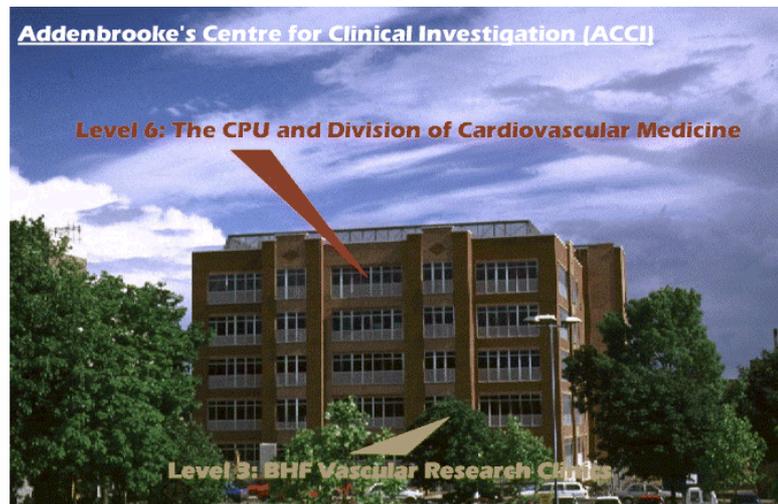


Guidelines for the Management of Hypertension



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These and other guidelines are also available at: - www.addenbrookes.nhs.uk

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I. Introduction

Hypertension is one of the most rapidly advancing fields in medicine. The last few years have seen an enormous number of randomised clinical trials and meta-analyses which have served to increase our knowledge and understanding of hypertension.

The purpose of producing this clinical management protocol is to achieve conformity in the management of patients diagnosed with hypertension. This protocol-based joint management strategy between primary and secondary/tertiary care will effectively optimise patient management, enhance specialist nurse prescribing and keep abreast of emerging newer studies and treatments and help rationalise prescribing-related costs.

These guidelines are based on those issued by the British Hypertension Society, National Institute of Clinical Excellence (NICE) and scientific evidence from recent major trials. They are drawn in consultation with the PCT and GPs and with cost-effectiveness in mind. However, the eventual management of each individual needs to be carefully tailored to their needs and depends upon the relationship that exists between the physician and patient.

The Clinical Pharmacology Unit has broad interests in vascular medicine and hypertension – from the molecular genetics to the physiology of the renin-angiotensin-aldosterone axis and the measurement of various haemodynamic parameters. We are also a specialist centre for the management of phaeochromocytomas and adrenal-related hypertension.

We are currently conducting research in to:

- drug-induced diabetes in hypertensive patients
- anti-hypertensive drug rotation studies
- young people with hypertension
- arterial stiffness and inflammation
- patients with polycystic kidney disease
- women with high blood pressure

We particularly welcome referrals for any patient with:

- suspected phaeochromocytoma / adrenal hypertension / Conn's syndrome
- borderline hypertension
- patients with resistant hypertension
- young patients with hypertension
- those with ACEI/ARB induced renal dysfunction
- hypertension associated with pregnancy, the Pill or HRT

It is well known that patients in clinical trials achieve much better control of their blood pressure because of increased motivation and compliance. Indeed, the A(B)/CD algorithm for treating hypertension was a direct product of research carried out in our Unit. We have a number of trials suitable for patient recruitment and we urge GPs to refer patients who are interested and may benefit from recruitment.

Currently, we have 3 multi-centre RCTs in progress in to which hypertensive patients are being enrolled:

PATHWAY-1: patients either untreated or receiving no more than 1 drug class in the preceeding 12 months

PATHWAY-2: patients receiving 3-5 drugs (or 2 out of ACD and intolerant of 3rd)

PATHWAY-3: on any permutation of ABCD or alpha-blocker, +1 component of metabolic syndrome (e.g. overweight)

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II. British Hypertension Society: classification of blood pressure levels

It is impossible to provide a precise definition of hypertension since blood pressure is a continuous variable within the population, having a skewed normal distribution. From a practical point of view, hypertension can be defined as the level of blood pressure which when treated, results in more benefit than harm. Most authorities consider blood pressure (BP) $\geq 140/90$ mmHg as being 'hypertensive'; importantly *either* an elevated systolic *or* diastolic pressure qualifies for the diagnosis.

