Blood pressure woes

Jasmine Tan

Greenlane Medical Specialists

Mr FT 68M
Labile BP

Background

1. Hypertension (2016)
   - CKD G2 A1
2. Coronary artery disease
   - C. angiogram (2022) – severe mid-LAD disease. Severe diagonal and OM1 requiring PCI
   - TTE (2022) – Normal LV size and function. Mild LVH; Mild diastolic dysfunction. Mildly dilated LA. No significant valvular abnormalities. Normal size aortic root.
   - Family history of CV events
3. Tachycardia, undefined
4. Dyslipidaemia
5. T4 N2 nasopharyngeal SCC (2016)
   - Neoadjuvant chemo and radiotherapy
6. Non-smoker, no excess alcohol

Medications

Metoprolol CR 47.5 mg nocte

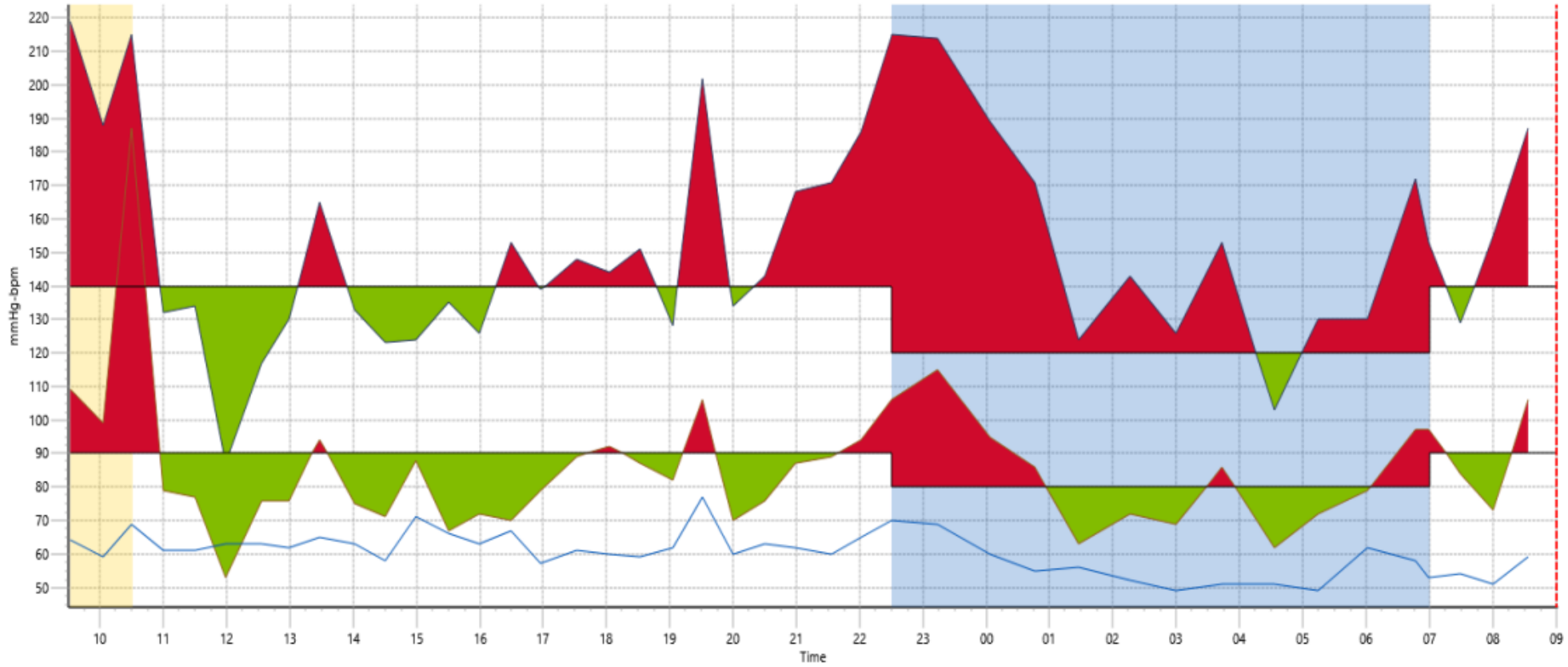
Aspirin EC 100 mg daily

Rosuvastatin 20 mg daily

Cetrizine 10 mg daily

24 hour ABPM

	Mean	Std. Dev.	Max (time)	Min (time)	CV
SYS (mmHg)	152	+/-31.9	219 (09:31)	87 (11:58)	21.0%
DIA (mmHg)	86	+/-21.2	187 (10:29)	53 (11:58)	24.7%



Overall average BP 152/86 mmHg (<130/80 mmHg); awake average BP 151/86 mmHg (<135/85 mmHg); asleep average BP 156/85 mmHg (<120/70 mmHg). Dip -3.4% SBP, 2.2% DBP

- Engineer, monitors home BP
- Previously well managed hypertension
- New orthostatic symptoms since 2022 post coronary angiogram
  - Post prandial symptoms, especially with high carbohydrate intake
  - Flushing and palpitations
  - Paroxysmal hypertension

