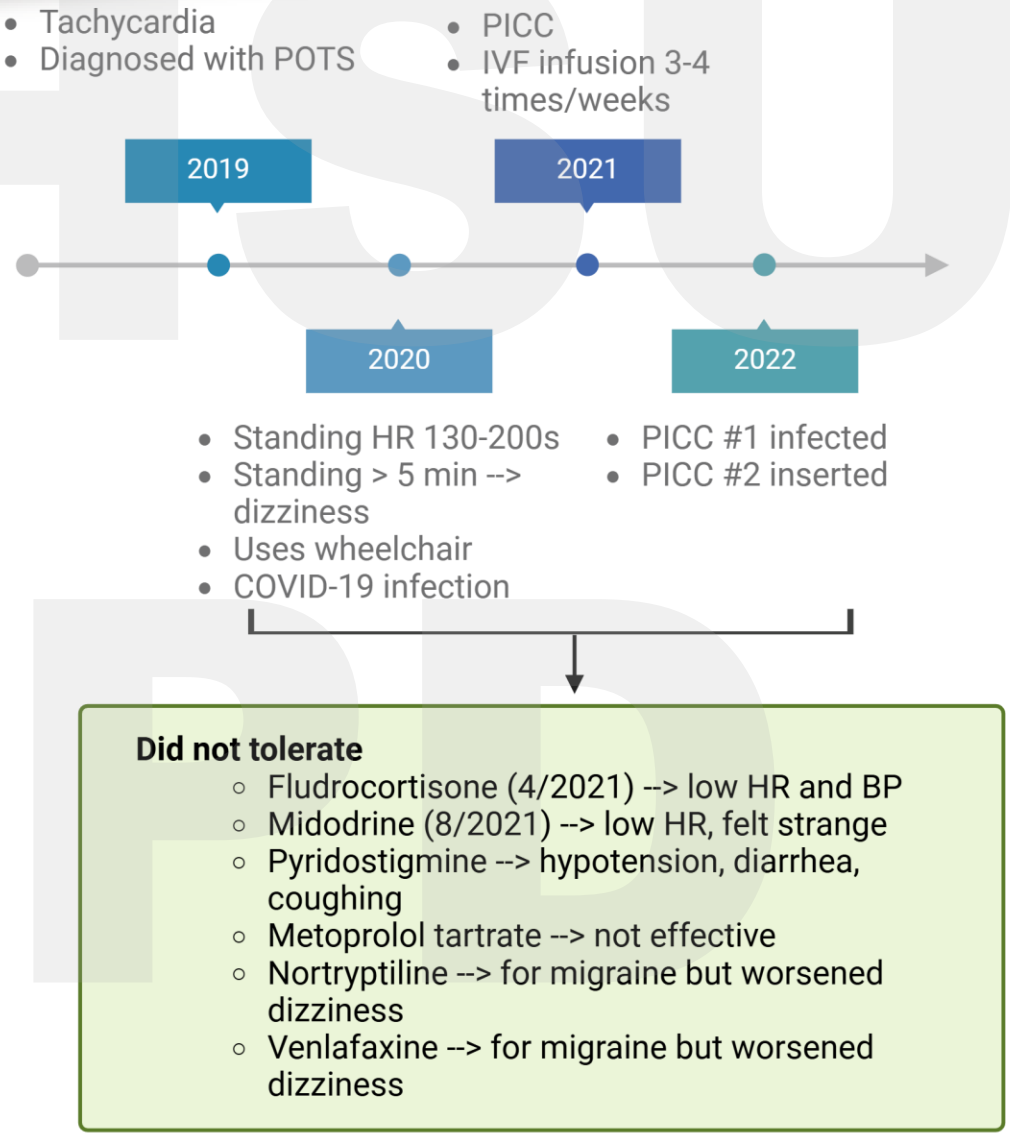
- Heterogenous
- Multiple mechanisms
- Atypical features overlap with other medical conditions
- Comorbid psychiatric conditions
- Clinician unfamiliar with condition

- 2 of 3 patients report at least 10 different symptoms
- In UK, ~ 4 years before correct diagnosis of POTS is made
- Patients see an average of 7 physicians before POTS diagnosis
- Of 4,835 self-reported patients:
  - Median time to diagnosis ~ 6-72 months
  - 27% saw >10 physicians
  - 83% given psychiatric diagnosis before POTS diagnosis

Aboseit DO et al. Cleveland Clinic J Med. 2023;90:439-477.

Case - History

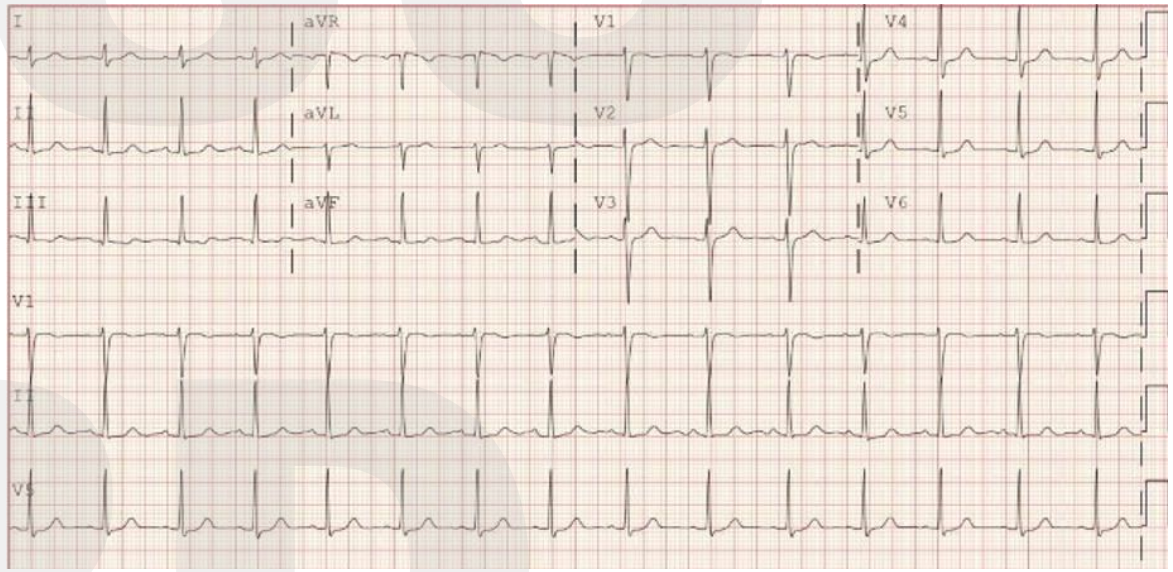
23 yo female with history of migraine and POTS diagnosed in 2019, referred to general cardiology clinic for management of POTS.



Case - History

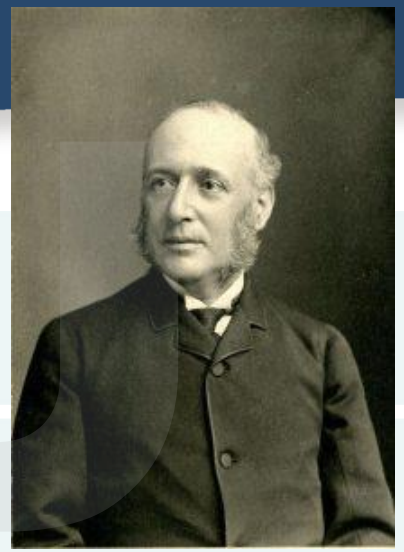
Vitals

- Sitting: Pulse 88 BP 125/70
- Standing: Pulse 133 BP 130/65
- Standing > 3min Pulse 88 BP 133/68
- Exam: no murmur, PIC in right UE with erythema around bandage
- ECG: NSR
- 24hour Holter Monitor: Mean HR 83, range 56-83 bpm, sinus arrhythmia, no ectopy
- TTE: normal



Historical Perspective

~1860 (Da Costa)	• Irritable heart syndrome
1918 (Lewis) 1941 (Wood)	• Soldier's heart • Da Costa syndrome
1982 (Rosen and Cryer)	• Postural tachycardia syndrome • Disabling tachycardia upon standing without orthostatic hypotension
1986 (Fouad)	• Idiopathic hypovolemia • Small degree of hypotension
1993 (Schondorf and Low)	• Current definition of POTS



Dr. Jacob M. Da Costa
https://www.civilwarmed.org/irritableheart/

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Symptom Characteristics

- Palpitations or tachycardia onset
  - 12.5% Acute (<1 month)
  - 13.8% Subacute (1-3 months)
  - 5.9% Insidious (>3 months)
- Frequency
- Impact on function and quality of life

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Symptoms

Postural Cardiac Symptoms

- Lightheadedness (99%)
- Tachycardia (97%)
- Presyncope (94%)
- Shortness of breath (88%)
- Palpitations (87%)
- Chest discomfort

Noncardiac Symptoms

- Mental clouding (brain fog)
- Tremulousness
- Blurred or tunnel vision
- Nausea
- * Headache
- * Sleep disturbances
- * Malaise
- * Abdominal pain, heartburn, diarrhea, constipation (last hours, multiple times/week

* Observed with chronic autoimmune disease

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.
Kichloo A et al. J Innov Cardiac Rhythm Manage. 2021;12:4607-4612.

Symptoms Context

Triggers

- Infection
  - COVID-19 (22%)
- Vaccination
  - HPV
- Surgery (12%)
- Trauma
- Pregnancy (9%)
- Childbirth
- Prolonged period of inactivity

Exacerbation

- Heat
- Fever
- Dehydration
- Morning hours
- Non-dippers
- Strong emotions
- Alcohol
- Menstruation
  - Worse pre or early cycle when estrogen and progesterone are low or decreasing

Aboseit DO et al. Cleveland Clinic J Med. 2023;90:439-477.
Bryarly M et al. JACC. 2019;73:1207-1228.
Sebastian SA et al. Curr Prob Cardiol. 2022:147;1-24.