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal blood pressure	<120	<80
Normal blood pressure	<130	<85
High-normal blood pressure	130–139	85–89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension (Grade 1)	140–159	<90
Isolated systolic hypertension (Grade 2)	≥ 160	<90

III. Evaluation of patients

All patients with hypertension require a thorough history-taking and physical examination but need a limited number of routine investigations. Assessment should be targeted to the following:

- Evaluation of possible secondary causes (e.g. hypokalaemia, history of palpitations, flushing, previous renal disease, unequal pulses on examination, renal bruits etc)
- Target organ involvement i.e. evidence of left ventricular hypertrophy, retinopathy and proteinuria or known cardiovascular disease
- Cardiovascular risk calculation (see separate section)
- Life-style assessment – smoking, alcohol, obesity, diet including salt and fat intake, and exercise
- Previous history of anti-hypertensive therapy including drug intolerances and contraindications
- Proper BP measurements (see below)

Blood pressure measurement

- Take **THREE** readings (ignore the first) on **THREE SEPARATE** occasions unless there is evidence of end organ damage
 - see http://www.bhsoc.org/how_to_measure_blood_pressure.stm
- USE A BHS VALIDATED DEVICE ONLY i.e. mercury or oscillometric device & NOT an aneroid one (see http://www.bhsoc.org/blood_pressure_list.stm).
- Ensure that an appropriate sized cuff is used for overweight patients
- Measure BP in both arms as part of the initial assessment to detect stenosis / occlusion of a large artery. A difference of >20 mmHg is significant and may indicate a stenosis in the arm with the lower BP. The arm with the higher BP reading should be used subsequently.
- Beware of heavily calcified arteries which can lead to falsely elevated measurements or *pseudohypertension* (palpable vessel despite cuff inflated to >SBP = Osler's manoeuvre/sign)

IV. Investigations

Routinely indicated: (*First visit*)

- Urinalysis for protein / blood
- Serum electrolytes, bicarbonate and creatinine
- Random plasma glucose – if elevated, repeat with fasting sample / formal OGTT
- Random lipid profile (including total cholesterol, HDL, LDL and triglyceride levels)
- ECG to look for LVH using voltage criteria

For selected patients:

- Echocardiography
 - borderline untreated hypertension, where the presence of LVH will influence the decision to treat
 - resistant hypertension, where a lack of severe LVH reduces the need to achieve a tight treatment target
- Plasma renin level
 - resistant hypertension (on ≥ 3 drugs)
 - renal impairment of unknown cause
 - increase in creatinine following ACE-I/ARB (>20% rise from baseline)
 - age <35
 - suspected Conn's syndrome (e.g. persistent hypokalaemia)
- Plasma aldosterone level - especially if the renin is low
- Plasma metanephrines / 24 hour urinary metanephrines
 - for patients with symptoms suggestive of a pheochromocytoma (palpitations, sweating, headaches, anxiety)

24-hour ABPM (Ambulatory Blood Pressure Monitoring)

- Ideally all patients should be considered for ABPM. As part of cost-effective management and treatment of hypertension, we recommend that GP practices invest in 24-hour BP monitors to aid monitoring of therapy. Home monitoring using a validated device is almost as good and should be done before referring patients for ABPM.
- Indications for ABPM include:
 - suspected “white-coat hypertension”
 - borderline hypertension
 - hypertension seemingly resistant to treatment
 - symptoms of ambulatory hypotension

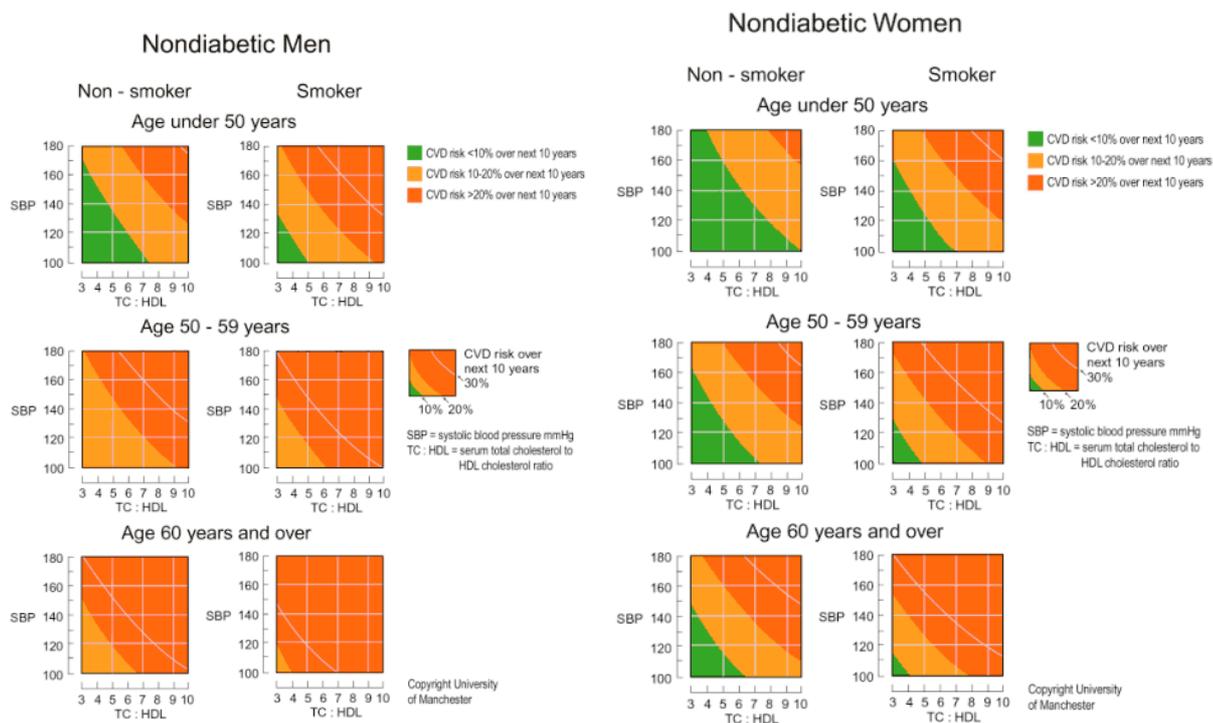
As a general rule, the *daytime average* is the figure we use, rather than the 24-hour mean value. Furthermore, threshold and targets for ABPM and home monitoring need to be lower and we usually **add 12/7 mmHg** (10/5 mmHg according to current BHS guideline) to the figures obtained in order to reflect “clinic values”.