- No tremors, no new onset diarrhea

- Amlodipine 2.5 mg commenced at night following 24 hour ABPM

On examination

BMI 22.2 kg/m^2

Seated BP 167/102 mmHg and standing 143/96 mmHg

No significant BP difference between either arm

HR 79 regular, no radial-radial delay

Heart sounds dual, no added

No tremors

Small thyroid gland, no bruits

No renal renal bruits

Strong pedal pulses

Laboratory results

Aldosterone 130 pmol/L; renin 2 mU/L; aldo/renin ratio 65; potassium 4.2 mmol/L

Sodium 134 mmol/L; creatinine 90 umol/L; eGFR 75 ml/min; urine ACR 1.5 mg/mmol

Calcium 2.35 mmol/L

TSH 3.1 mU/L

24 hour urine metanephrines normal

HbA1c 44 mmol/mol

Ms HI 74 female

Orthostatic hypotension

Background

1. Parkinsons disease
   - Associated autonomic orthostatic hypotension on midodrine, previously on fludrocortisone
2. Acute onset encephalopathy with features of PRESS on MRI brain (Aug 2017)
   - Presented with hypertensive emergency, on fludrocortisone and midodrine
   - Use of citalopram and quetiapine
3. Paroxysmal AF with 2 unsuccessful ablation
4. Amiodarone induced thyroiditis type 2
5. Osteopenia, previous single dose of Aclasta
6. Non smoker

Medications

Midodrine 2.5 mg mane

Sinamet 25/100 mg TDS

Colecalciferol 1.25 mg monthly

Flecainide 100 mg mane, 100 – 200 mg nocte

Rivaroxaban 20 mg daily

Mirtazapine 30 mg nocte

Gabapentin 300 mg TDS ?? Neuropathic pain

- Frequent light-headedness while mobilizing around especially in the morning
- Aware of postural symptoms and sits down quickly
- Worse after meals
- No previous falls or fractures; independent with ADLs and drives
- Had stopped fludrocortisone as did not noticed improved symptoms

- Sleeps on an incline; has trialed compression stockings and abdominal band
- Tries to keep up with oral fluids
- No history of CV disease
- Non smoker
- Drinks minimal alcohol

On examination

Weight 62.7 kg, BMI 23 kg/m^2

Seated BP 95/68 mmHg, 91/63 mmHg (left arm) and 100/73 (right arm)

Standing BP 68/56 mmHg

Heart sounds dual no murmurs

Clinically dry

No carotid bruits

No palmar hyperpigmentation

No pedal oedema, dry skin

Laboratory tests

LDL 3.4 mmol/L, rest of lipid profile normal

Sodium 134 mmol/L (135 – 145); creatinine 66 umol/L; eGFR 79ml/min

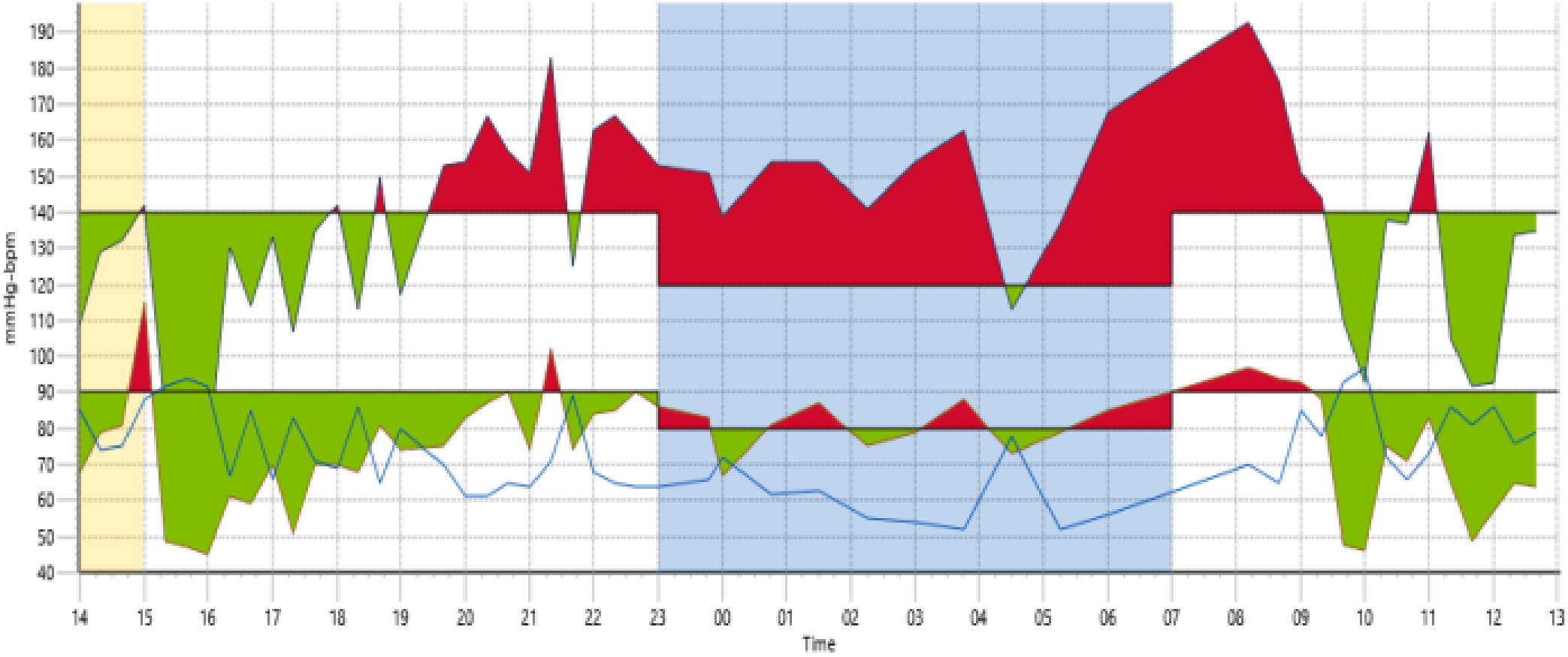
urine ACR 1.3 mg/mmol

Calcium 2.36 mmol/L

TSH 1.3 mU/L

24 hour ABPM

	Mean	Std. Dev.	Max (time)	Min (time)	CV
SYS (mmHg)	137	+/-27	193 (08:12)	71 (16:00)	19.7%
DIA (mmHg)	75	+/-15.4	115 (15:00)	45 (16:00)	20.5%