Dietary and Exercise Habits & Culprit Medications

Diet and Functional Status

- Diet
  - Amount of salt and volume of water intake
  - Size of meals
- Exercise tolerance
  - Quantify amount of activity and reduction over period of time
  - List physical activities that no longer can be performed

Medications that can exacerbate POTs

- Antidepressants
  - Serotonin-norepinephrine reuptake inhibitors
  - Monoamine oxidase inhibitors
- Antipsychotics (phenothiazines)
- Anticholinergics
- ADHD medications
- Diuretics
- Vasodilators and venodilators
- Oral contraceptive pills that contain antimineralocorticoid (drospirenone)
- Stimulants (caffeine, nicotine)

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Detailed Autonomic Review of Systems

Musculoskeletal

- Muscle fatigue
- Weakness
- Pain

Gastrointestinal

- Nausea
- Bloating
- Dysmotility
- Gastroparesis
- Diarrhea
- Constipation
- Pain
- Irritable bowel syndrome
- Weight loss

Nervous System

- Headache
- Migraine
- Cognitive impairment
- Brain fog
- Photophobia
- Phonophobia
- Blurred vision
- Neuropathic pain
- Sleep disorder
- Involuntary movement

Respiratory

- Short of breath
- Hyperventilation
- Bronchial asthma

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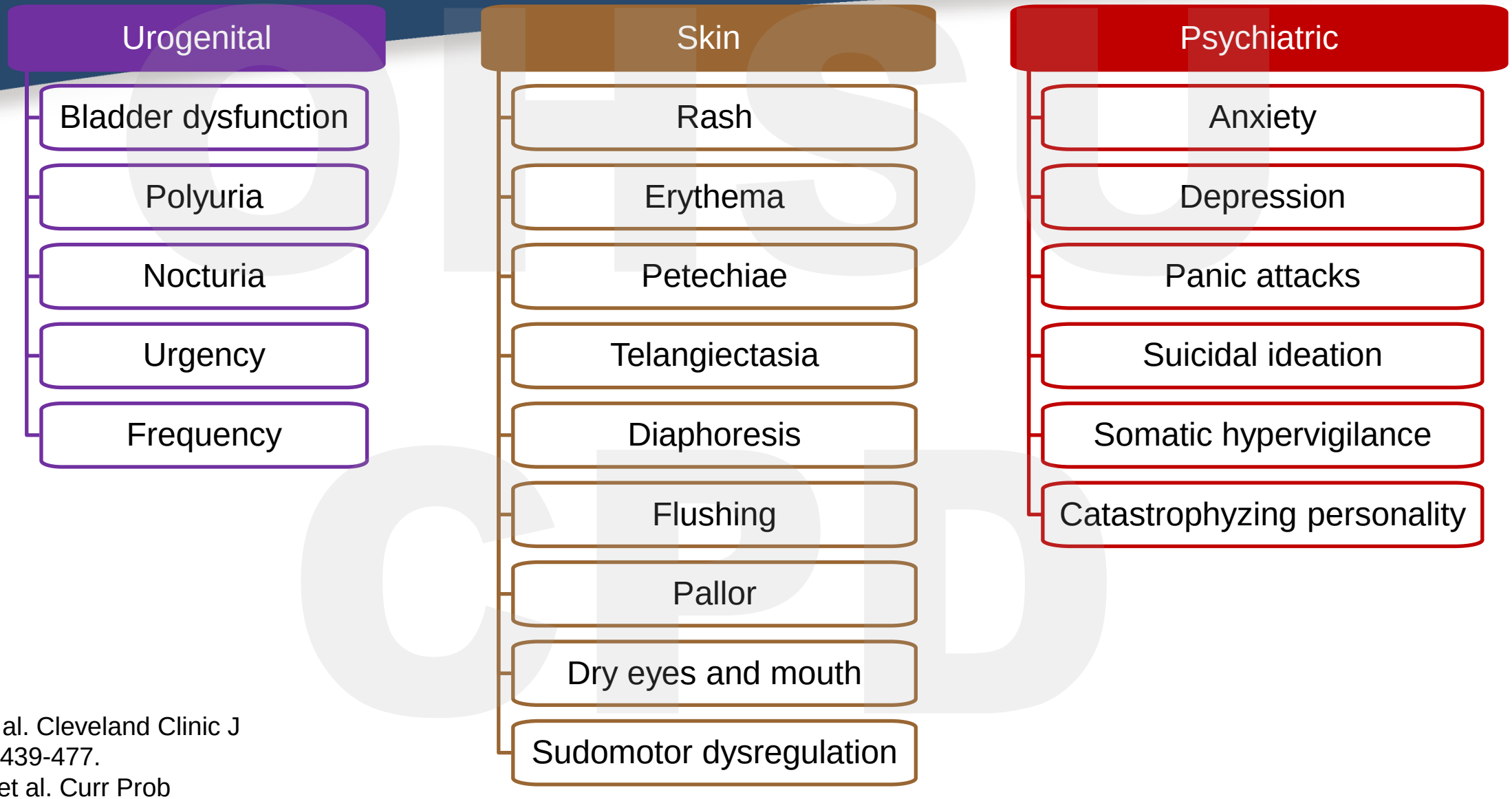
Sebastian SA et al. Curr Prob Cardiol. 2022;47:1-24

Detailed Autonomic Review of Systems



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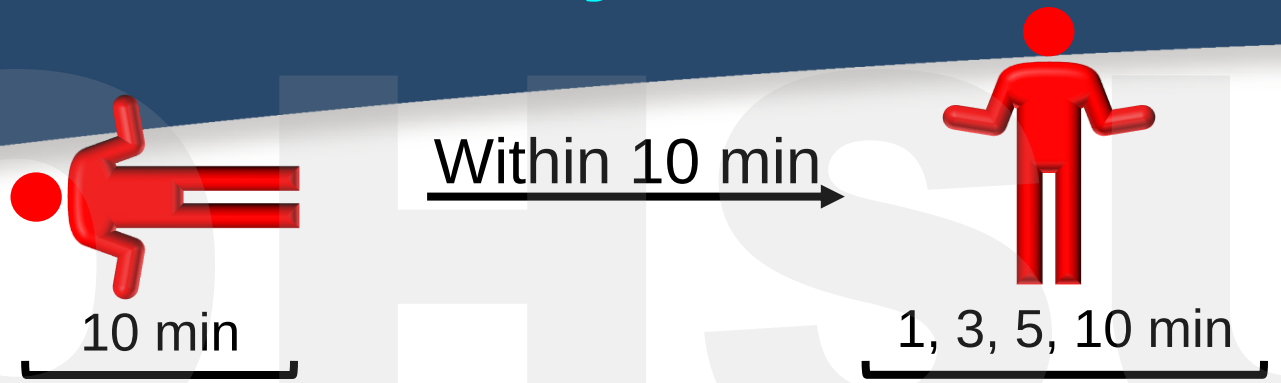
Sebastian SA et al. Curr Prob Cardiol. 2022;47:1-24

POTS vs. Postural Tachycardia



Upright Tachycardia

- ≥30 bpm >19 years old
- ≥40 bpm 12-19 years old
- Sustained tachycardia >30 s
  - 2 measurements at least 1 min apart
- No orthostatic hypotension (↓ ≥20/10 mmHg by 3 min)

+

Chronic

- ≥6 months
- >3 months
  - Canadian CV Society

+

Associated with Symptoms

Orthostatic
- Lightheadedness
- Palpitations
- Tremulousness
- Atypical chest discomfort

Not orthostatic
- Fatigue
- Blurred vision
- Pre-syncope
- Bloating, diarrhea, constipation
- Headache
- Brain fog
- Exercise intolerance

+

Absence of other conditions

- Acute dehydration
- Infection
- Anemia
- Hyperthyroidism
- Pheochromocytoma
- Medications-induced
- Recreational drugs effects
- Sustained bed rest
- Anxiety or panic attacks

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.
Aboseit DO et al. Cleveland Clinic J Med. 2023;90:439-477.

Physical Exam

"POTS feet"

Acrocyanosis (dark, red-blue discoloration of lower legs that is cold to touch (~50%)

Raj SR. Circulation. 2013;127:2336-2342.

Basic Laboratory and Other Tests

- CBC
- Basic metabolic panel
- TSH, free T4

ECG

Ziopatch monitor

- Arrhythmia
- Inappropriate sinus tachycardia (>100 bpm at rest supine and standing, with mean 24-hour rate >90 bpm) and associated with palpitations

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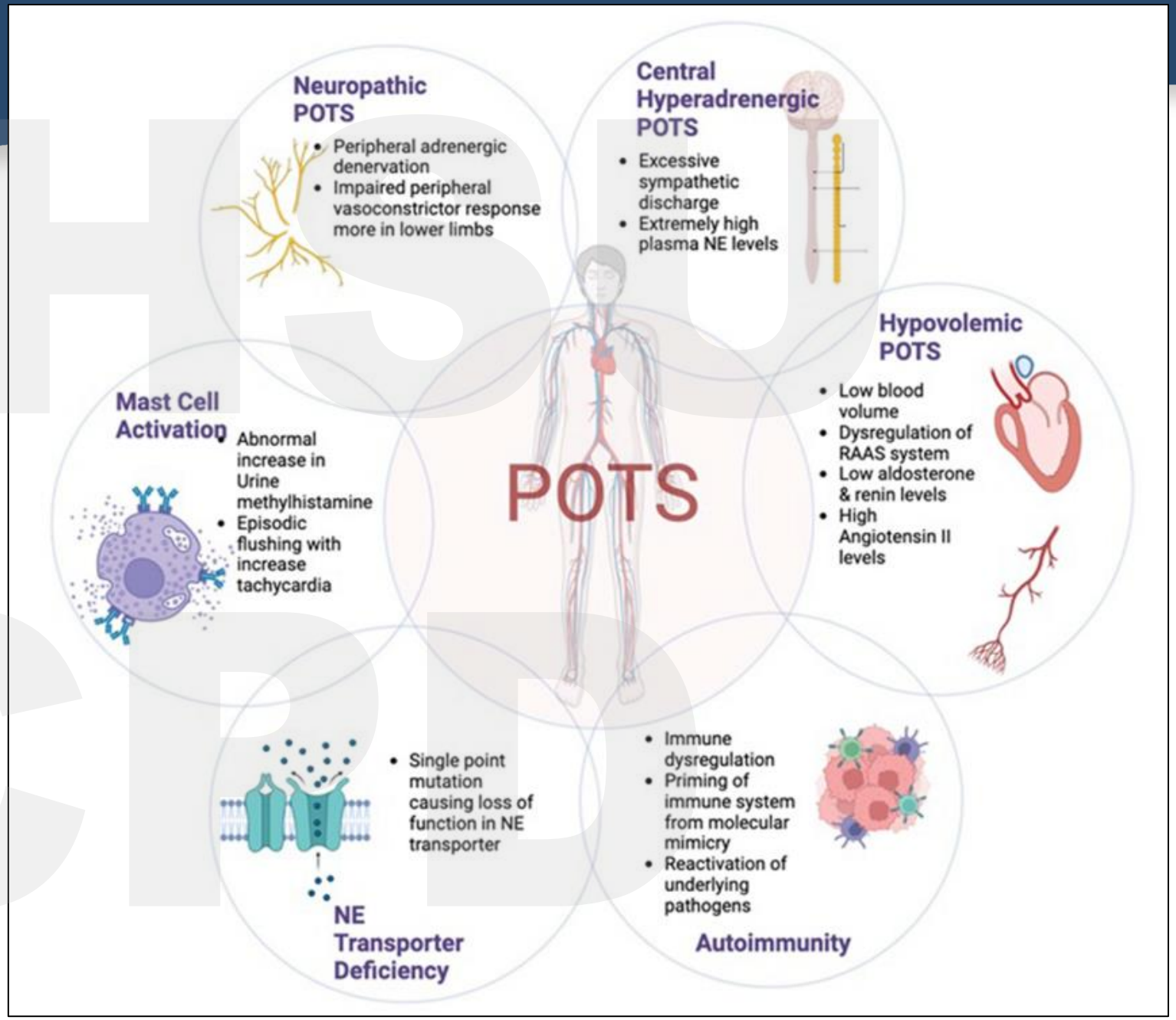
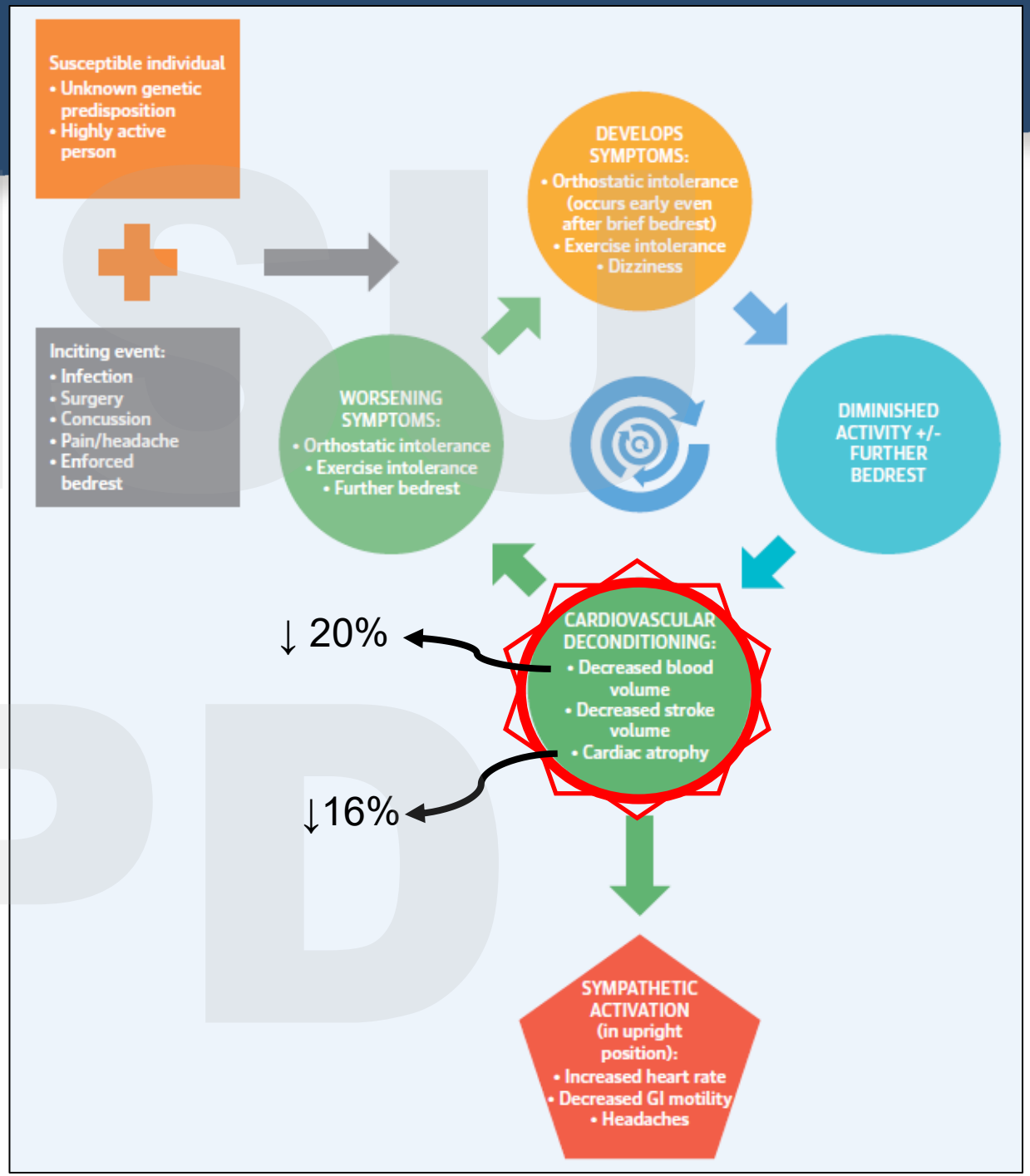
POTS Subtypes