- *Home Monitoring*
 - This should be performed using a validated device. Patients should take their readings having sat down and rested for 5 minutes, using the same arm supported. They should take 3 consecutive readings, but omit the first of the three readings and record the last 2. This can be repeated at different times up to 3-4 times per week.

V. Management of hypertension

V.1. Cardiovascular disease (CVD) risk assessment

- The Joint British Societies (JBS 2) have issued recommendations on preventing CVD, including a CVD risk chart, based on the Framingham database (see below).
- Note that these charts are designed for **primary prevention** and are an aid to making clinical decisions about when to intervene on lifestyle and whether to use anti-hypertensives, lipid lowering medication or aspirin. **Patients with persistently elevated BP >160/100 or those with target organ damage should have their blood pressure treated, irrespective of the calculated risk.**
- For patients from the Indian subcontinent, assume CVD risk is 1.5 times higher than that predicted from the charts
- Treatment is recommended if the 10 year CVD risk for the individual is $\geq 20\%$
- The charts are **NOT** for individuals who have:
 - overt evidence of coronary heart disease
 - familial hypercholesterolaemia or other inherited dyslipidaemias
 - chronic renal dysfunction
 - diabetes mellitus
 - age <35



<http://www.bhsoc.org/CardiovascularRiskPredictionChart.stm>

V.2. Lifestyle interventions

i) Measures to reduce blood pressure

Recent trials have confirmed that lifestyle changes can indeed lower BP. The degree of reduction is variable but the effects are synergistic.

Intervention	Recommendation	Expected systolic BP reduction (range)
weight reduction	maintain ideal body mass index (20–25 kg/m ²)	5–10 mmHg per 10 kg weight loss
diet	consume diet rich in fruit, vegetables and fibre, but low in fat	8–14 mmHg
reduced sodium intake	<100 mmol/day (<6 g of sodium chloride or <2.4 g of sodium per day)	2-8 mmHg
physical activity	regular aerobic physical activity e.g., brisk walking for at least 30 min at least 5 days/wk	4-9 mmHg
alcohol moderation	no more than 3 units/day in men no more than 2 units/day in women	2-4mmHg

ii) Other measures to reduce CVD risk rather than lowering BP *per se*

- cessation of smoking
- reduced total fat and saturated fat intake
- replacement of saturated fats with mono-unsaturated fats
- increased oily fish consumption (1-2 portions per week)
- relaxation techniques (controversial!)

V.3. Thresholds for Treatment

- Initiate anti-hypertensive medication if BP consistently $\geq 160/100$ mmHg.
- If systolic BP is between **140-159** mmHg and/or diastolic BP **90-99** mmHg, treatment is required if there is:
 - presence of diabetes, renal impairment or established cardiovascular disease
 - target organ damage
 - 10-year CVD risk of $\geq 20\%$

Quarterly re-assessment is warranted if none of these conditions applies. Note that the potential for becoming resistant to treatment later in life is likely to be higher the longer treatment is delayed.

In addition, 6-monthly BP measurement for patients with high normal readings (SBP 130-139 mmHg and/or DBP 85-89 mmHg) is also recommended.

V.4. Treatment Targets

Recommendations are based on the Hypertension Optimal Treatment (HOT) trial and BHS guidelines. Note that these treatment targets are lower for patients with diabetes, established cardiovascular disease or renal impairment.

