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CHALLENGES IN ACHIEVING BP CONTROL IN SEVERE CKD

1. No specific recommendations on how HPT should be treated in this context
   - prospective RCTs are lacking
2. The pharmacology tolerability of BP medications change in advanced CKD
   - increases incidence of drug-induced side effects (eg. Peripheral oedema, hyperkalemia, worsening of GFR)
3. Tendency to resistant HT
   - multiple pathogenic mechanisms.
4. Patients with CKD have high pill burdens
   - up to >20 pills per day, depending on the severity of their disease, more tendency to poor medication adherence in advanced CKD

   (Burnier et al NDT 2015)

WHAT IS THE TARGET BP IN CKD?

Guideline: Malaysian CKD CPG 2011

BP in CKD without proteinura	BP in CKD with proteinura
<140/<90	<130/<80

Standardized office BP measurement is recommended

MANAGEMENT OF HYPERTENSION IN SEVERE CKD

1. NON-PHARMACOLOGY

Salt restriction

i. Most CKD patient s have salt-sensitive HPT
ii. Declining nephron number -> Limited ability for rapid NaCl excretion
iii. Limitation of sodium intake to 5-6g NaCl/day is effective to lower BP and albuminuria through every stage of CKD
iv. Excess salt
   - exacerbates resistance to antihypertensive treatment.
   - Dampens antiproteinuric effects of ACEi and ARBs
   - Diminishes night-time dipping of BP in salt-sensitive HPT

Practical advice to reduce dietary sodium

Eat more fresh foods, especially fruit and vegetables

Read labels: Choose foods with low salt labels or brands with lowest percentage of sodium on the food label, eg <200mg Sodium or <10% daily value per serving

Wash canned foods/salty foods in water before use

Use spices to add taste

Less eating outside at restaurants/fast food outlets

Use less sauces on food

Avoid salty foods eg ikan masin/pickles/belacan/cencaluk/etc

- Not easy to change pt's behaviour

Other Lifestyle Therapies in Hypertensive Adults

Intervention	Target	
Dietary patterns	DASH diet	
Weight loss	BMI <25 kg/m²	
Alcohol restriction	≤ 2 drinks/day	
Physical activity	30-60 minutes 4-7 days/week	
Smoking cessation	Smoke free environment	
Waist Circumference	**Men**	**Women**
- Europid	<94 cm	<80 cm
- South Asian, Chinese	<90 cm	<80 cm

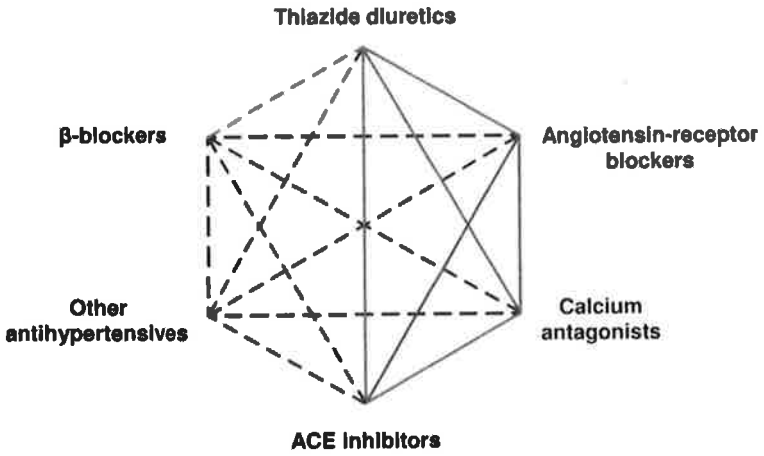
Diet and BP control in severe CKD

- Patients with hypertension and a preserved GFR (GFR>60 mL/min/1.73m2)
  - increasing the potassium content of the diet lowers BP and reduces the incidence of stroke (Aburto et al 2013)
- The situation is very different in CKD patients with stages 3b–4
  - may already have slightly elevated serum potassium levels at baseline
    → v. high risk of hyperkalaemia, especially for patients with type 2 diabetes
- If eGFR < 45 mL/min/1.73m², avoid prescribing potassium supplements or drugs ↑ing serum potassium (such as non-steroidal anti-inflammatory drugs)