Narasimhan B et al. Vascular Health and Risk Management. 2023;19:303-3016.

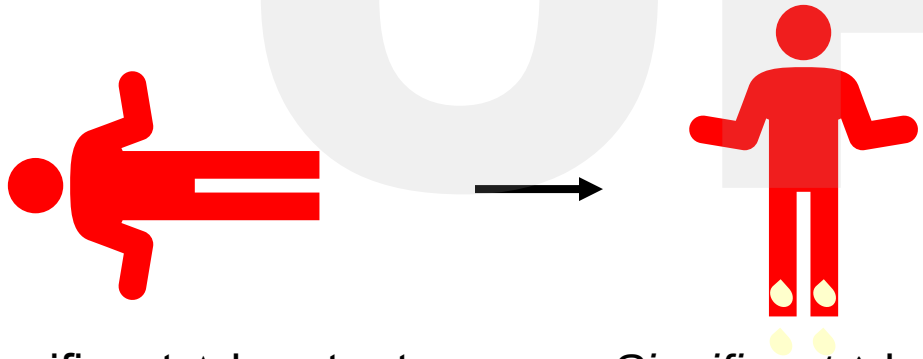
POTS Downward Spiral



Adpated from Bryarly M et al. JACC. 2019;73:1207-1228.

Hypovolemic POTS

~ 70% prevalence

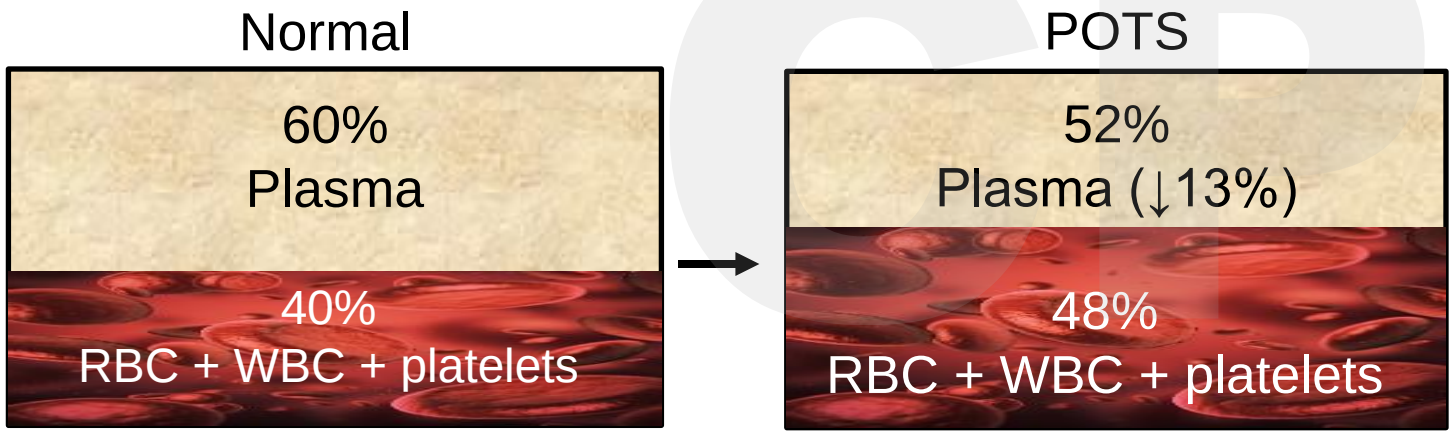


Insignificant Δ heart rate and norepinephrine level

Significant ↑ heart rate and norepinephrine level

Blood pooling
↓
↓ Cardiac output
↓
Tachycardia

Impaired renin-angiotensin-aldosterone regulation
↓
↓ Sodium retention
↓
Hypovolemia



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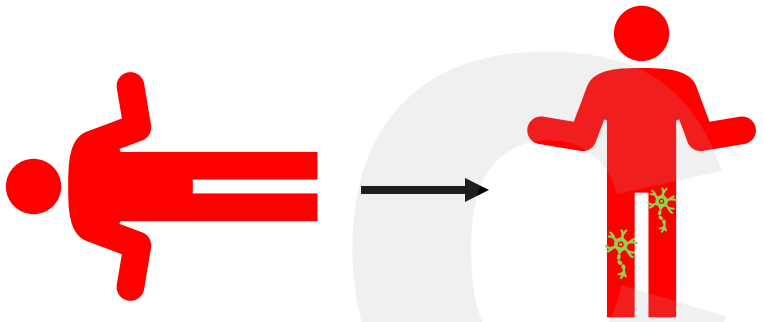
Neuropathic POTS

~ 50% prevalence

Sympathetic denervation, lower limbs

Lower supine/standing heart rate

Less anxiety and depression



Inadequate vasoconstriction

↓

↓ Venous return

↓

↓ Stroke volume

↓

Compensatory ↑ sympathetic tone

↓

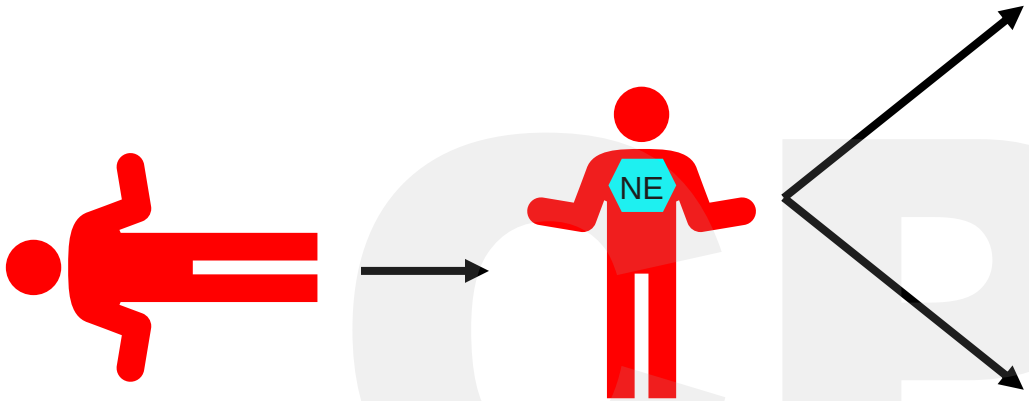
Tachycardia

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Hyperadrenergic POTS

~ **50% prevalence**

Palpitations, anxiety, tremulousness, hyperhidrosis



Tricyclic antidepressant (nortriptyline)
Serotonin-norepinephrine reuptake inhibitors (bupropion)
Attention-deficit disorder medications (methylphenidate)

↓

High standing norepinephrine levels
(≥ 600 – 1,000 pg/mL)

↓

↑ Systolic blood pressure ≥ 10 mmHg within 10 min of standing

↓ Norepinephrine transporter density
(rare genetic mutation)

↓

↓ Norepinephrine clearance of synaptic norepinephrine

↓

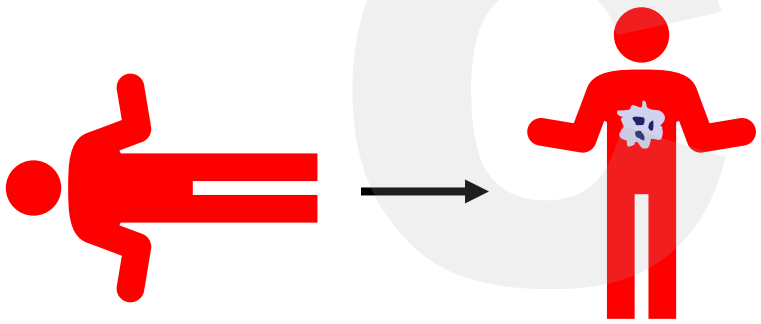
↑ Sympathetic nerve activation

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Mast Cell Activation Syndrome

9% prevalence

- Strong allergic symptoms
- Food sensitivities
- Dermatographism
- Frequent urticaria
- Severe Flushing
- Shortness of breath
- Neuropathy



Histamine release

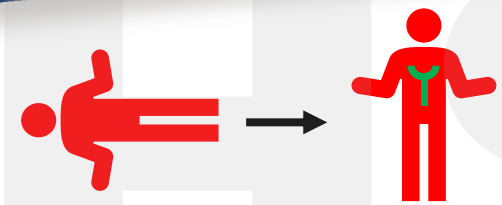
↓

↑ Urine methylhistamine

> 230 µg/g creatinine in 4 h urine collection

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.
Raj SR et al. Can J Cardiol. 2020;36:357-372.