Overall average BP 137/75 mmHg (<130/80 mmHg); awake average BP 133/73 mmHg (<135/85 mmHg); asleep average BP 148/80 mmHg (<120/70 mmHg). Dip -10.9% SBP, -9.7% DBP

- Increased Midodrine 5 mg 8am, 5 mg 1 pm
- Restarted fludrocortisone 100 mcg 9am
- Bolus 500 ml water on waking
- High waisted underpants
- Gabapentin reduced and taken at night due to symptomatic neuropathic pain

- Subsequent follow ups:
  - Multiple adjustments to Midodrine dose and timing
  - Good and bad days
  - 3 falls, no fractures

MR FT

- New onset labile BP
- Post prandial hypotension
- Previous neck irradiation

MS HI

- Autonomic orthostatic hypotension
- Nocturnal hypertension
- Post prandial hypotension
- Parkinson’s disease

24 hour ABPM

Helpful to circumvent some of the limitations of office & home BP measurements

Provides insights to short-term BP control and circadian effect on BP

Main measurements with prognostic value:

Average 24 hour, daytime, and night-time BP
Pulse pressure
Nocturnal dipping status
BP variability

ABPM components	Prognostic implications
Average ambulatory daytime and night-time BP	• Strongly predicts for major CV events and mortality when compared with overall average BP <135-140/85–90 mmHg • Night-time ambulatory BP superior to daytime BP to predict major CV events (PUMA, PAMELA study)
Pulse pressure (difference between SBP and DBP)	• Increased rates of CV events in 3 tertiles (≤45 mmHg, 46–53 mmHg, and >53 mmHg) 1.19, 1.81, and 4.92 respectively. • Increased rates of fatal events 0.11, 0.17, and 1.23 (p< 0.01)
Nocturnal dipping status (> 10% average daytime BP)	• Associated with target organ damage (CKD, LVH) • Prognosis appear to be significant in the absence of CKD and LVH
BP variability (SD of BP measurements over day- and night-time median BP)	• Associated with target organ damage • SD > 10.8 mmHg of night-time SBP is an independent predictor for CV events

Diagnostics (Basel). 2023 Apr 30;13(9):1601.

BP variability

N= 2,649; Follow up = 6 years
Mean age 51 years, 47% F
6.9% Diabetes

BP variability estimated by SD of day or night-time SBP and DBP.
Low: ≤ group median; High: > group median