2. PHARMACOLOGICAL TREATMENT

a. Multiple drugs are needed to achieve target BP
b. Rational combinations

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) - J Hypertension 2013;31:1281-1357



Green continuous lines: preferred combinations; **green dashed line**: useful combination (with some limitations); **black dashed lines**: possible but less well tested combinations; **red continuous line**: not recommended combination. Although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

c. Chronotherapy to try to restore nocturnal dips and smoothen BP control

Bedtime Dosing of Antihypertensive Medications Reduces Cardiovascular Risk in CKD (Hermida et al, JASN 2011)

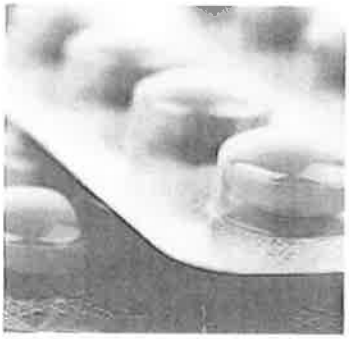
Results :

- Follow-up : 5.4 years
- Pts who continued to take all antihypertensive drugs in the morning - No cha nocturnal BP nor proportion of nondippers
- Pts with at least 1 bedtime medication
  - significant changes in * nocturnal BP (from 129/73 to 117/65 mmHg)
  * % of nondippers (65% → 41%)
  * major vascular events - MI, stroke, or CV death (2.7 vs 7.8 %)

Review medications

1/ Look out for other medications that interfere with BP control

- Nonsteroidal anti-inflammatory agents
- Sympathomimetics (diet pills,nasaldecongestants)
- Stimulants eg methylphenidate, amphetamines
- Oral contraceptives
- Licorice
- Erythropoeitin, Cyclosporine/FK506, Steroids



Remembering advanced CKD pts are at higher risk of nonadherence. be aware of potential barriers to adherence

Barriers to adherence	Potential Solutions
Socioeconomic factors	Low-cost, generic medications
Treatment complexity	Long acting, Once-daily medications /Fixed-dose Combination formulations, unit-of-use packaging eg blister packs
Cognitive problems e.g. memory deficits, physical problems	Family support, written instructions, medication posters, pill boxes
Adverse medication effects	Patient education, advice to contact the medical facility if any s/e arise, and address the complaints
Motivation , commonly affected by - Depression - lack of belief in the benefit of treatment - lack of insight into illness	Patient education(ideally by *multidisciplinary team)* Shared decision-making Patient empowerment for self-management including use of HBPM, patient apps etc. Telemedicine consults Rx depression

RASi (ACEi or ARBs) in RX of HT in CKD

NB : KDIGO 2021 recommendations extends only to CKD G1-G4 - there are no RCTs for G5

Recommendation 3.2.1: We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.

Recommendation 3.2.2: We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes *(2C)*.

Recommendation 3.2.3: We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes *(1B)*.

Practice Point 3.2.1: It may be reasonable to treat people with high BP, CKD, and no albuminuria, with or without diabetes, with RASi (ACEi or ARB).

Practice Point 3.2.2: RASi (ACEi or ARB) should be administered using the highest approved dose that is tolerated to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Practice Point 3.2.3: Changes in BP, serum creatinine, and serum potassium should be checked within 2–4 weeks of initiation or increase in the dose of a RASi, depending on the current GFR and serum potassium.

Practice Point 3.2.4: Hyperkalemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi.