Autoimmune POTS



16% prevalence

- Preceding viral illness
- 7% Antiphospholipids antibodies
- 6% Hashimoto thyroiditis
- 3% Celiac disease
- 3% Sjögren syndrome
- 2% Rheumatoid arthritis
- 2% SLE

- 87% prevalence auto antibodies to M1, M2, and M3 muscarinic receptors
- 25% prevalence antinuclear antibodies
- Cardiac lipid-raft-associated proteins (cardiac dysautonomia)
- Adrenergic G-protein coupled receptors antibodies
  - α_1-adrenergic receptors
  - B_1- and β_2-adrenergic receptors
- Angiotensin II type 1 receptor antibodies

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.
Aboseit DO et al. Cleveland Clinic J Med. 2023;90:439-477.
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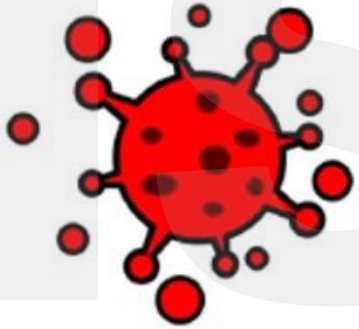
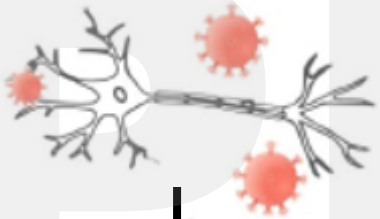
Possible Underlying Mechanism of Long COVID-19 and POTS

Long COVID-19

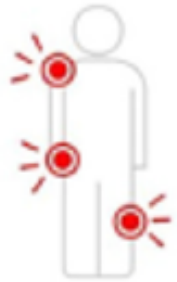


↓ Blood Volume & Deconditioning of the heart

Neural propagation of COVID-19



Inflammatory & Autoimmunity

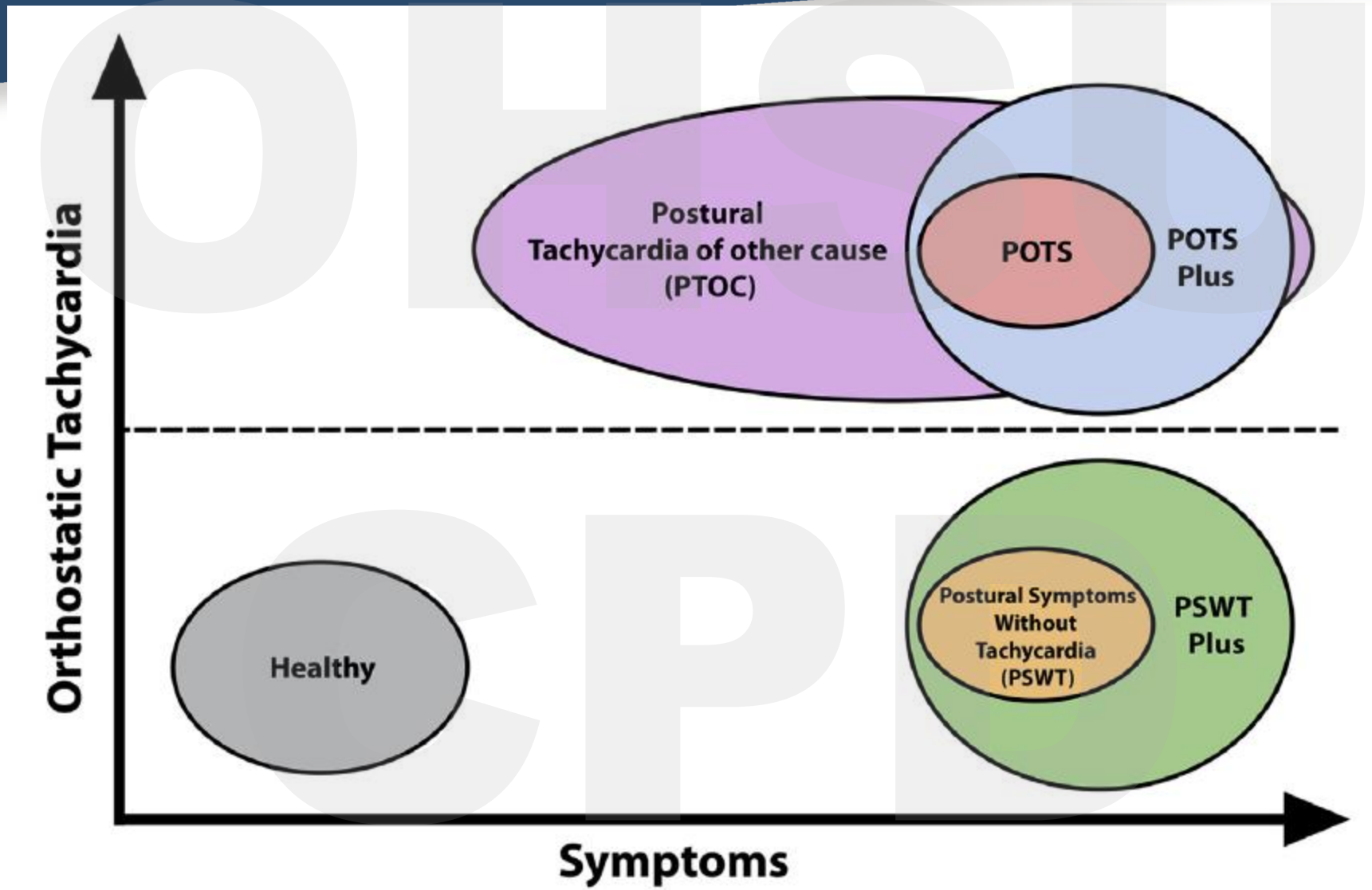


Dysautonomia

POTS

Adapted from Sebastian SA et al. Curr Prob Cardiol. 2022;47:1-24

POTS and Related Disorders



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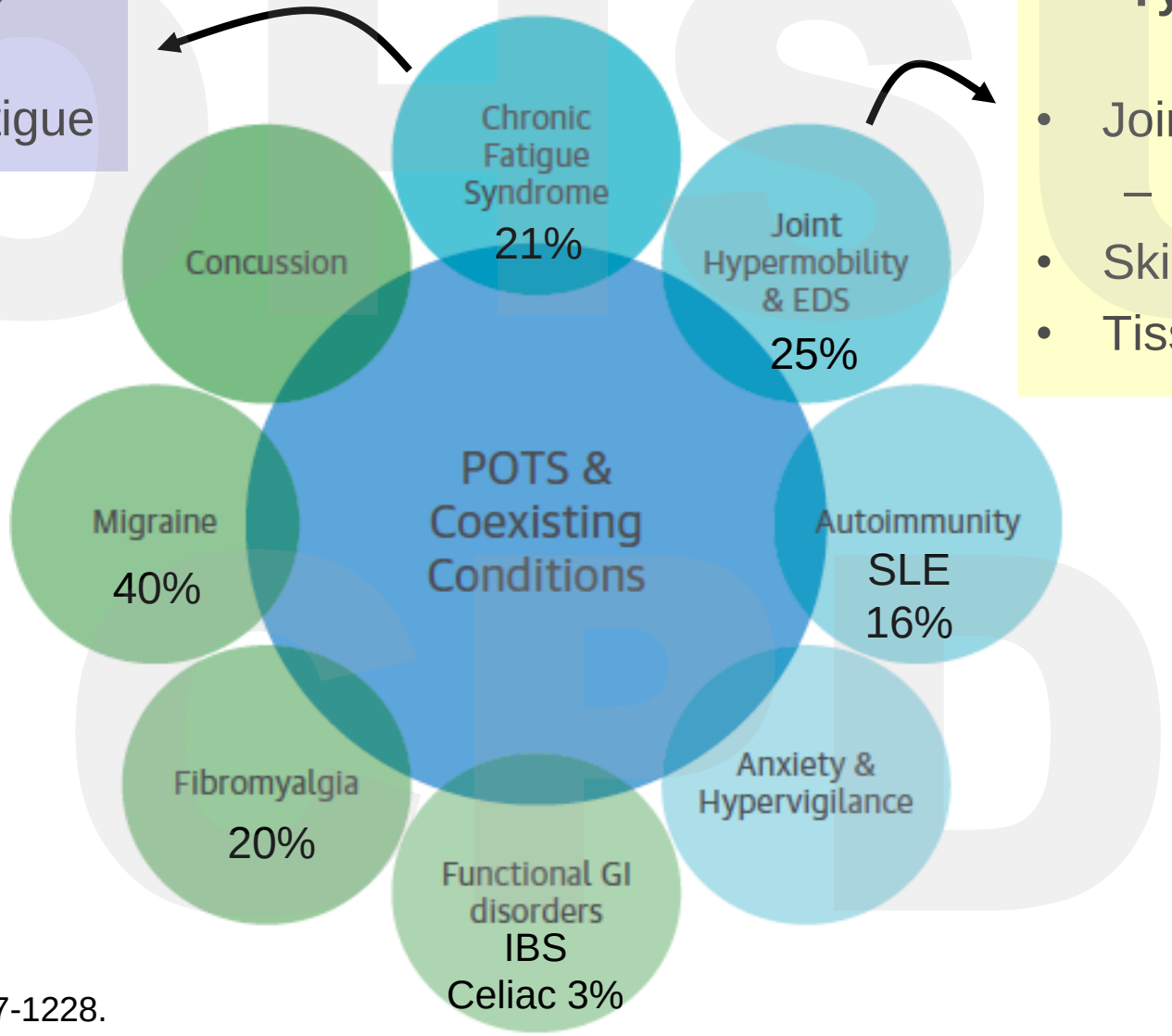
Co-existing Conditions with POTS

Chronic Fatigue Syndrome

- 75% of POTS – fatigue



Type III Ehlers-Danlos Syndrome

- Joint hypermobility
  - Autonomic dysregulation
- Skin hyperextensibility
- Tissue fragility

Bryarly M et al. JACC. 2019;73:1207-1228.
Raj SR et al. Can J Cardiol. 2020;36:357-372.

