PRIMARY (ESSENTIAL) HYPERTENSION

Investigations

Recommendations for communicating the diagnosis of hypertension are presented in Table 1. History and physical examination should enquire about cardiovascular risk, organ damage and secondary hypertension. Screening for management of other modifiable CVD risk factors is mandatory. Recommended laboratory tests are presented in Table 2, and Figure 1. Genetic testing is useful only in the suspicion of monogenic disorders or phaeochromocytoma (Table 3).

Therapy

General principles

Low salt diet (<100 mmol/day, ie 2.4 g Na or 6 g NaCL), weight loss, exercise 3-4 sessions up to 40 min per week) and alcohol restriction (up to 2 drinks a day, ie 1 oz or 28 g of alcohol for men, and 1 drink for women) are the best way for small but significant blood pressure reductions, [1-5] and are recommended in all hypertensive patients, regardless of drug therapy (Tables 4 and 5, and Figures 2-4). High sodium intake has been associated with an increased risk in hypertensive populations. The maximum recommended intake level advised by the World Health Organization is 2 g/d, and in a dose–response meta-analysis of clinical trials, a progressively large reduction in BP with decreases in sodium consumption down to levels as low as 1 to 1.5 g/d were demonstrated.[6] However extremely low sodium intake (intake<2.3 g) may be detrimental,[7,8] and a moderate sodium intake (3-5 g/day) is probably a reasonable recommendation.[9] Extreme low-salt diets in patients on thiazides should be avoided to prevent an increased risk of hyponatremia.[10] Increased dietary potassium intake is essential for patients who are not at high risk for hyperkalemia.[11] Although systolic blood pressure temporarily raises after coffee, chronic caffeine consumption is not associated with increased risk of hypertension.[12] Smoking cessation should be encouraged. There is no causal association of smoking heaviness with blood pressure but smoking increases the resting heart rate.[13] Small additional amounts of exercise are associated with lower blood pressure.[14] High-risk patients with hypertension should also receive a statin and low-dose aspirin.[15] Drug-induced hypertension should be considered. Non-steroidal anti-inflammatory agents are the main cause, but paracetamol use also increases blood pressure in patients with coronary artery disease.[16] Digital therapeutics that utilizes technology-based software algorithms or smartphone applications to facilitate disease management is a promising new approach to facilitate the implementation and effectiveness of life style modifications.[17]

Target Values

Thresholds for initiation of therapy and ***target values*** in the general population are shown in Table 6 and Figures 5 and 6. In general, initiation of medication therapy to lower blood pressure in addition to lifestyle interventions is recommended for all adults with average blood pressure ≥140/90 mm Hg and/or for selected adults with average blood pressure ≥130/80 mm Hg who have clinical cardiovascular disease, previous stroke, diabetes, chronic kidney disease, or increased 10-year predicted cardiovascular risk (using risk models such as the PREVENT, SCORE2 and SCORE-OP).[18-20] In the SPRINT trial on 9361 patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure < 120 mm Hg was compared with < 140 mm Hg. At a median of 3.33 years of follow-up, the rate of the primary outcome a composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes, and all-cause mortality during the trial were significantly lower in the intensive-treatment group than in the standard-treatment group (rate of the primary outcome, 1.77% per year vs. 2.40% per year; all-cause mortality, 1.06% per year vs. 1.41% per year). Serious adverse events of hypotension, electrolyte abnormalities, acute kidney injury or failure, and syncope were significantly more frequent in the intensive-treatment group.[21] It seems that a more intensive blood pressure lowering (<130 mmHg) is beneficial especially by means of reducing the risk of stroke and even <120 mm Hg in high-risk patients, such as those with cardiovascular disease, renal disease, or diabetes,[22-25] although this was not the case in a recent RCT on Type 2 diabetes.[26] In a meta-analysis of 48 randomised trials, a 5 mm Hg reduction of systolic blood pressure reduced the risk of major cardiovascular events by about 10%, irrespective of previous diagnoses of cardiovascular disease, and even at normal or high–normal blood pressure values.[27] In a subsequent individual patient data meta-analysis, systolic blood pressure target <120 mm Hg or <130 mm Hg provided a net benefit between the reduction in cardiovascular events and the increase in adverse events, including renal events.[28] However, in the VALUE trial, a target of 140/90 mm Hg was found appropriate for most high-risk hypertensive patients.[29] In an analysis of data from the ONTARGET/TRANSCEND studies, high on treatment BP levels (>=160 or >=90 mmHg) were associated with increased risk of cardiovascular outcomes and death, but also low levels (<120 or <70 mmHg) were associated with increased cardiovascular outcomes (except stroke) and death.[30] Thus, a target <120 mm Hg was considered rather inappropriate.[31] In patients with type 2 diabetes, thresholds are lower (see below). In normotensive persons without cardiovascular disease antihypertensive medication has not been found beneficial (HOPE-3).[32] Intensive BP lowering may lead to renal function decline,[33] and a systolic BP<100 mmHg is associated with increased cardiovascular mortality in patients over 60 years old.[33,34] The appropriate therapeutic target for the diastolic BP (ie <80 mm Hg as per ACC/AHA, or 90 mm Hg as per ESC) is also debatable. [19,35] In middle age or older individuals a target of 90 mm Hg is probably reasonable.[36] Differences in patient characteristics are an important determinant of the association between achieved blood pressure and adverse outcomes. The J-curve phenomenon refers

to increase in cardiovascular events with very low systolic or diastolic blood pressures achieved by therapy. [37,38] A probable association of a diastolic BP <=70 mmHg with cerebral atrophy has been reported,[39] and these low values should be avoided, especially in the presence of concomitant coronary heart disease, [37,40-42] and in elderly patients.[43] Diastolic values <60 mmHg are detrimental, especially if the systolic BP exceeds 120 mmHg.[44] A Mendelian randomization analysis, however, has suggested that the detected relationship between low diastolic BP and MI does not appear to represent a causal phenomenon, and may be the result of reverse causation or unobserved residual confounding.[45] In general, therapy should target patients at greatest cardiovascular risk, not just those with the highest blood pressure levels.[46] The BP lowering effect should last 24 hours, and drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration should be preferred.