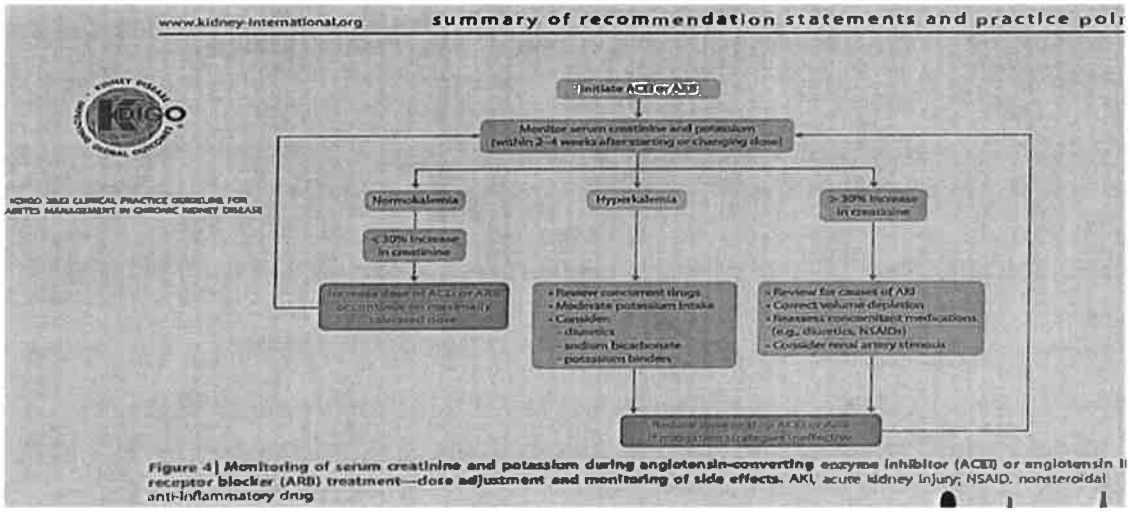


Figure 4 | Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) treatment—dose adjustment and monitoring of side effects. AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug

Issues with the use of RAS blockers in advanced CKD

- risk of hyperkalaemia, which is known to increase the occurrence of cardiac events and sudden deaths. In CKD stages 4 and 5, the incidence of hyperkalaemia defined as a plasma K > 5.5 mmol/L can reach 30%.
- **Haemodynamic effects on eGFR -> question of whether withdrawal of RAS blockers would gain some kidney function and delay the need of kidney replacement therapy.**

Diuretics in severe CKD

- **General concept: for patients with GFR<30 mL/min/1.73m², thiazide and thiazide-like diuretics are quasi-ineffective**
- **In advanced CKD, most guidelines recommend the use of short (furosemide) or long-acting (torasemide) loop diuretics.**
- **However, this dogma has been challenged as an increasing number of small studies have demonstrated that thiazide diuretics can lower BP even in advanced CKD**
- **A loop diuretic can be combined with chlorthalidone to improve BP control in patients with advanced CKD stage 4 and uncontrolled/ resistant hypertension (Agarwal et al, NEJM 2021)**

NB : ** Increase in dose, especially in more advanced CKD

Calcium Channel Blockers (CCBs) in CKD

- Classical 1st and 2nd generation DHP calcium antagonists, such as nifedipine or amlodipine cause afferent arteriolar vasodilation→
  ↑ intraglomerular pressure and hence possibly ↑ GFR
  also ↑ proteinuria (unless they induce a marked reduction in BP)
- In large CKD clinical trials their impact on kidney progression was repeatedly inferior to that of RAS blockers, despite a comparable reduction in BP (Zanchi et al 1995)
- In contrast, DHP calcium antagonists of the third generation such as lercanidipine, (acts directly on the afferent and efferent renal arteriole) have a different effect on kidney function as they lower proteinuria (Burnier 2013)

Issues with Calcium Channel Blockers (CCBs) in severe CKD

- The most prevalent s/e of CCB is peripheral oedema
  - may compound the problems of oedema in CKD due to Na+ and water retention
- Verapamil and Diltiazem, a non-DHP calcium antagonists, lower proteinuria and BP in patients with CKD
  - Diltiazem is a weaker antiHTive agent & has > 600 drug interactions described

Beta blockers

- In many recent HT guidelines, beta-blockers have been relegated to the 4th or even 5th line of therapy, unless there is a cardiac indication such as CHD or heart failure.
- However the prescription of beta- blockers remains high in the general population & patients with CKD, even in the absence of cardiac comorbidity