	BP Measured in clinic		Mean daytime ABPM or home BP	
	No	Yes	No	Yes
Diabetes/CVD/ renal impairment	No	Yes	No	Yes
Target BP	<140/85	<130/80	<130/80	<120/75

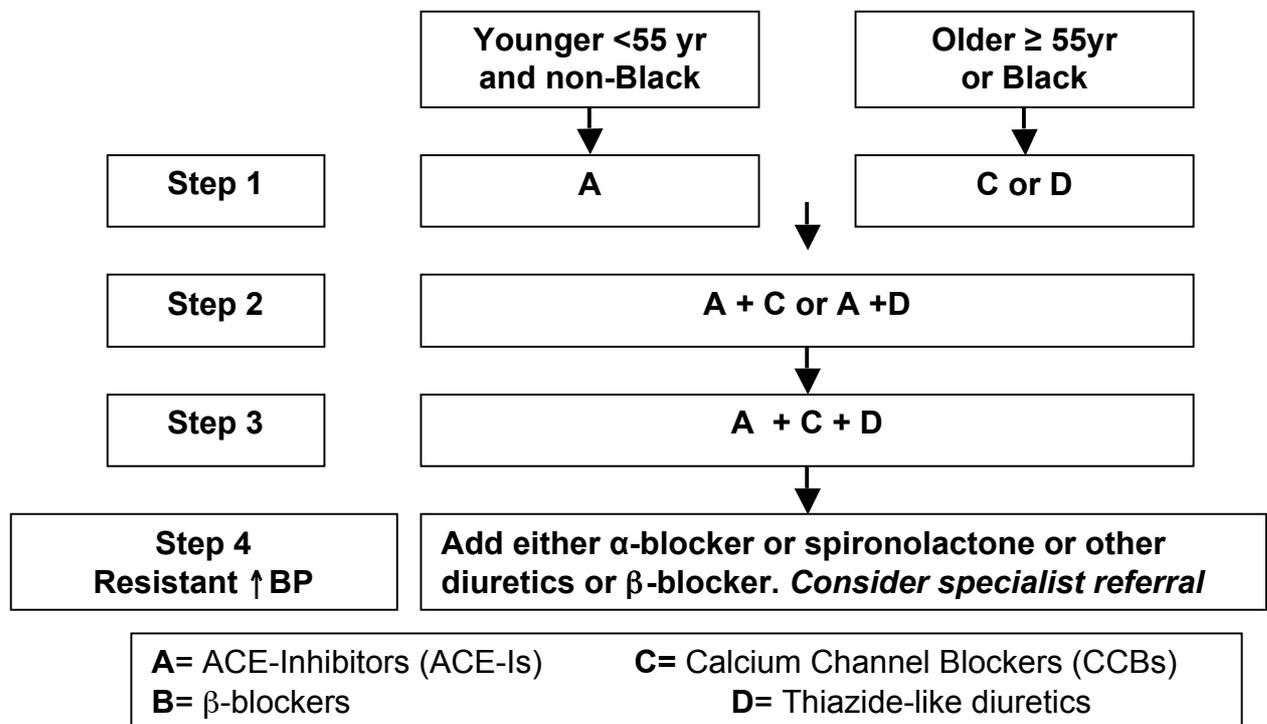
V.5. Choice and combination of anti-hypertensive drugs

NICE and the BHS have issued joint guidelines for the management of hypertension. Both groups emphasise the importance of BP lowering to reduce cardiovascular risk and that optimal cardiovascular outcome is most consistently linked with BP control rather than with the drug class used to achieve it.

Trials have also suggested that β -blockers (and atenolol in particular), may be less efficacious when compared with other drug classes, especially in older patients. Thus we recommend that *β -blockers are not used as first or second line* in older patients with isolated systolic hypertension. In younger subjects, β -blockers are effective and may still be used although atenolol is probably best avoided. Similarly, the combination of β -blockers and thiazide diuretics has been shown to increase the risk of developing diabetes in high-risk groups and should be avoided if possible in patients who are predisposed to diabetes mellitus.

Tolerability, availability and cost are considered when proposing the order of drug therapy. If no convincing indication exists for use of a specific class of anti-hypertensive medication (e.g. ACE inhibitors in patients with diabetic nephropathy), we recommend using the Cambridge A/CD rule as a guide to choice of drugs and their combination.

A/CD rule



Note: a) Black patients = African/Carribean descent only
b) For those intolerant of ACE-Is, Angiotensin Receptor Blockers (ARBs) may be used

V.6. Monitoring renal function:

- Renal function may occasionally deteriorate with ACE-I/ARB therapy; this is usually seen in patients with pre-existing kidney impairment. An increase in creatinine of >20% from baseline should alert one to the possibility of underlying renal artery stenosis / renovascular disease.
- Hyperkalaemia is sometimes problematic in patients on potassium sparing diuretics (e.g. spironolactone or amiloride), particularly when used in combination with ACE-Is/ARBs. Often the delay in the blood sample reaching the biochemistry lab results in haemolysis and erroneously high results. Hence, minimising the time taken between sampling blood and transportation to the lab is important. If in doubt, sampling should be repeated.
- There are no clinical symptoms or signs that reliably indicate severe hyperkalaemia (K >7.0 mmol/L), although paraesthesia, muscle weakness and depressed tendon reflexes may be seen. Note that chronic hyperkalaemia is better tolerated than acute changes in plasma potassium.
- Based on new local guidelines, if a patient has a **serum potassium of >7 mmol/L OR ECG changes consistent with hyperkalaemia** (i.e. tall, tented T waves, increased P-R interval, small/absent P-waves, widened QRS complexes), they should be transferred to hospital IMMEDIATELY and given two 5mg **salbutamol** nebulisers en route. Otherwise, all potassium sparing drugs / dietary supplements should be stopped and the blood test repeated in 24-48 hrs.
- We usually advise checking of serum electrolytes and creatinine 7-10 days after starting treatment with an ACE-I/ARB or potassium-sparing diuretic, especially if there is a possibility of underlying renovascular disease. **Patients should be advised to stop taking such drugs and seek medical advice if they develop persistent diarrhoea and/or vomiting.**
- As a general rule, repeat blood tests are not necessary when up-titrating the dose of an ACE-I or ARB. However, they should be considered ~2weeks after increasing the dose of potassium-sparing diuretics in those patients also taking ACE-Is/ARBs.
- It is worth considering checking serum electrolytes and creatinine every ~6 months in patients taking ACE-Is/ARBs in combination with potassium-sparing diuretics.