Low BPV vs. high BPV in both day and night- time

167 CV; 122 Cerebrovascular (11% of group)

High BPV associated with both increased CV and cerebrovascular events

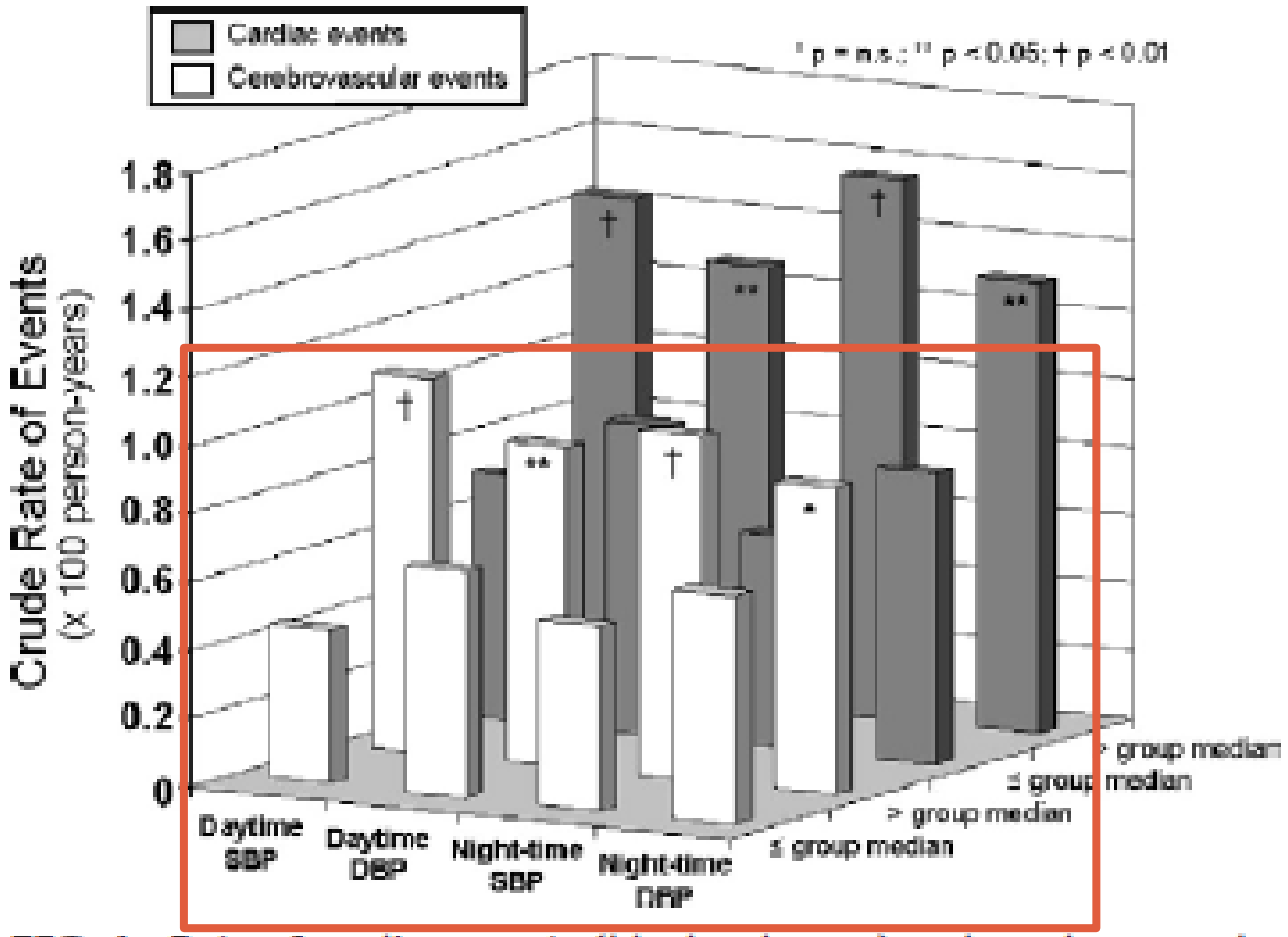


FIG. 1. Rate of cardiac events (black columns) and cerebrovascular (white columns) events according to high or low blood pressure variability.

Am J Hypertens 2007; 20:154–161

Am J Hypertens 2007; 20:154–161

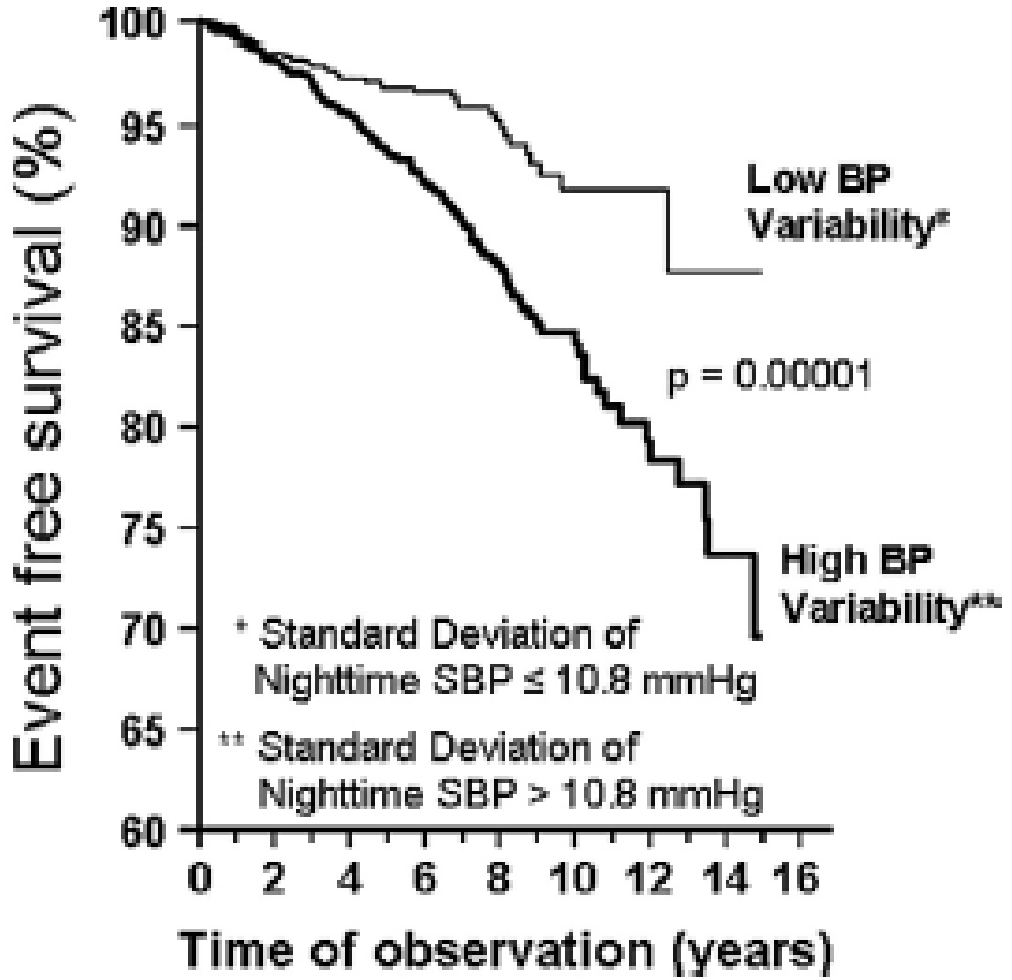


FIG. 4. Cardiac events during follow-up in hypertensive subjects with low and high variability of night-time systolic blood pressure at entry.