- may be partly justified : activity of the sympathetic nervous system is ↑d in all CKD stages and particularly when GFR is < 30 mL/ min/1.73m²

(Penne et al 2009; Converse et al 1992)

Mineralocorticoid receptor antagonists

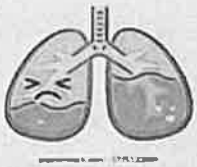
- Useful in resistant HT (ASPIRANT, PATHWAY-2 trials)
- Can reduce risk of renal disease progression in DKD and non-diabetic nephropathies (2 systematic reviews and metanalyses : Currie et al 2016; Cochrane Database SR 2020)
- Main limiting factor in advanced CKD is hyperkalaemia , especially if patients are on RASb
- However newer potassium binders e.g. patiromer have made it possible for continuation of MRA therapy

Sympatholytic Agents – moxonidine , clonidine , methyldopa

- The place of sympatholytic agents in the management of patients with hypertension and advanced CKD is poorly defined
- No large RCTs to demonstrate that this class of agents is able to reduce CV events or slow the progression of kidney disease
- Relatively safe in patients with CKD.

Vasodilators – Minoxidil, Hydrallazine

- Fluid retention and reflex tachycardia may occur, hirsutism (minoxidil)



- Diuretics and Beta blockers should be on board

Take home messages : #1

Achieving BP control in advanced CKD will require

1. Multiple antihypertensive agents - appropriate combinations & doses
2. Multidisciplinary care
3. Measures to promote medication adherence including
   - simplification of prescriptions
   - good patient education and engagement.
4. Referral/consultation with Nephrologists/physicians with special interest in HT if BP remains uncontrolled