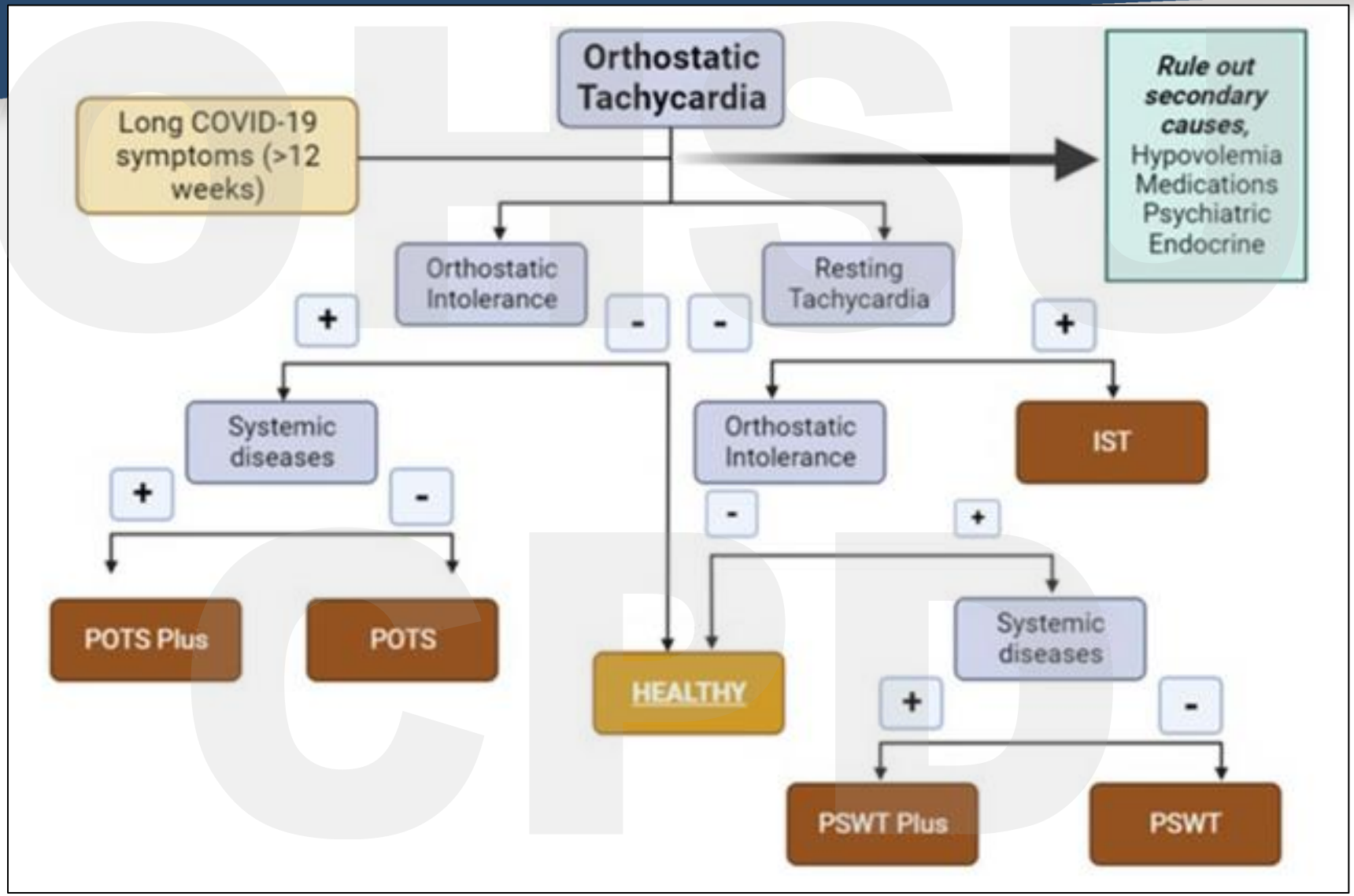
Differential Diagnoses

- Hyperthyroidism
- Infection
- Pheochromocytoma
  - Palpitations, lightheadedness, flushing while supine
  - Plasma norepinephrine higher than POTS
  - ↑ Metanephrines
- Inappropriate sinus tachycardia
  - HR ≥ 100 bpm at rest
  - Mean 24-hour heart rate ≥ 90 bpm
  - Associated with palpitations

- Acute dehydration
- Exercise
- Physical deconditioning
- Panic attacks
- Pain
- Alcohol
- Caffeine
- Medication-induced or exacerbated

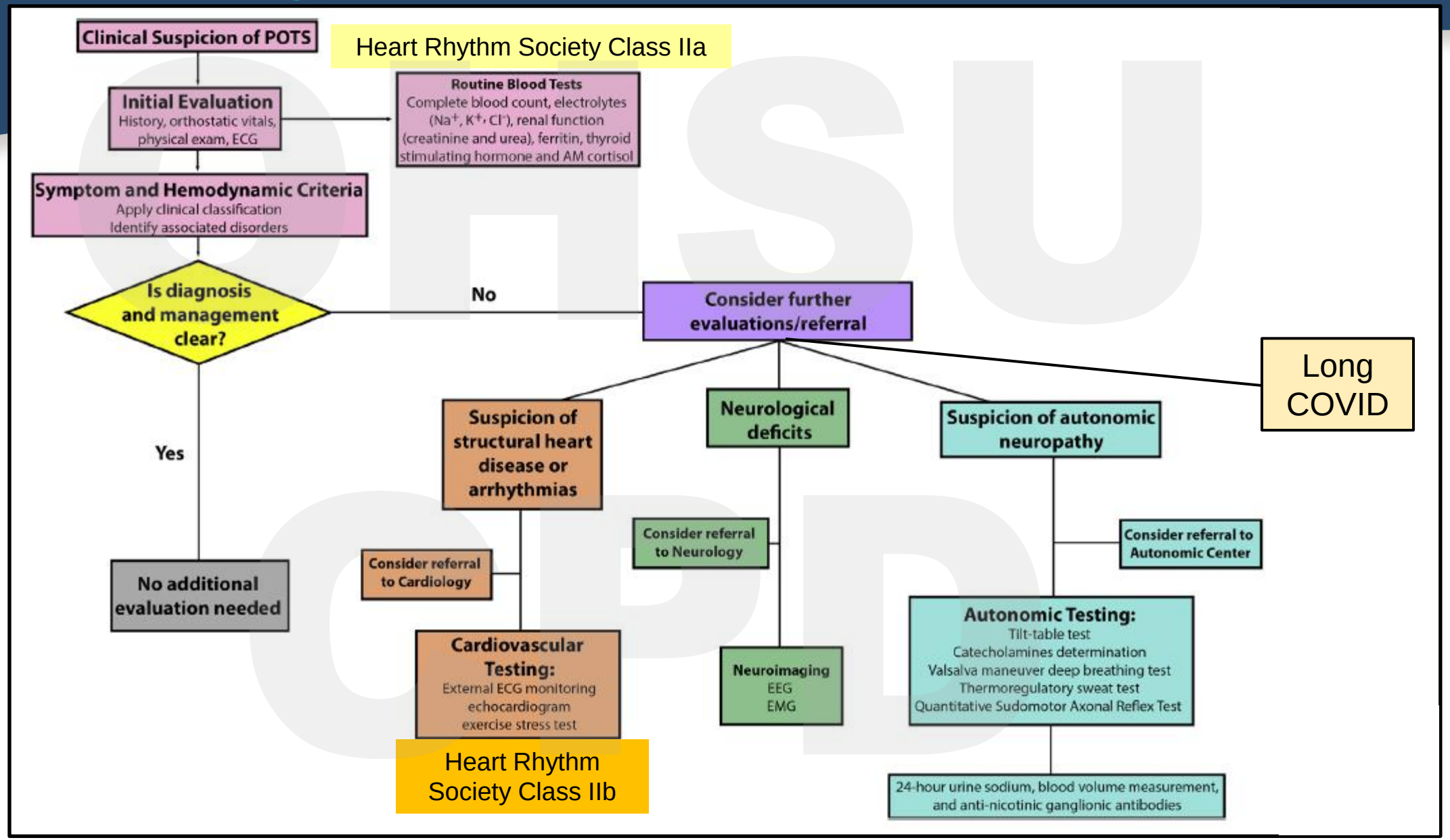
Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344.

Diagnostic Algorithm



Adapted from HSR 2015 Guidelines and CCS position statement 2020

Diagnostic Algorithm – Referral?



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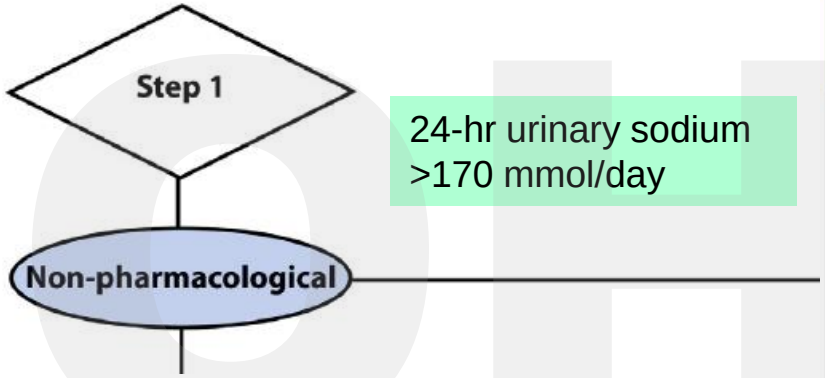
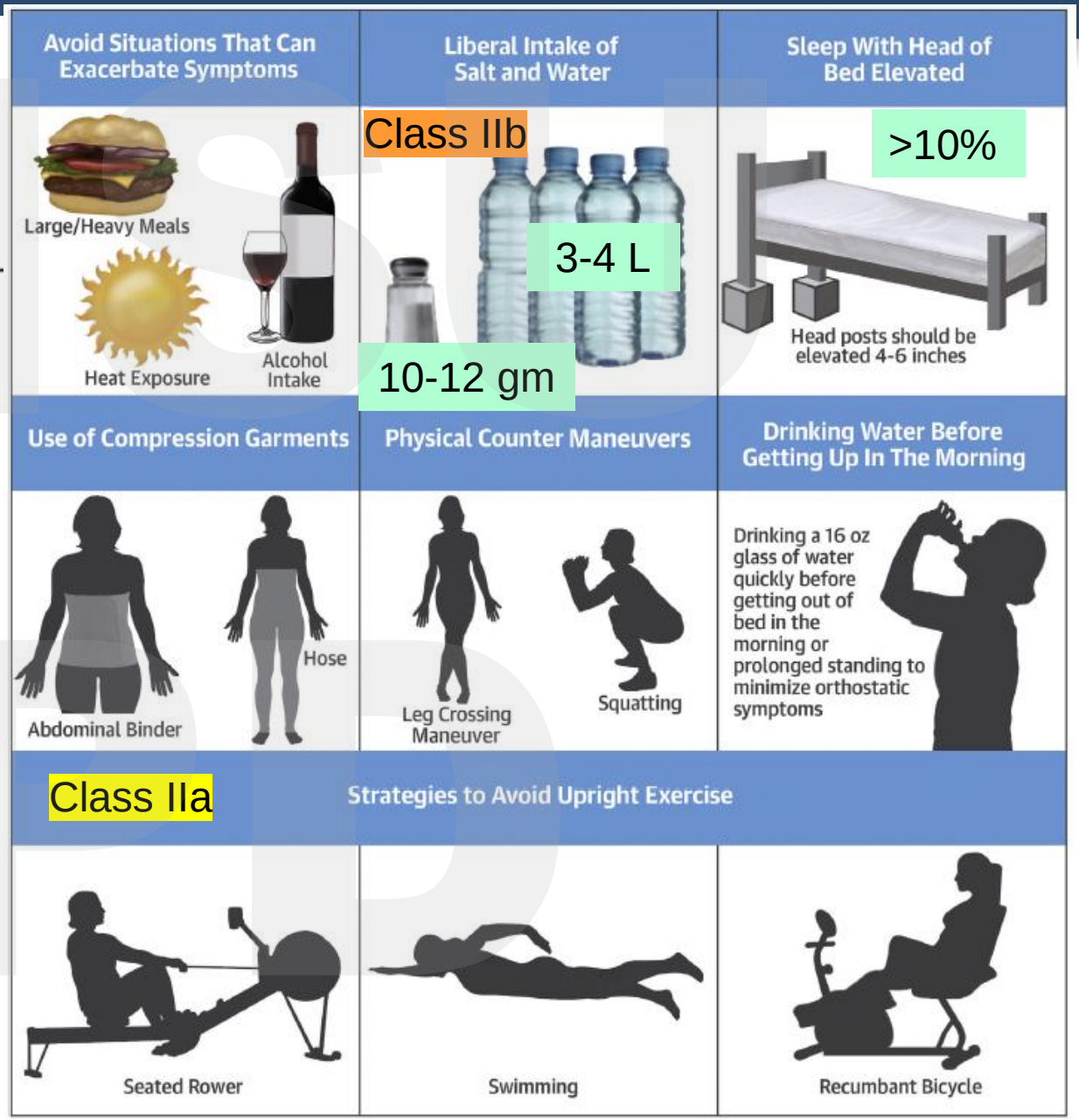
Nonpharmacologic Treatment Options