Multivariate analysis: 51% higher risk of cardiac events associated with high BP variability at night remained significant (p=0.024)

Antihypertensive agents and effect on BP variability

Table 1 SBP trough-to-peak ratios for antihypertensive monotherapies

Drug class	Monotherapy	SBP T:P ratio or range thereof	$t_{½}$, or range thereof (h)	Source
ARB	Azilsartan	0.95[a]	11	58, 81
	Telmisartan	0.92[b]	Up to 24	62, 82
	Candesartan	0.82[a]	9	58, 83
	Olmesartan	0.60–0.80[c]	13	65, 65
	Valsartan	0.65[a]	6	66, 84
	Losartan	0.62[a]	2 (6–9 for metabolite)	62, 85
	Irbesartan	0.57[a]	11–15	62, 84
CCB	Amlodipine	0.85[a]	35–50	70, 86
	Diltiazem SR	0.20–0.80[a]	6–8	87, 88
	Nitrendipine	0.10–0.80[a]	12–14	87, 89
ACE inhibitor	Lisinopril	0.63[d]	12.6	90, 91
	Ramipril	0.50–0.63[a]	13–17	87, 92
	Captopril	0.25[a]	2	87, 93

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; SBP, systolic blood pressure; SR, sustained release; $t_{½}$, plasma elimination half-life; T:P, trough:peak ratio.
[a]Mean values.
[b]Ratio of reduction in trough BP to reduction in maximal diurnally-adjusted BP.
[c]Not mentioned.
[d]Median value.

Trough: peak ratio close to 1, indicates optimal therapeutic coverage of the agent

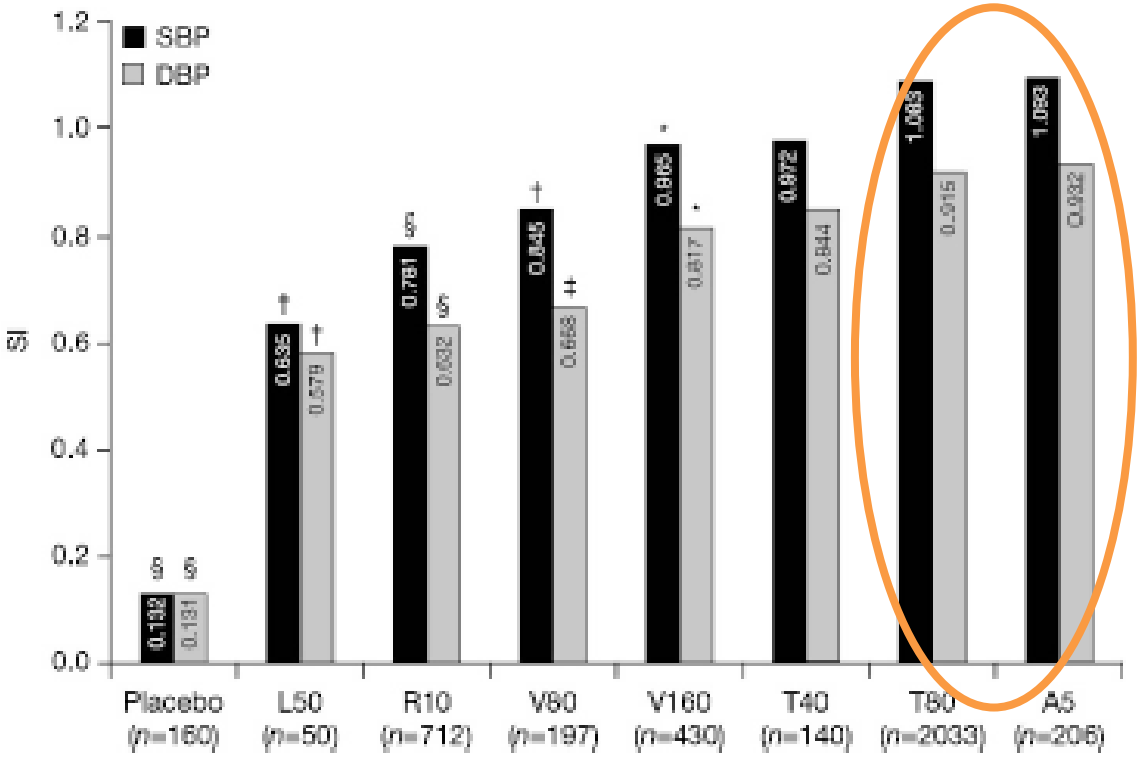


Figure 3 Comparison of the 24 h SBP/DBP SIs for seven antihypertensive monotherapies. A5, amlodipine 5 mg; DBP, diastolic blood pressure; L50, losartan 50 mg; R10, ramipril 10 mg; SBP, systolic blood pressure; T40, telmisartan 40 mg; T80, telmisartan 80 mg; V80, valsartan 80 mg; V160, valsartan 160 mg. *$P<0.05$; †$P<0.01$; ‡$P<0.001$; §$P<0.0001$ P-values indicate lower SI *vs.* telmisartan 80 mg. Data are based on nine trials involving 3928 monotherapy-treated patients.