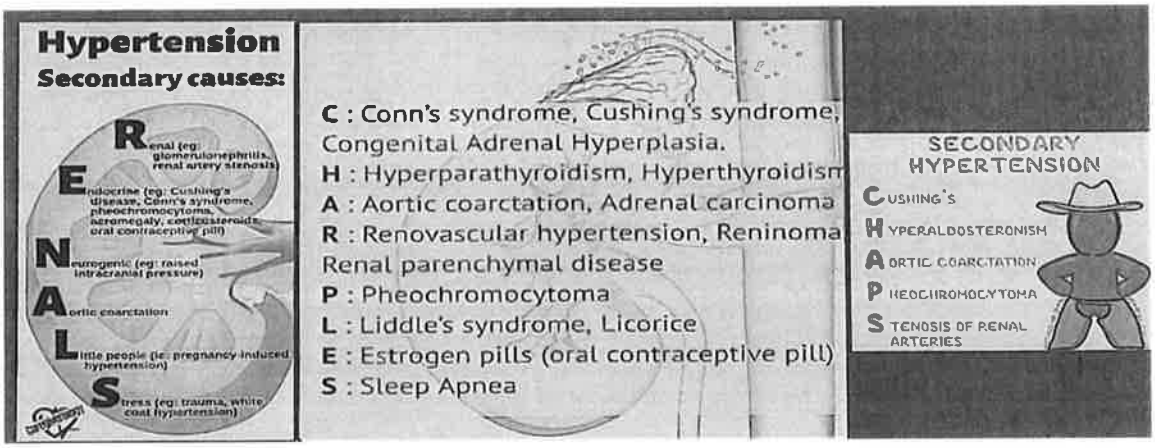
SECONDARY HYPERTENSION

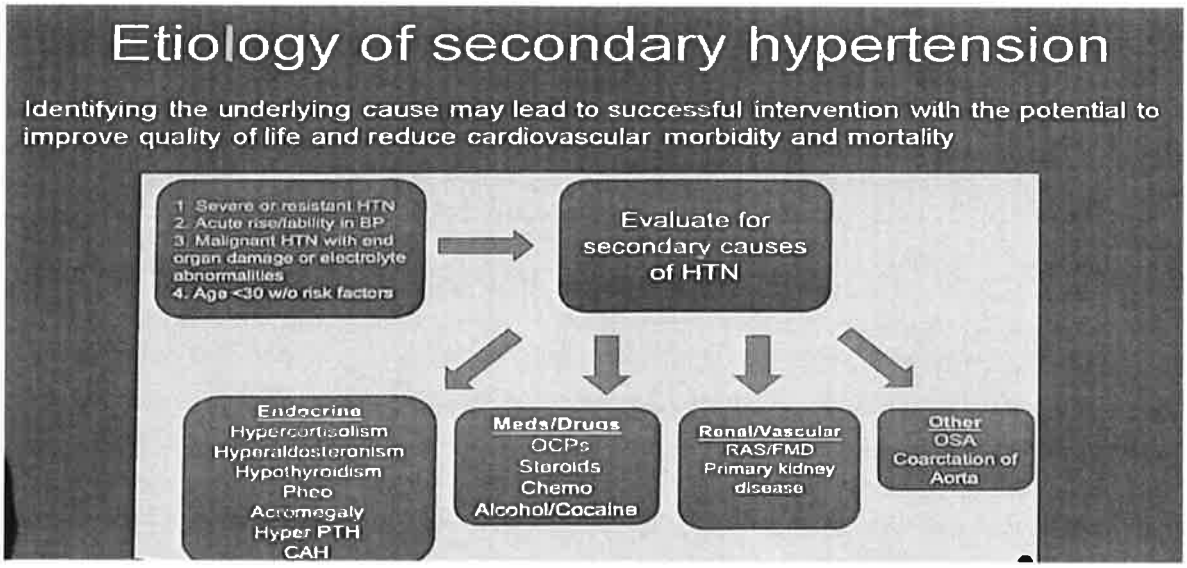
Secondary Hypertension: Definition

- Secondary hypertension is defined as elevated blood pressure secondary to an **identifiable cause**
- Prevalence is low, a specific cause can be identified in **5%–10%** of hypertensive patients
- Often affects **younger patients, 70- 85% HPT in < 12 years**
- and those with **resistant or refractory hypertension**
- Early diagnosis and the institution of appropriate targeted treatment have the **potential to cure** hypertension in some patients, improve BP control/reduce the no. of prescribed antihypertensive medications

Resistant Hypertension

- Affects around **10%** of hypertensive individuals
- Seated office BP **>140/90 mmHg in a patient treated ≥ 3 antiHPT medications** at optimal (or maximally tolerated) doses including diuretic
- Excluding **pseudoresistance** (poor BP measurement technique, white coat effect, nonadherence and suboptimal choices in antihypertensive therapy) as well as the substance/drug-induced and secondary HPT
- Increases the risk of coronary artery disease, chronic HF, CVA, ESRD and all-cause mortality
- Approximately 50% of patients with resistant HPT have pseudoresistance

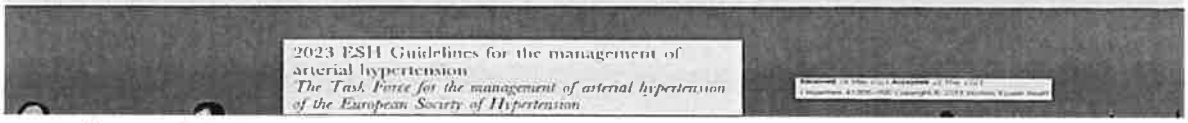




Secondary Hypertension - when to suspect? ESH 2023 Guidelines

TABLE 13. Patient characteristics that should raise the suspicion of secondary hypertension

Younger patients (<40 years) with grade 2 or 3 hypertension or hypertension of any grade in childhood
Sudden onset of hypertension in individuals with previously documented normotension
Acute worsening of BP control in patients with previously well controlled by treatment
True resistant hypertension hypertension
Hypertensive emergency
Severe (grade 3) or malignant hypertension
Severe and/or extensive HMOD, particularly if disproportionate for the duration and severity of the BP elevation
Clinical or biochemical features suggestive of endocrine causes of hypertension
Clinical features suggestive of renovascular hypertension or fibromuscular dysplasia
Clinical features suggestive of obstructive sleep apnea
Severe hypertension in pregnancy (>160/110 mmHg) or acute worsening of BP control in pregnant women with preexisting hypertension