V.7. Formulary recommendations

ACE-Inhibitors (A)

lisinopril (10 – 40mg once daily)

Angiotensin Receptor Blockers (ARBs)

losartan^{*/} (50 – 100mg once daily)**
candesartan (8 – 32mg once daily)

ACE-Is and ARBs may sometimes be combined in nephropathy with heavy proteinuria

** also available in fixed dose combinations with hydrochlorothiazide*

***has a unique mild uricosuric effect*

Calcium Channel Blockers (C)

amlodipine (5 – 10mg once daily)
nifedipine (long-acting formulation) (20 – 90mg once daily)
lercanidipine* (10 – 20mg once daily), or non-dihydropyridine* e.g. diltiazem

** associated with less ankle swelling*

Thiazide / Thiazide-like Diuretics (D)

chlortalidone (25 – 50mg once daily)
co-amilozone* (2.5/25 – 5.0/50mg once daily)

** ineffective when serum creatinine >150 μ mo/l; loop diuretics b.d. may be used as alternative*

α -Blockers

doxazosin* (4 – 8mg once daily)

** preferable to use generic modified release preparation e.g. doxazosin XL 4mg; alternatively start with 1mg dose and titrate up*

Aldosterone Antagonists / K^+ -sparing diuretics

spironolactone (25 – 50mg once daily)
amiloride (5 – 20mg once daily)
eplerenone (50-100mg)*

** reserved for a select few cases by specialists only – please refer to Hypertension Clinic*

β -Blockers (B)

bisoprolol (2.5 – 10mg once daily)
nebivolol* (5mg – 10mg once daily)

* highly β_1 -selective; may have additional vasodilating properties

Direct Renin Inhibitors

aliskiren* (150- 300mg once daily)

**specialist use only in patients with high renin hypertension despite maximum therapy with β -blocker/ARB (e.g. patients with a reninoma, renal artery stenosis); or those with multiple drug intolerances*

V.8. Indications for specialist referral

Urgent treatment needed

- accelerated-phase (malignant) hypertension (i.e. severe hypertension - usually DBP >120 mmHg - with papilloedema, retinal haemorrhages or exudates)
- impending complications (e.g. transient ischaemic attack, left ventricular failure)
- hypertensive emergency (e.g. encephalopathy, eclampsia, aortic dissection)

Possible underlying cause

- any clue in history or examination of a secondary cause e.g. hypokalaemia with increased or high normal plasma sodium (Conn's syndrome); bruits
- elevated serum creatinine
- proteinuria or haematuria
- sudden-onset or worsening of hypertension
- "resistance" to a multi-drug regimen i.e. ≥ 3 drugs, especially at a young age (<35 years age)

Therapeutic problems

- multiple drug intolerances
- multiple drug contra-indications
- persistent non-adherence or non-concordance