Hypertension Research (2014) 37, 187–193

Mechanism of BP variability

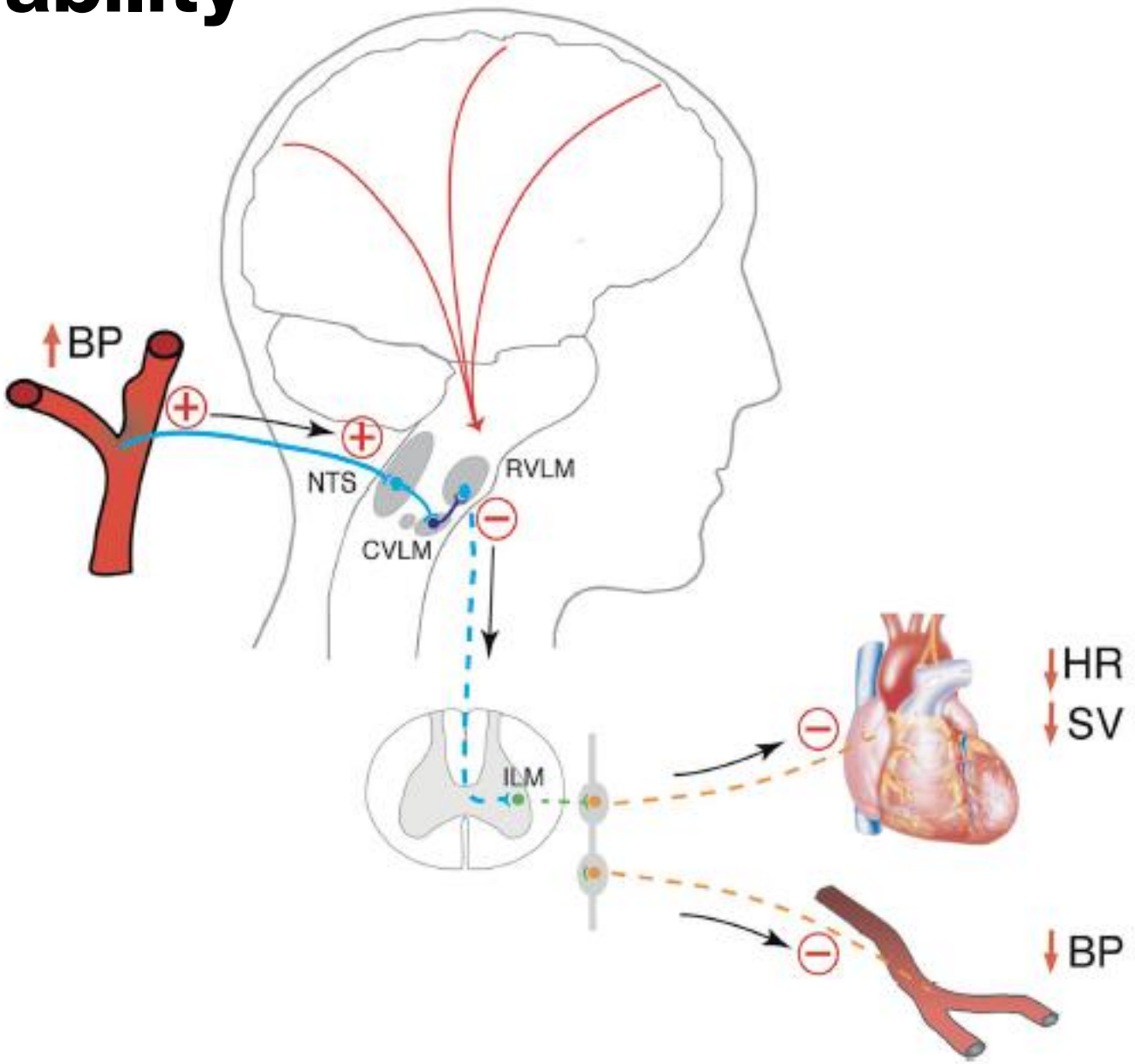
- Baroreflex functions to regulate BP

- Increase in BP → (-) afferent baroreceptors in the carotid sinus → activates nucleus tractus solitarri (NTS) of the brainstem → inhibits the SNS at the medulla:

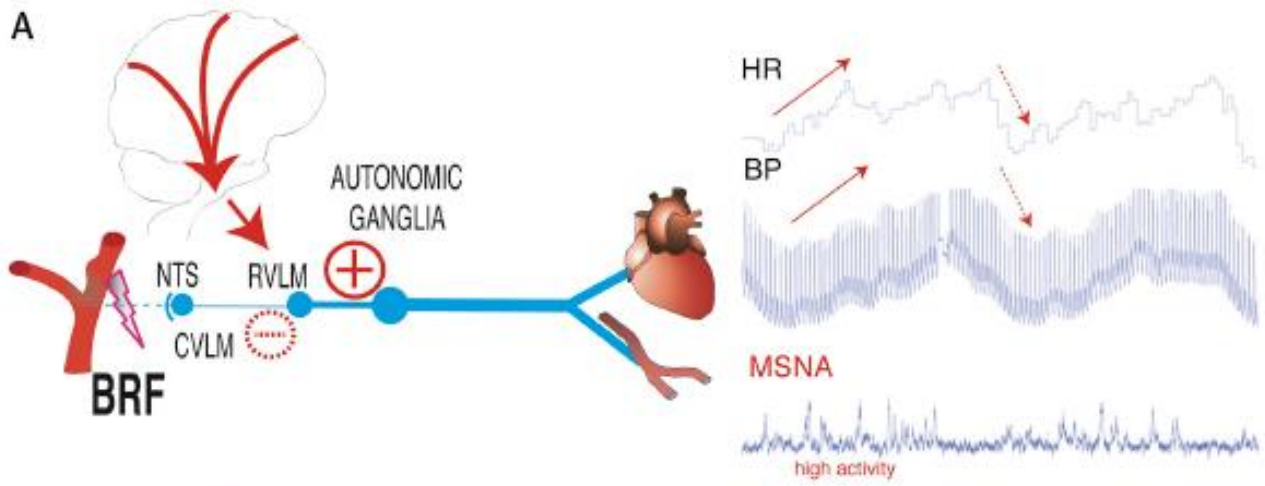
(1) Reduce sympathetic tone

(2) Decrease efferent fibres in the heart and blood vessels

- Decrease in BP → (+) baroreceptors → Compensatory Upregulation of sympathetic tone and reflex tachycardia