24-hr urinary sodium
>170 mmol/day



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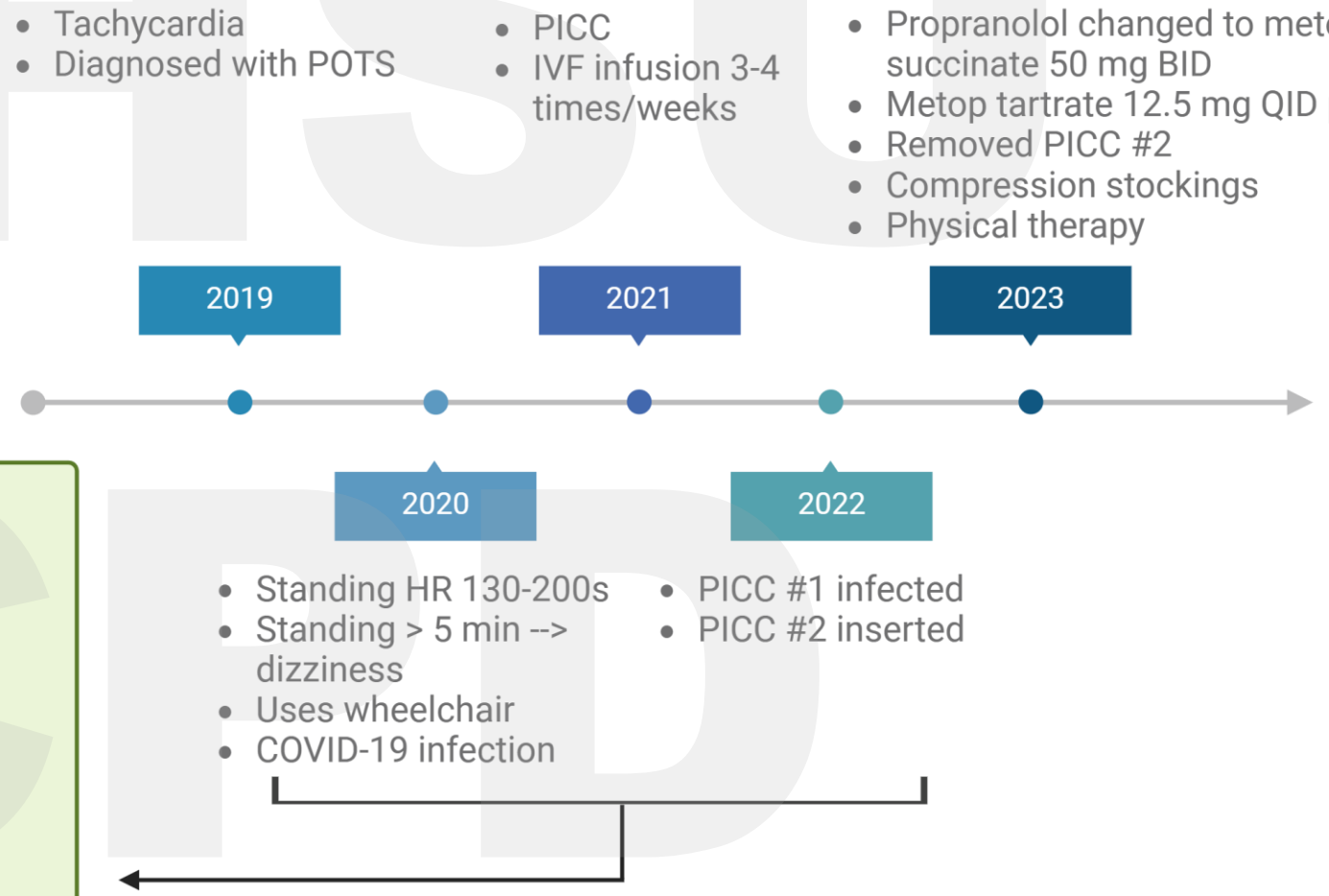
Case - Management



Did not tolerate

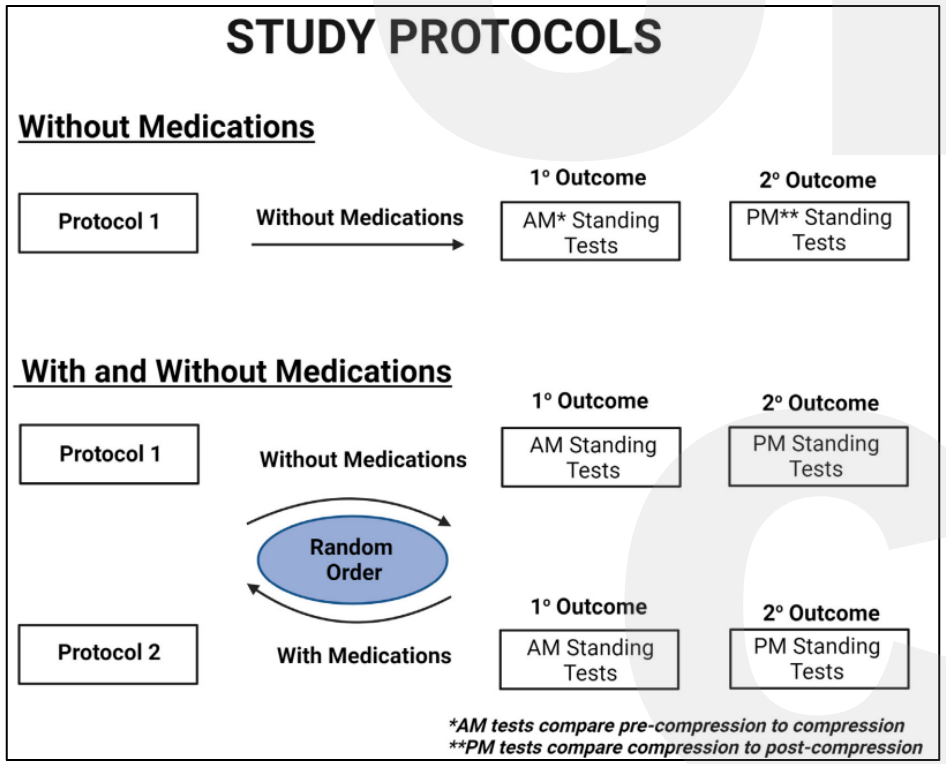
- Fludrocortisone (4/2021) --> low HR and BP
- Midodrine (8/2021) --> low HR, felt strange
- Pyridostigmine --> hypotension, diarrhea, coughing
- Metoprolol tartrate --> not effective
- Nortryptiline --> for migraine but worsened dizziness
- Venlafaxine --> for migraine but worsened dizziness

Nonpharmacologic Therapies

Therapy	Dosage	Pathologic mechanisms addressed	Potential drawbacks	Comments
Exercise	≥ 30 min at least 3 times a week	All	Worsened symptoms at the outset, prolonged fatigue	Gradually progress from non-upright to upright endurance and resistance exercises
Dietary fluid	2–3 L per day	All	Hyponatremia	
Dietary salt	10–12 g per day	All	Difficult to augment sufficiently through diet alone	Supplement with sodium chloride tablets, if necessary
Compression stockings	Waist high 30 40 mmHg	All	Difficult to put on	
Sleep with head elevation	4-6 inches	All		
Salt tablets	1 g tablet 3 times daily	Hypovolemia	Poor taste, nausea, dyspepsia	Recommended for use after meals
Acute intravenous normal saline	1 L over 1–3 hours	Hypovolemia	Inconvenient, medical setting required	Heart Rhythm Society Consensus Statement class IIa recommendation (benefit probably exceeds risk)
Chronic intravenous normal saline	1 L every 2 days	Hypovolemia	Access complications and infection with central line	Heart Rhythm Society Consensus Statement class III recommendation (recommends against)

Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344

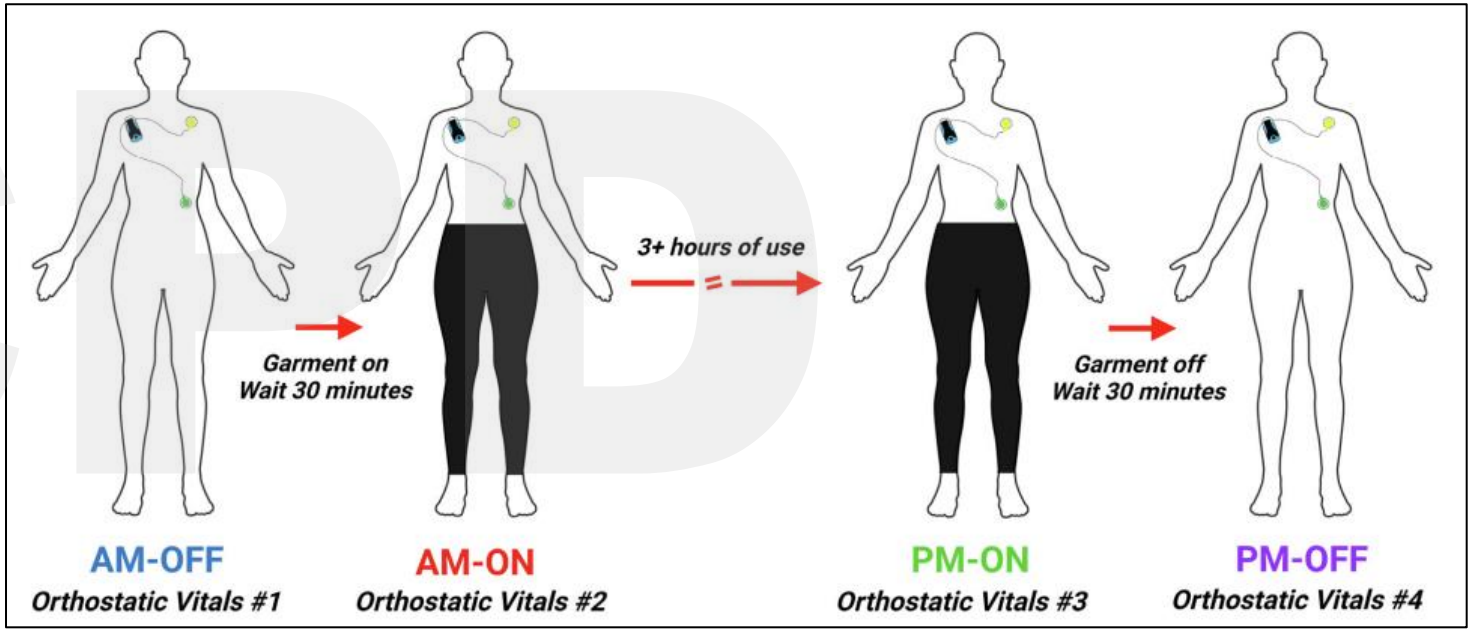
Compression Garments



N= 26 female
Age: 16-54 years old
Race: White n=21; South Asian n=1; Indigenous n=1, Multiple n=3
Meds:

- Beta-blockers (71%, n=17)
- Midodrine (31%, n=8)
- Pyridostigmine (12%, n=3)

Commercial medical compression garment (65%, n=17)
Athletic style (17%, n=4)

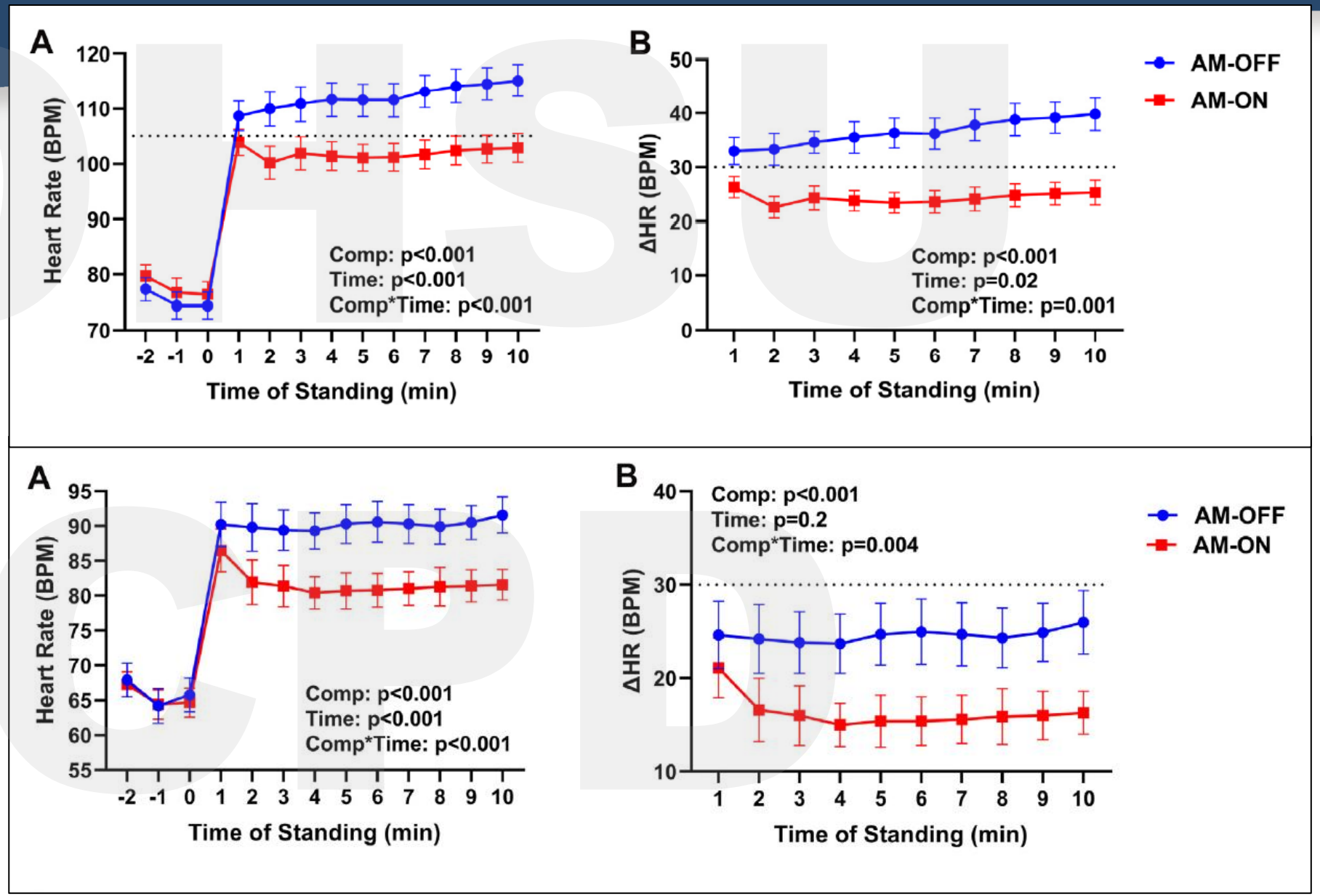


Bourne KM et al. JACC Clin Electrophysiol. 2024

Compression Garments

NO MED

WITH MED



Bourne KM et al. JACC Clin Electrophysiol. 2024

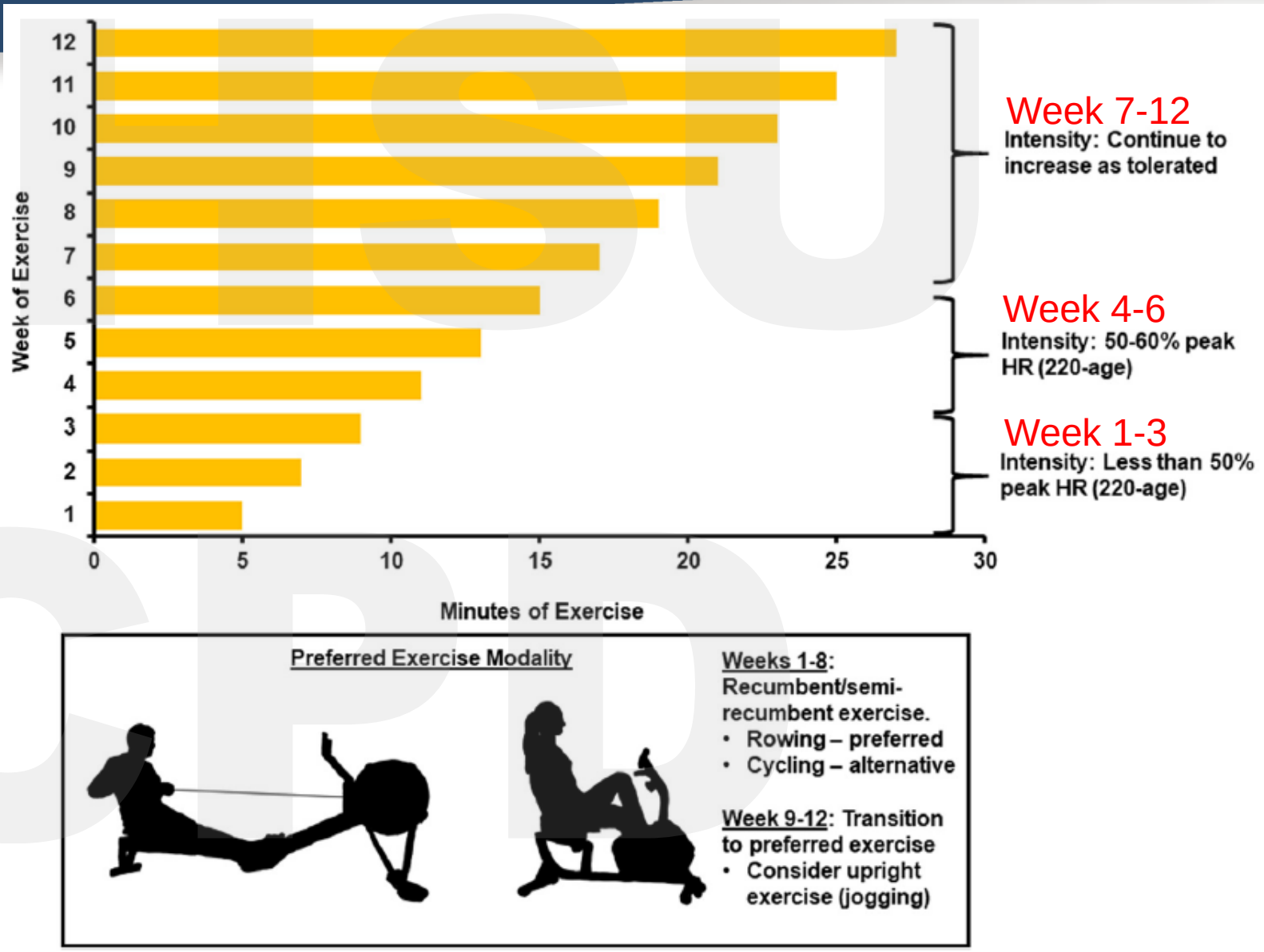
Exercise Prescription

Endurance:

- 5 min warm-up, 5 min cool-down
- Recumbent
  - 3-4 times/week for 25-30 min for 2 months
- Upright bike or walking on treadmill
  - 5-6 times/week for 45-60 min