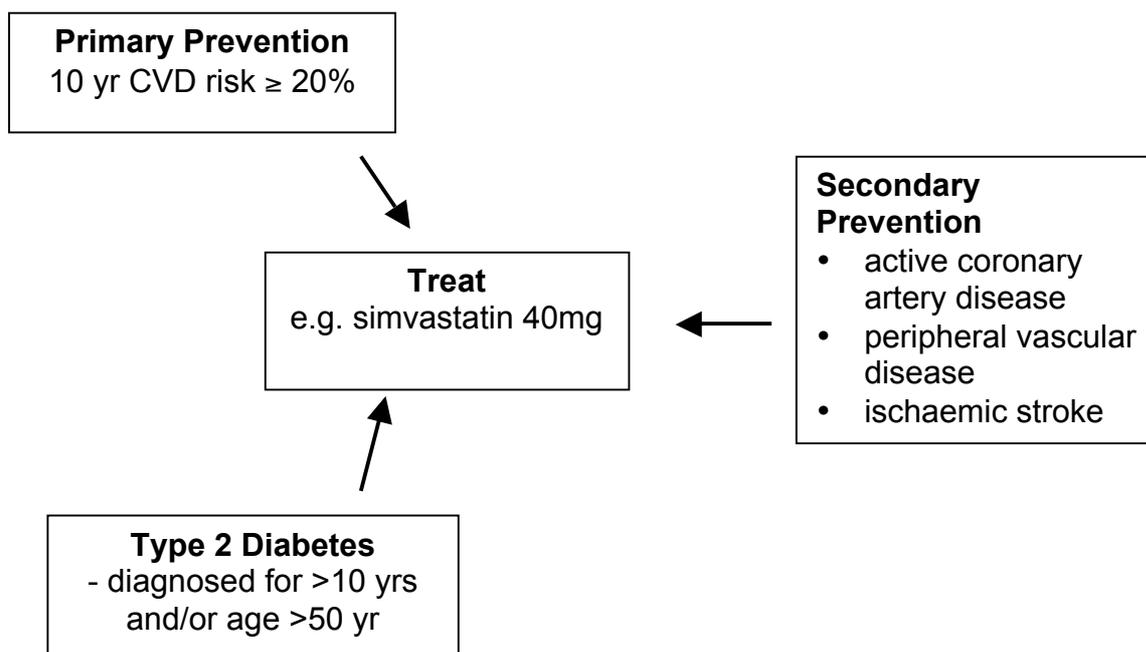
Special situations

- unusual blood pressure variability
- possible white-coat hypertension
- hypertension in pregnancy or with HRT/the Pill

VI. Other drugs

Statins and the hypertensive Patient

HMG CoA-reductase inhibitors



Aspirin 75mg/d and hypertension

1) Primary prevention

Consider aspirin 75mg o.d. if

- age ≥50 years and the following apply:
 - controlled BP <150/90mmHg
 - target organ damage or 10-year CVD risk ≥20%
 - no contraindication

2) Secondary prevention

Such patients should already be on aspirin, unless there is a specific contraindication.

VII. Special patient groups

Hypertension in the elderly

- CHD and stroke remain the major causes of death in people over the age of 65 years, with hypertension the commonest treatable risk factor
- trial data show that older people have benefited as much, if not more, from such interventions
- elderly patients usually have ISH (isolated systolic hypertension).
- thiazides and / or calcium channel blockers are treatments of choice; alternatively, long-acting oral nitrates may be considered (e.g. ISMN MR 60mg o.d.)

Hypertension and stroke

- hypertension remains the most important treatable risk factor for the prevention of stroke and its recurrence
- after acute cerebral haemorrhage or infarction, BP levels are usually increased, with more than 80% of patients having levels >160/95mmHg within the first 48-hr of the event.
- there are potential pros and cons for both raising and lowering BP in the acute situation - however, to date, very few trials exist of either pressor or depressor interventions in the acute stroke period
- treatment to lower BP is appropriate when BP is grossly elevated immediately (<48h) post-stroke (SBP >220mmHg or MAP >130mmHg). Otherwise it is best to start treatment at least 10-14 days later. Please follow the separate guideline available from the Stroke Unit for more details
- thiazides or CCBs are appropriate first line therapies for most subjects as they take some time to have the desired effect

Hypertension in people with diabetes

- hypertension is twice as common in people with diabetes
- it greatly increases the already elevated CVD risk - the risk of coronary disease is increased two-fold in men with diabetes and four-fold in diabetic women.
- ACE-Is/ARBs are recommended as first line agents in such patients because of their reno-protective effects

Hypertension in pregnancy

- hypertension occurs in 8–10% of pregnancies, and may precede impending pre-eclampsia (associated with proteinuria and oedema after 20 weeks gestation)
- elevated BP/proteinuria at <20 weeks' gestation implies it preceded pregnancy
- there is often a fall in BP between 12-26 weeks of pregnancy
- treatment during pregnancy (and breast-feeding) should be avoided if possible
- aim to keep BP $\leq 150/100$ mmHg; $\leq 140/90$ mmHg if target organ damage present
- ACE-Is/ARBs should be avoided in pregnant women or those planning one
- NICE guidelines suggest that diuretics should not be used during pregnancy
- women who are classified as 'high risk' for developing pre-eclampsia should be offered aspirin 75mg od from 12 weeks gestation until delivery (unlicensed indication; informed consent should be obtained and documented)
- **pregnant women with either severe hypertension (BP>160/110mmHg) or with pre-eclampsia should be admitted to hospital and followed up thereafter in secondary care. This includes formal follow-up in a specialist clinic post-partum.**

Drug therapy for pregnant / breast-feeding women with hypertension

- lowest dose required to control blood pressure recommended

labetalol nifedipine (long-acting formulation) methyldopa
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VIII. Recommended further reading