Mechanisms of BP variability



- Afferent baroreflex failure

BAROREFLEX FAILURE

- Exaggerated BP responses to pressor and depressor stimuli
  - Paroxysmal hypertensive surge and increase in HR

  (triggered by mental stress or exertion)
  - Facial flushing during hypertensive crisis
  - Symptomatic hypotensive episodes
  - Orthostatic hypotension

AUTONOMIC FAILURE

- Characterized by supine hypertension and orthostatic hypotension
- Hypersensitivity to pressor agents or depressor stimuli

Afferent baroreflex failure

- Causes of afferent baroreflex failure:
  - Radiation therapy for head and neck cancer most common
  - Bilateral resection of neck tumours (with damage to carotid sinus nerve)
  - Familial dysautonomia (hereditary sensory and autonomic neuropathy type 3)
  - Brainstem lesions
  - Carotid endardectomy (usually transient BP lability post op)

- Overt baroreflex failure occurs in a minority of patients, usually years after the procedure, secondary to radiation injury and fibrosis involving the carotid sinus

Diagnosis

- 24 hour ABPM

- Valsalva maneuver response may be supportive:
  - No increase in heart rate during the drop in BP induced during strain, and
  - No decrease in heart rate during the BP overshoot triggered during release

- Cold pressor response (immersion of hand in ice water for 60–90 seconds) to document an exaggerated pressor response specific for afferent baroreflex failure

Management
Hypertension

- Hypertension in baroreflex failure is driven by sympathetic surges
- Central sympatholytics should be the mainstay of the treatment of labile hypertension & paroxysmal hypertensive crises
  - Long-acting central sympatholytics (methyldopa, clonidine) or combined alpha- and beta- blockers at low doses initially, then titrated to avoid hypotensive episodes
- Addressing mental stress which is the most common trigger of hypertensive crisis in afferent baroreflex failure (benzodiazepines, cannabinoids)
- High CHO drink to control hypertensive episodes
- In those with pre-existing essential hypertension, or CV disease
  - Avoiding agents that can worsen orthostatic hypotension (ie diuretics, CCB)

Cleve Clin J Med 2010; 77(5): 298 – 306.

Autonomic/baroreflex failure

- Orthostatic hypotension
  - At least 20 mmHg SBP drop, or 10 mmHg DBP drop within 3 min of standing
  - Postural hypotension is detected by arterial baroreceptors → reflex tachycardia and vasoconstriction (compensatory)→ restores normotension in upright position

  - Common in elderly people; up to 68% in institutionalized patients and 6% in community
    - Neuropathic (diabetic or autoimmune neuropathies) or central (Multiple system atrophy, Parkinson Disease)
    - Non neurogenic causes (cardiac impairment, dehydration)
    - Drugs (diuretics, alpha blockers, CCB, tricyclic antidepressants, levodopa)

Cleve Clin J Med 2010; 77(5): 298 – 306.

Management
Autonomic orthostatic Hypotension

- Non pharmacological treatment options in the form of low sympathetic tone
  - 500 - 1000 ml cold water bolus (elicits pressor effect)
  - Abdominal binder compression
  - Muscle contraction from waist down (30 seconds/time) (ie toe raising, leg crossing & contraction, leg elevation, bending at the waist, slow marching in place)

Cleve Clin J Med 2010; 77(5): 298 – 306.

Management
Autonomic orthostatic Hypotension

- **Midodrine**
  - Vasopressor which is safe when treating neurogenic orthostatic hypotension
  - Need to ensure patient well hydrated
  - Duration of action: 2-4 hours; time in the morning, before lunch and mid-afternoon
  - Risk of nocturnal supine hypertension.
  - Omission of last dose if supine or sitting BP > 180/100 mmHg
  - Start dose 5 – 10 mg TDS
  - SE: supine hypertension, scalp parathesia, goose bump
- **Fludrocortisone**
  - Mineralocorticoid with pressor effect, expanding plasma volume and increase alpha adrenoreceptor sensitivity
  - Useful in the setting of low plasma volume in spite of salt supplementation or those with inadequate reponse to midodrine
  - 0.1 – 0.2 mg/day; 0.4 – 0.6 mg/day in refractory orthostatic hypotension

Cleve Clin J Med 2010; 77(5): 298 – 306.

Differential

- Pseudopheochromocytoma
  - Paroxysmal hypertension
  - Presents as dramatic episodes of abrupt and severe BP elevation
  - No biochemical evidence of catecholamine excess

Management with alpha1 and beta blockers

Psychological support to manage stress

Antidepressant drug therapy

- Postural orthostatic tachycardia syndrome

Cleve Clin J Med 2010; 77(5): 298 – 306.