Clinical Approach to secondary HPT - Other Causes

Secondary Hypertension	Clinical History and Physical Examination	Basic Biochemistry and Urine Analysis	Further Diagnostic Tests
Coarctation of the aorta	• Higher blood pressure in upper than lower extremities • Delayed or absent femoral pulses		• Echocardiogram • Computational tomography angiogram • Magnetic resonance angiogram
Obstructive sleep apnea	• Increased BMI • Snoring • Daytime sleepiness • Gasping or choking at night • Witnessed apnoea during sleep • Nocturia		• Home sleep apnea testing (eg, leve 3 sleep study) • Overnight polysommography testing
Thyroid disease	• Symptoms of hyperthyroidism: heat intolerance, weight loss, tremor, palpitations • Symptoms of hypothyroidism: cold intolerance, weight gain, dry brittle hair	• TSH, Free T4	

DRUGS THAT CAUSE SECONDARY HYPERTENSION

i. NASAIDs
ii. Sodium-containing antacids
iii. Drugs used to treat ADHD. Methylphenidate, amphetamine, dexmethylphenidate, dextroamphetamine
iv. Anti-depressant: Monoamineoxidase inhibitors, tricyclic antidepressants, and serotonin-norepinephrine reuptake

v. Inhibitors
vi. Atypical antipsychotics like clazine, olanzapine
vii. Decongestants that have phenylephrine or pseudoephedrine
viii. Apeptie suppressants
ix. Herbal supplements like St John Wort, ephedra and yohimbine
x. Systemic corticosteroids like dexamethasone, methylprednisolone, prednisone and fludrocortisone
xi. Mineralcorticosteroids like carbenoxolone, licorice, 9-alpha fludrocortisone, ketoconazole
xii. Estrogens, androgens and OCP
xiii. Immunosuppressants like cyclosporine
xiv. Chronic recombinanthuman erythropoietin
xv. Recreational drugs: cocaine, methamphetamine, MDMA. Bath salts
xvi. Nicotine, alcohol
xvii. Chemotherapeutic agentslike gemcitabine (which causes microvascular injury)

Keypoints

- Secondary hypertension is present in 1 out of 10 – 20 patients with hypertension
- Screening all HPT patients for secondary hypertension is not feasible or cost-effective
- More common causes: primary aldosteronism, renal parenchymal disease and renovascular disease
- Pts with resistant hypertension should undergo testing for commoner causes and screening for drugs that may induce HPT, and OSA depending on age, symptoms, comorbidities
- Rarer causes of secondary HPT should be considered depending on the clinical picture
- Secondary hypertension can result in target organ damage independent of the effects of blood pressure alone, which can be mitigated with appropriate management.
- Greater attention is needed to identify causes of secondary hypertension, which can be pivotal to improving blood pressure control and preventing cardiovascular events in these high-risk patient

What is the association between HPT and severity of cognitive impairment?

Most of the vascular alterations induced by hypertension contribute to cognitive impairment by leading to hypoperfusion, ischemic and hemorrhagic stroke, and white matter injury.

Vascular dementia (VD) is one of the leading causes of dementia, and hypertension is a known risk factor for VD. Hypertension treatment guidelines have previously discussed an optimal blood pressure goal to prevent further cardiovascular complications with long-term management. The treatment of hypertension can prevent stroke, kidney failure, and perhaps prevent cognitive decline as well.

Meta-analysis, RCT, and clinical trials on 22 articles showed that the risk factors that affect cognition include hypertension, stroke, age, BPV, and LVH. The use of AHM was associated with a reduced risk of stroke, dementia, cognitive impairment to various degrees. Studies showed that anti-hypertension medication (AHM) might be useful across dementia pathologies such as Alzheimer's disease and Vascular Dementia. Many AHM classes were individually associated with reducing the risk of cognitive impairment; however, comparing the AHM class effect on cognition was difficult.