- | | Guidance |
|---|-----------------|
| a) JNCVIII
http://www.nhlbi.nih.gov/guidelines/hypertension/jnc8full.htm | |
| b) WHO-ISH Guidelines J Hypertens. 2003 Nov; 21(11) :1983-1992 | |
| c) Updated BHS & NICE Guidelines www.nice.org.uk/CG034 | |
| d) Quick reference BHS/NICE guidelines
http://guidance.nice.org.uk/CG34/quickrefguide/pdf/English | |
| e) Hypertension in Pregnancy NICE guideline CG107
www.nice.org.uk/guidance/CG107 | |

Treatment Guideline for Essential Hypertension

(SBP>140 AND/OR DBP>90 mmHg)

NOTES

Routine investigations

- U&E, creatinine, glucose
- Total, HDL, LDL cholesterol and Triglycerides
- 12 lead ECG
- Urinalysis

Other investigations to be considered

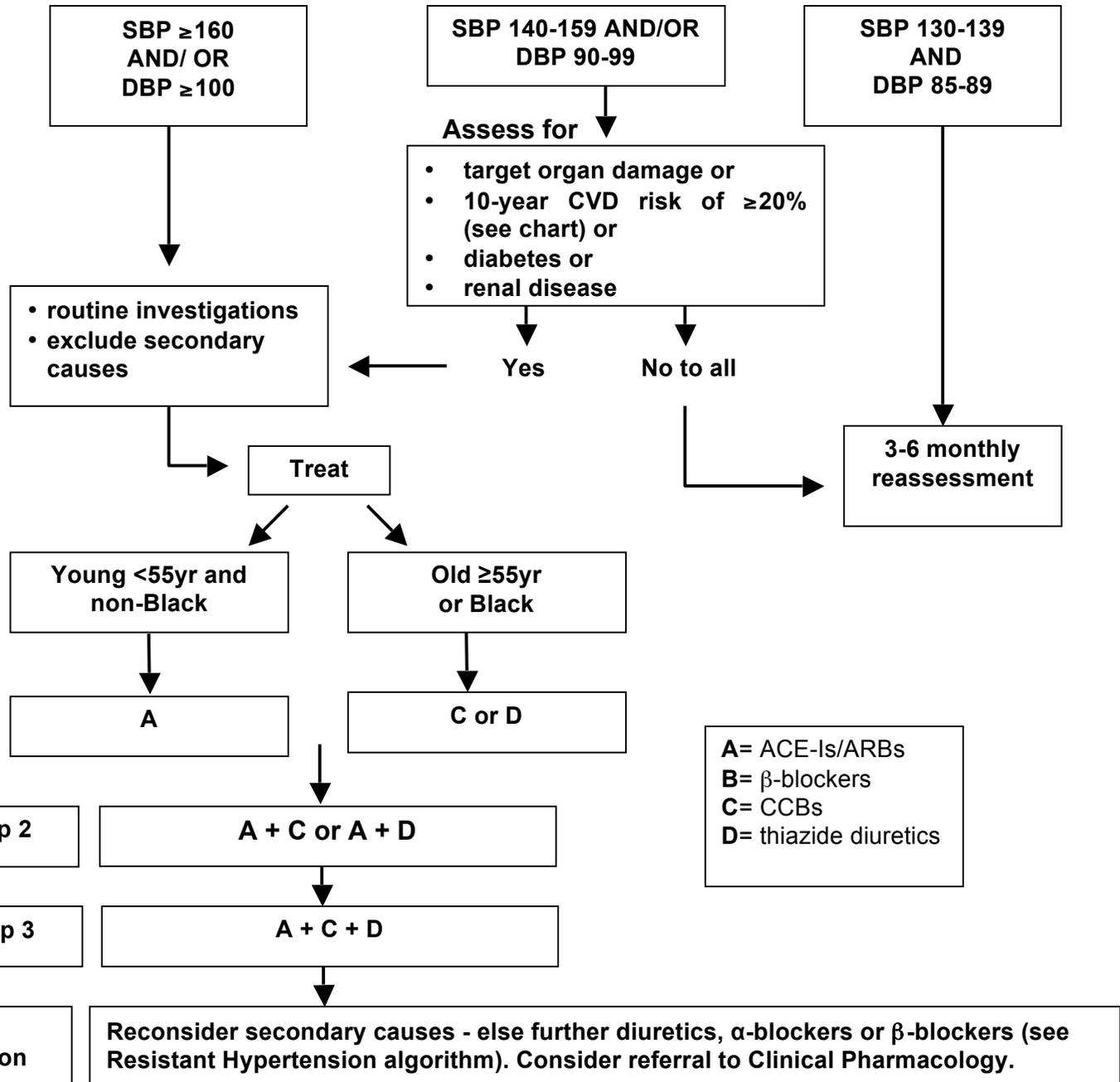
- Urinary/plasma metanephrines
- Renal tract ultrasound scan
- Echocardiogram
- Serum renin and aldosterone levels

Additional points

- Refer patients under 20-yrs age
- If possible, avoid the combination of a thiazide and β -blocker
- Use ARB if cough on ACE-I
- Renal impairment is NOT itself a contraindication to ACE-I/ARB, but they should be introduced cautiously and renal artery stenosis excluded if suspected
- Should check U&Es 7-10 days after ACE-I /ARB therapy commenced