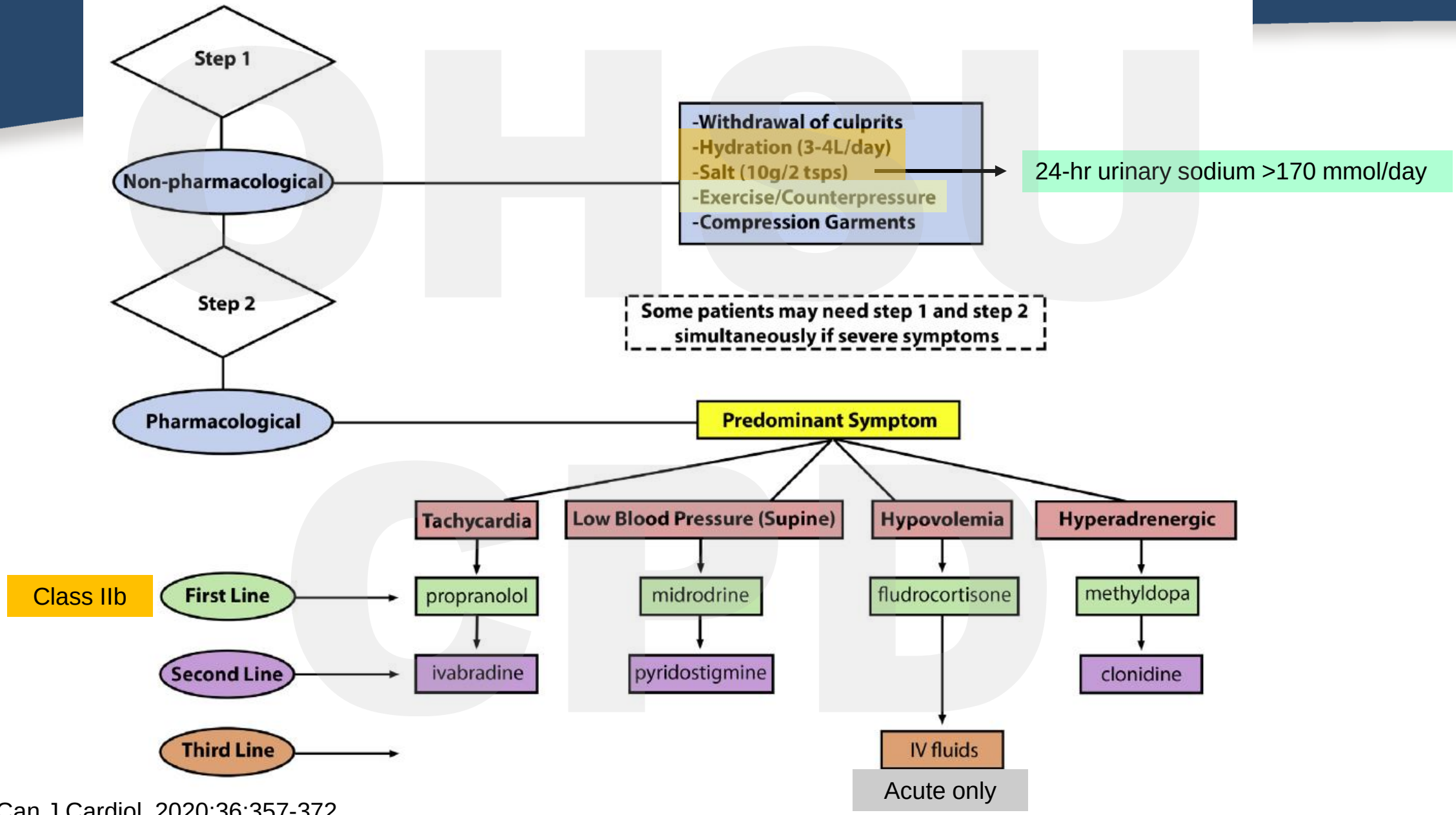
Resistance

- Weight-lifting once/week, 15-20 min/session
- Increase 2 times/week, 30-40 min/session



Adapted from Rudofker EW et al. J Am Coll Cardiol Case Rep. 2022;4:31344-1347.

Treatment Algorithm - Pharmacotherapy



Raj SR et al. Can J Cardiol. 2020;36:357-372.

Pharmacologic Therapies

NO medication has been FDA-approved specifically for POTS.
The following medications have been studied in clinical trials

Therapy	Dosage	Pathologic mechanism addressed	Potential drawbacks	Comments
Blood volume expanders				
Fludrocortisone IIb	0.05–0.1 mg twice daily	Hypovolemia	Hypokalemia, hypertension, fatigue, headache, fluid retention, edema	
Desmopressin	0.1–0.2 mg 3 times daily	Hypovolemia	Hyponatremia, headache, edema	Only for occasional use; must monitor blood sodium, 1x/week
Erythropoietin	2,000–3,000 IU subcutaneously 1–3 times per week	Hypovolemia	High cost, requires injection, risk of vascular complications	Reserved for patients with symptoms refractory to more common treatments
Heart rate-lowering agents				
Propranolol IIb	10–20 mg 3–4 times daily	All	Hypotension, fatigue, drowsiness, wheezing	Not well tolerated at higher dosages
Ivabradine	5–7.5 mg twice daily	All	Palpitations, headache, dizziness, constipation	

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Pharmacologic Therapies

Therapy	Dosage	Pathologic mechanism addressed	Potential drawbacks	Comments
Clonidine	0.05–0.2 mg twice daily	Hyperadrenergic	Mental clouding, fatigue, drowsiness, constipation	Can be associated with rebound hypertension and tachycardia
Methyldopa	125 mg once or twice daily	Hyperadrenergic	Hypotension, fatigue, headache, drowsiness, constipation	Rare lupus-like syndrome reported
Other drugs				
Midodrine IIb	2.5-15 mg every 4 hours, 3 times daily only	Neuropathic	Hypertension, goose bumps, urinary retention	15-30 min before getting out of bed in AM Not recommended for use within 4-5 hours of sleep
Pyridostigmine IIb	30–60 mg 3 times daily	All	Abdominal cramping, diarrhea, increased sweating	May increase gastrointestinal motility
Droxidopa	100–600 mg 3 times daily	All	Nausea, palpitations, urinary symptoms	May worsen tachycardia
Modafinil	100–200 mg twice daily	"Brain fog"	Headache, dizziness, anxiety, insomnia	May improve cognitive symptoms
H_1 and H_2 histamine receptor blockers			Avoid concomitant beta-blocker	Drowsiness, dizziness

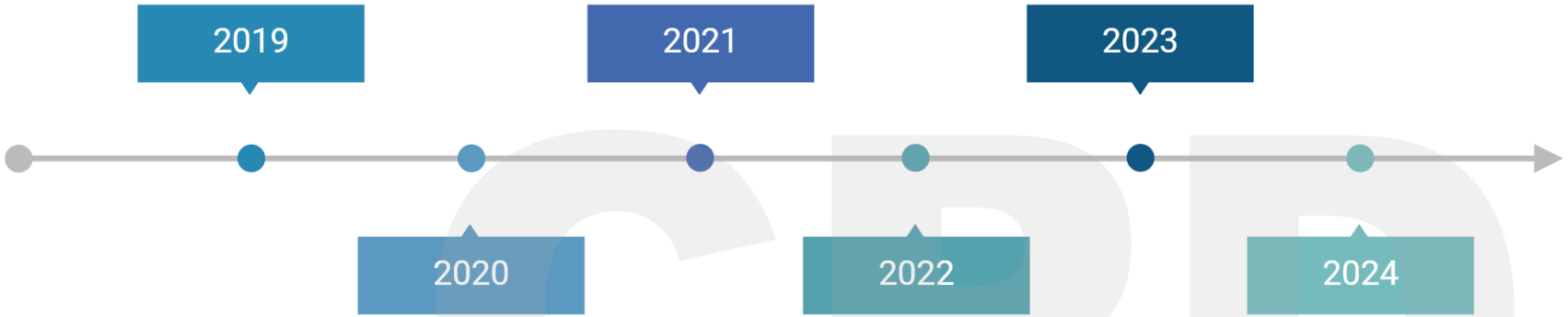
Lei LY et al. Cleveland Clinic J Med. 2019;86:333-344
Bryarly M et al. JACC. 2019;73:1207-1228.

Case - Management

- Tachycardia
- Diagnosed with POTS

- PICC
- IVF infusion 3-4 times/weeks

- Propranolol changed to metoprolol succinate 50 mg BID
- Metop tartrate 12.5 mg QID prn
- Removed PICC #2
- Compression stockings
- Physical therapy

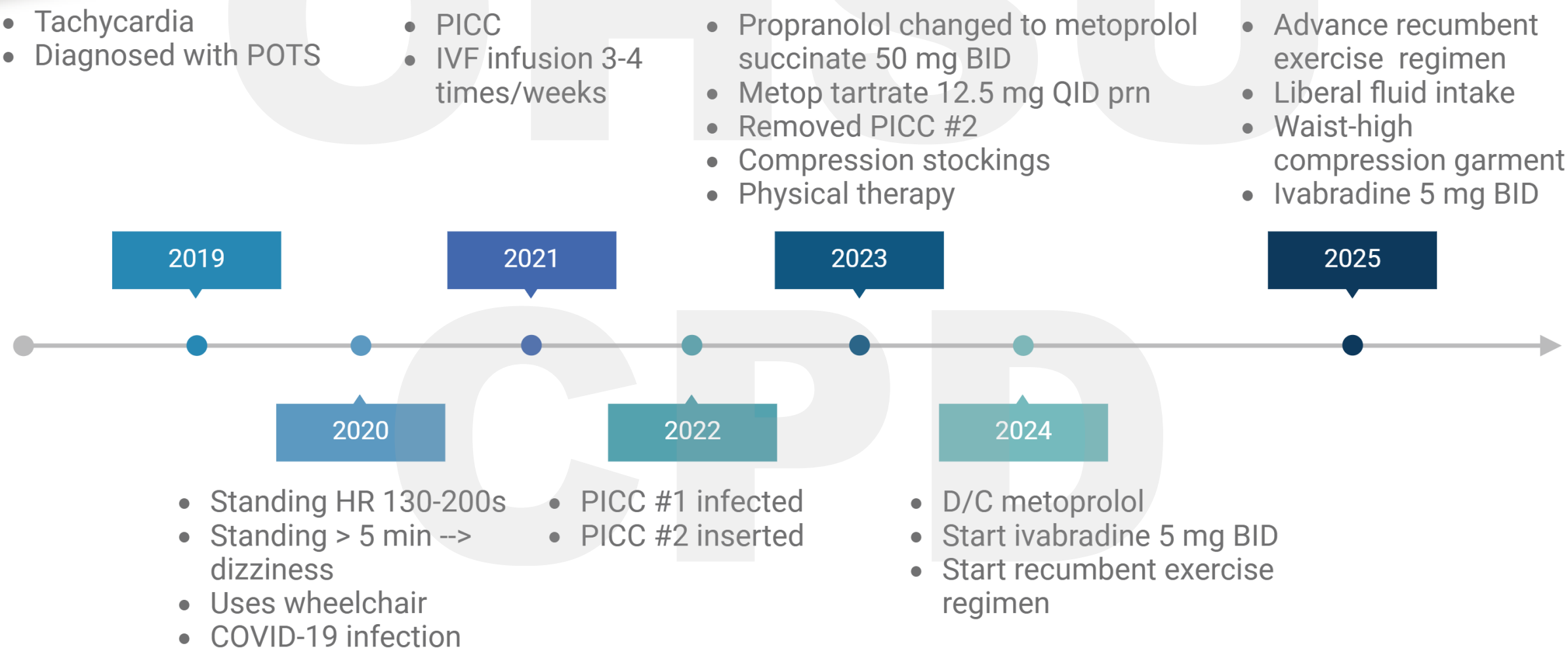


- Standing HR 130-200s
- Standing > 5 min --> dizziness
- Uses wheelchair
- COVID-19 infection

- PICC #1 infected
- PICC #2 inserted

- D/C metoprolol
- Start ivabradine 5 mg BID
- Start recumbent exercise regimen

Case - Management



Key Points

- Etiology and mechanisms of POTS are not fully understood
- 80% occur in premenopausal women
- Heterogenous pathophysiology
- Features overlap with other conditions
- Clinical diagnosis: history, exam, basic diagnostic tests
- Graded treatment:
  - Avoid known triggers
  - Optimize fluid and salt intake
  - Compression garments
  - Regimented exercise program
  - Pharmacotherapy for refractory symptoms