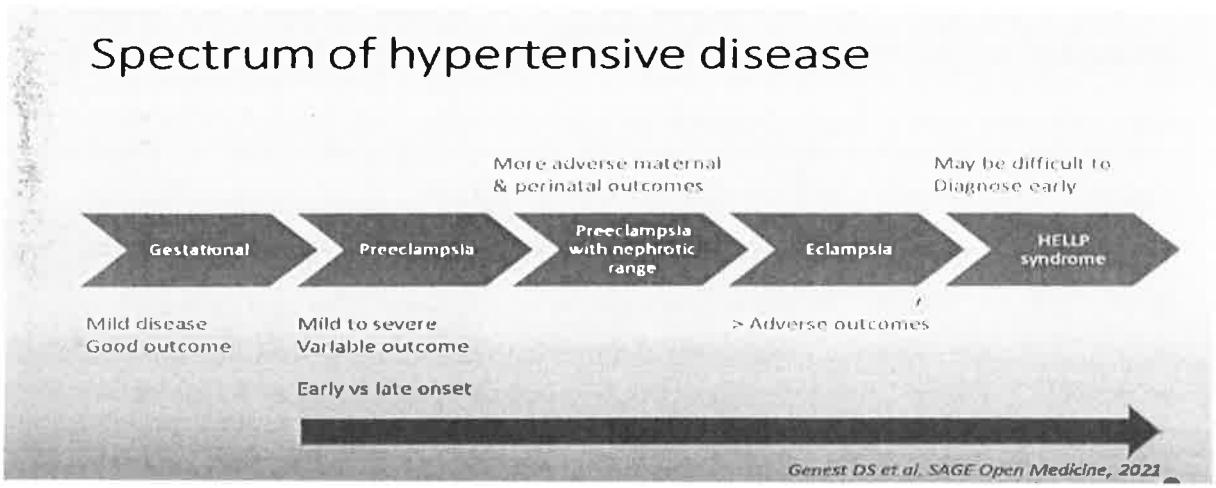
Should BP to Targets be Adjusted according to age and when should AHM be stopped in the elderly?

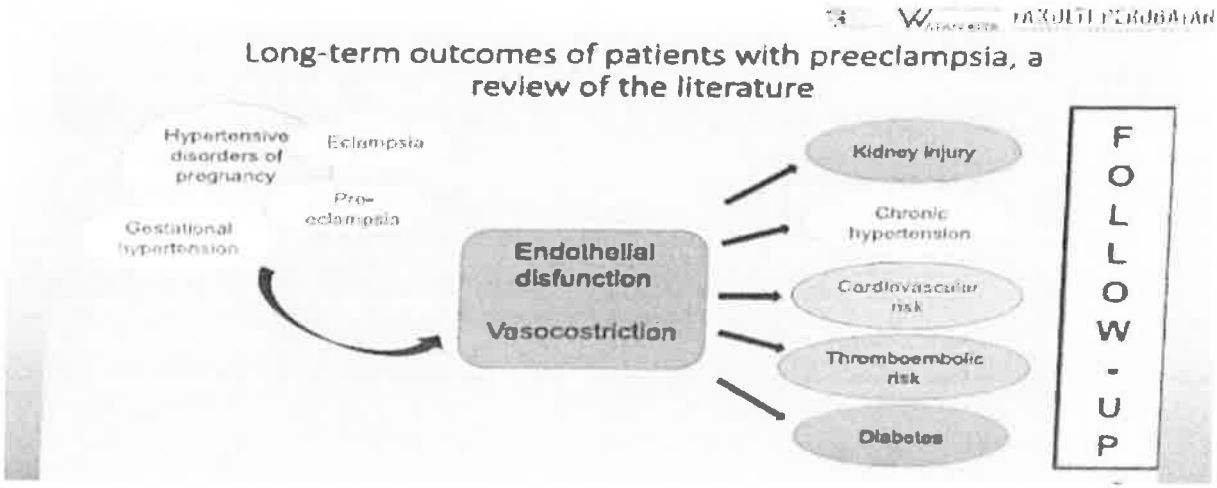
Hypertension is a common disease in the elderly associated with significant morbidity and mortality, and challenging disease in geriatric population. Although the benefits of BP control in the elderly are well documented, the optimal BP target in this group is still controversial.