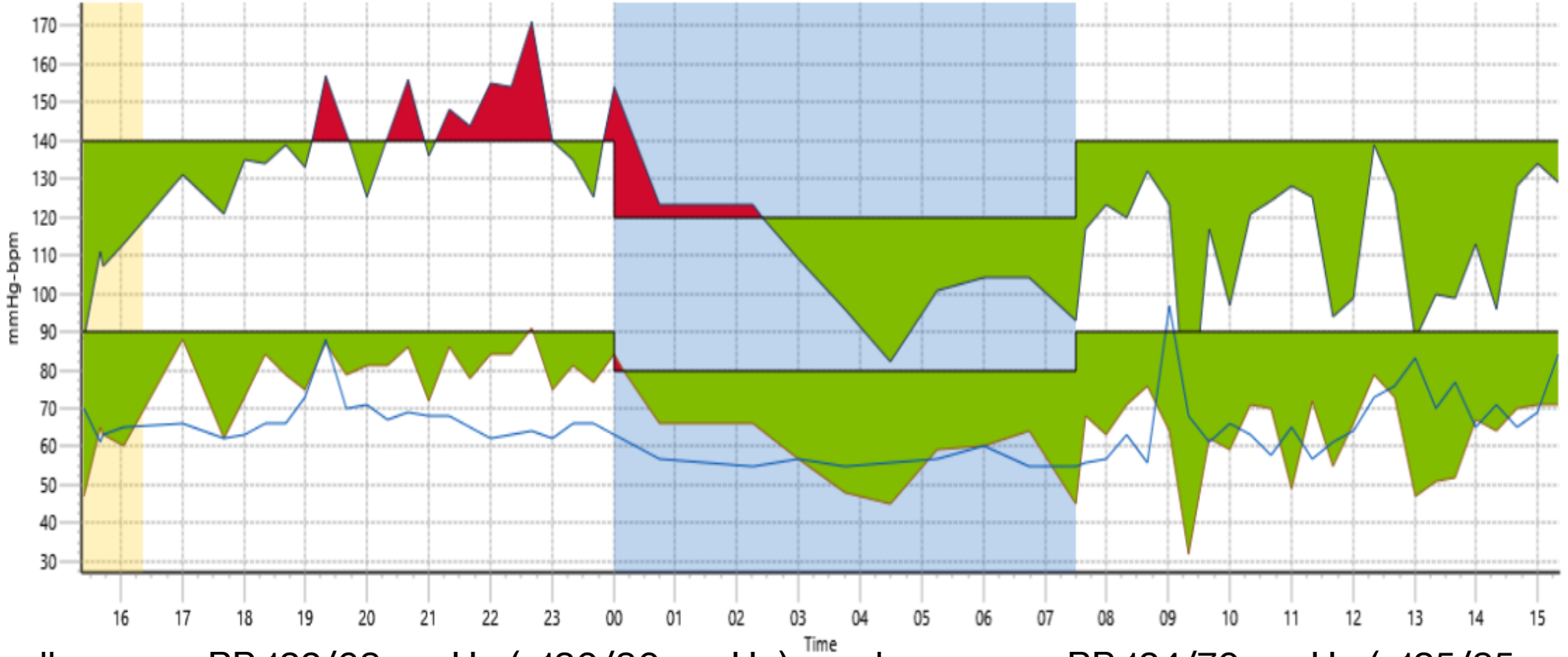
Back to our patients

MR FT

- Labile hypertension – baroreflex failure
- Commenced on Doxazosin 0.5 mg 8am, 0.5 mg 3 pm, 0.5 mg 10pm
- Changed Metoprolol to Bisoprolol 1.25 mg mane, 2.5 mg nocte
- Less fluctuations on home BP monitoring

24 hour ABPM
MR FT

	Mean	Std. Dev.	Max (time)	Min (time)	CV
SYS (mmHg)	122	+/-21.8	171 (22:40)	58 (09:20)	17.9%
DIA (mmHg)	68	+/-13	91 (22:40)	32 (09:20)	19.1%



Overall average BP 122/68 mmHg (<130/80 mmHg); awake average BP 124/70 mmHg (<135/85 mmHg); asleep average BP 111/61 mmHg (<120/70 mmHg). Dip 10.5% SBP, 12.2% DBP

Back to our patients

MR FT

- Labile hypertension – baroreflex failure
- Commenced on Doxazosin 0.5 mg 8am, 0.5 mg 3 pm, 0.5 mg 10pm
- Changed Metoprolol to Bisoprolol 1.25 mg mane, 2.5 mg nocte
- Less fluctuations on home BP monitoring

MS HI

- Autonomic orthostatic hypotension
- Nocturnal hypertension associated with midodrine use
- Still continues to have daytime postural hypotension
- Restarted fludrocortisone, increase oral fluids
- Titrate midodrine dose, latest taken at 2pm
- Started Verapamil

24 hour ABPM
Ms HI

	Mean	Std. Dev.	Max (time)	Min (time)	CV
SYS (mmHg)	140	+/-26.4	196 (18:30)	85 (17:50)	18.9%
DIA (mmHg)	78	+/-14.9	109 (03:00)	44 (12:10)	19.1%

Overall average BP 140/78 mmHg (<130/80 mmHg); awake average BP 137/76 mmHg (<135/85 mmHg); asleep average BP 150/84 mmHg (<120/70 mmHg). Dip =9.8% SBP, -10.1% DBP

Summary

- Afferent baroreflex failure and autonomic failure remain challenging conditions to manage

- Night time BP variability is associated with increased CV risk; but may not be as prognostic in the setting of CV risk factors (ie CKD/LVH)
  - Reflects diffuse atherosclerotic processes
  - Associated with progression of organ damage

- 24 hour ABPM helpful to identify BP variability and nocturnal hypertension and affect treatment

- Goals of treatment is to reduce BP variability to improve QoL, rather than normalise BP

J Am Coll Cardiol. 2019 December 10; 74(23): 2939–2947.

Thank you
Questions?