Treatment Targets

- No diabetes <140/85
- Diabetes or CVD <130/80



A= ACE-Is/ARBs
 B= β -blockers
 C= CCBs
 D= thiazide diuretics

Treatment Algorithm for Resistant Hypertension (renin-based protocol)

(SBP>140 **AND/OR** DBP>85 mmHg on 3 drugs)

NOTES

1. Renin

- low ≤ 10 mU/L
- high >100 mU/L
- difficult to interpret on β -blocker and beware of local variations

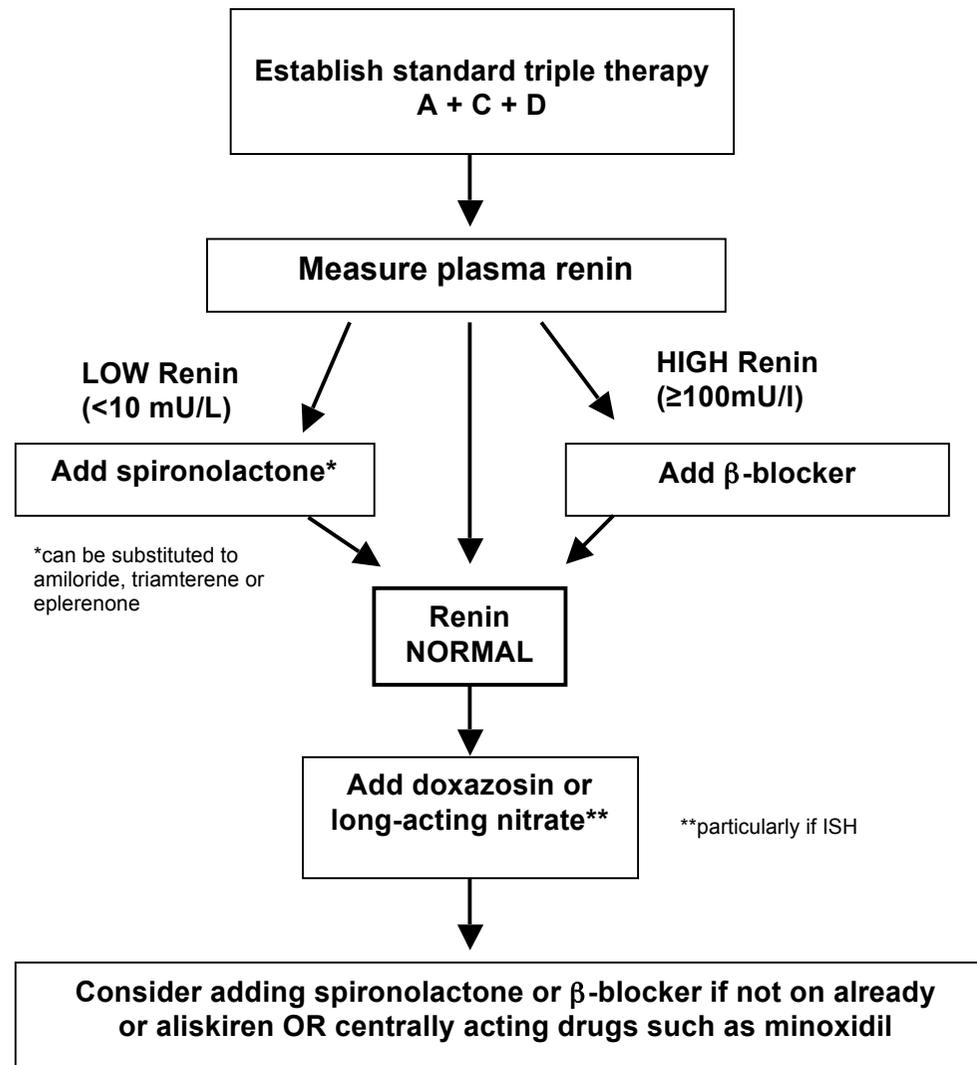
2. *Combination of spironolactone and ACE-I/ARB may increase the risk of hyperkalaemia, especially if patient has chronic renal failure, and therefore advice is to monitor U&E every 4-6 months, or if indicated, earlier (e.g. development of diarrhoea or vomiting, which should trigger the temporary stoppage of these drugs anyway). There is some anecdotal evidence to suggest risk of hyperkalaemia is less with ARBs than it is with ACE-Is.*

3. *Always re-consider secondary causes*

4. *Clues to a Conn's adenoma requiring further investigation include:*

- BP fall >20 mmHg on spironolactone
- $K^+ < 3.5$ mmol/L
- fall in serum K^+ with thiazide therapy

5. *Doxazosin should be started at a low dose and titrated up or alternatively, we suggest using a slow release formulation in order to avoid first- dose postural symptoms*



Suggested approach to the management of resistant hypertension