The most recent guidelines suggested a treatment goal of 130/80 mmHg in patients older than 65 years. Although the safety of lowering SBP to <120 mmHg is debated, Systolic Blood Pressure Intervention Trial study has shown no increased risk of falls, fractures, or kidney failure in elderly patients with SBP lower than this threshold.

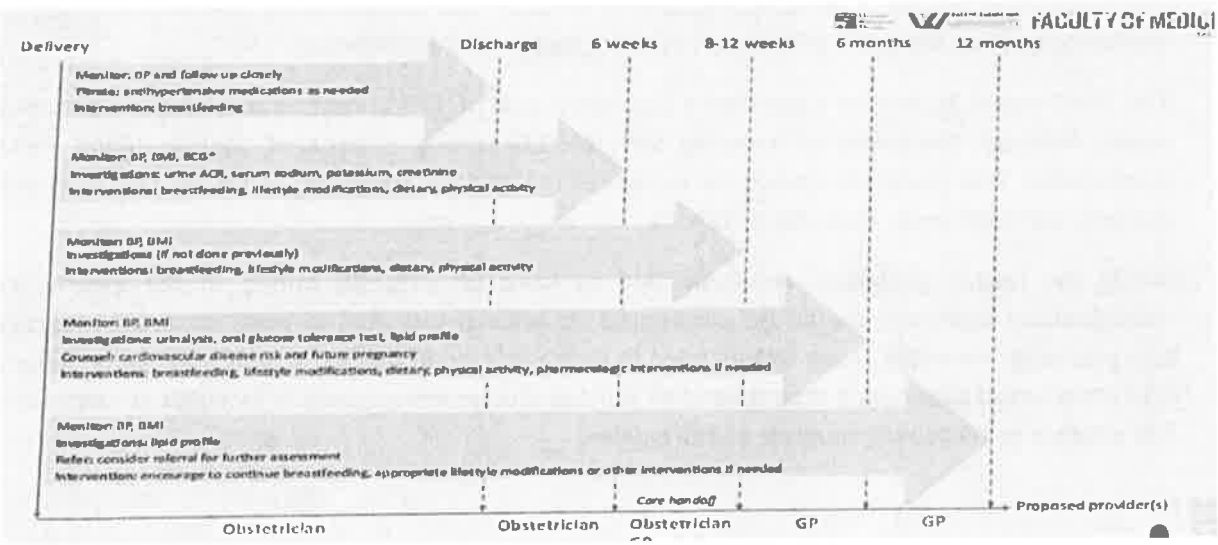
While the recent guidelines recommended to keep BP <130/80 mmHg in the elderly, more individualized approach should be considered to achieve this goal in order to avoid undesirable complications. However, many factors need to be considered to reach this goal, and clinical judgment and team-based approach is recommended. Further studies are required to evaluate BP target in very old patients or those with multiple comorbidities.

HYPERTENSION IN PREGNANCY





HYPERTENSION IN PREGNANCY



THE ROLE OF SALT SUBSTITUTES IN HYPERTENSION MANAGEMENT

A salt substitute, also known as low-sodium salt, is a low-sodium alternative to edible salt (table salt) marketed to circumvent the risk of high blood pressure and cardiovascular disease associated with a high intake of sodium chloride while maintaining a similar taste.

Salt substitutes have been principally shown to reduce urinary sodium excretion and increase potassium excretion in varying populations.

In conclusion, the results of meta-analysis from ten studies, comprised of 11 trials and 1119 participants, highlight that salt substitutes are an efficacious supplement for the lowering of SBP and DBP in patients with stage 2 HTN. Thus, it is conceivable that salt substitution may be a feasible dietary approach for population-level control of HPT.