The reduction of heart rate in patients with hypertension and/or CV disease is associated with a reduction in CV outcomes and improved survival, independently of BP, and values around 65–70 bpm appear to be the optimal treatment targets.[47]

Elderly patients

Reduction of blood pressure produces benefits in the elderly, and, probably, there is no age threshold beyond which hypertension treatment cannot be justified,[48,49] although no data exist for patients beyond the age of 90 years.[50] In older hypertensive patients, intensive BP control (systolic BP mm Hg <140 mm Hg) reduces cardiovascular adverse events, heart failure and cardiovascular mortality, but may increase the risk of renal failure.[51] The SPRINT trial in adults aged >=75 years also showed that a systolic BP target < 120 mm Hg significantly reduced cardiovascular events and mortality compared to a target of < 140 mm Hg.[52] In the STEP RCT, in patients 60-80 years old with hypertension, intensive treatment with a systolic blood-pressure target of 110 to <130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to <150 mm Hg.[53] As discussed, a systolic BP<100 mmHg,[33,34] and a diastolic BP <70 mm Hg should be avoided in elderly patients,[39,43] and especially in octogenarians since values below which vital organ perfusion is impaired are not known.[54] In the (non-randomized) Berlin Initiative Study, blood pressure values even below 140/90 mmHg during antihypertensive treatment were associated with an increased risk of mortality in octogenarians or elderly patients with previous cardiovascular events.[55] In a UK Registry, BP<130/80 mm Hg was also associated with increased mortality in patients >=75 years.[56] However, in a meta-analysis using individual participant-level data from RCTs, pharmacological blood pressure reduction is effective into old age, with no evidence that relative risk reductions for prevention of major cardiovascular events vary by systolic or diastolic blood pressure levels at randomisation, down to less than 120/70 mm Hg.[49] Hypertension raises the risk for dementia, and antihypertensive therapy reduces the risk of dementia of both the vascular and Alzheimer's type,[57,58] although aggressive lowering may have opposite effects in the elderly due to cerebral hypoperfusion.[59,60] However, discontinuation of antihypertension therapy in older patients with mild cognitive defects does not

improve cognitive or general functioning within the next 16 weeks.[61] The JNC 8,[19] in patients >=60 years without diabetes or chronic kidney disease had recommended a goal BP <150/90 mm Hg, and this recommendation was also adopted by the American College of Physicians.[62] A minority report from 5 of the authors has argued in favor of keeping the target to 140 mm Hg,[63] and this is important especially in patients with concomitant coronary artery disease.[64] In the INFINITY trial , intensive treatment of ambulatory blood pressure in people >=75 years of age was well tolerated and accompanied by lower numbers of cardiovascular events. Thus, a 24-hour average systolic blood pressure ≤130 mm Hg was recommended.[65] In an analysis of the Women's Health Initiative data, an SBP level <130 mm Hg was associated with the highest probability of survival to 90 years of age for healthy older women ≥65 years of age with or without blood pressure medication.[66] Frailty of patients should be taken into account (Table 7, and Figure 5).

ARBs, calcium channel blockers, and thiazides reduce the risk of stroke more than other antihypertensive drugs,[67] and ARBs, ACE inhibitors, and calcium channel blockers are the drugs that have been associated with a beneficial effect on cognitive function beyond blood pressure reduction.[68] However, for patients older than age 55 years as well as in blacks, thiazides or calcium channel blockers are more effective that ACE inhibitors and ARBs in achieving desirable blood pressure reduction (low renin group).[69] In addition, thiazides are associated with a lower risk of hip and pelvic fracture compared with ACEs and, probably, CCBs.[70] Aging seems to be associated with a subclinical form of aldosterone excess and mineralocorticoid receptor antagonists may be also a reasonable therapeutic option.[71] Standing BP should always be checked for excessive orthostatic decline. The first stage of pharmacological treatment of *orthostatic hypotension* involves repletion of central blood volume by drug dosing adjustment and increased fluid intake. If unsuccessful, this should be followed by treatment with sympathomimetic agents.[72] In patients treated with calcium channel blockers, concurrent use of CYP3A4 inhibitors, such as clarithromycin, should be considered with care to avoid hypotension and acute kidney injury.[73] In patients receiving ACE inhibitors or ARBs, co-trimoxazole is also associated with an increased risk of sudden death probably due to unrecognized severe hyperkalemia.[74] Antihypertensive medications have been associated with an increased risk of serious fall injuries in the elderly, particularly among those with previous fall injuries. This should be taken into account when treating older adults with multiple chronic conditions.[75] Increased day-to-day blood pressure variability is, independently of average home blood pressure, a significant risk factor for the development of dementia, and Alzheimer disease in the elderly.[76]

Young patients

In young patients BP should be reduced to <140/90 mmHg. The case may be different for young individuals with isolated systolic hypertension (diastolic BP<90 mmHg), but the value of treatment is controversial. However, in adults aged 18 to 49 years, isolated systolic hypertension is associated with higher risk for cardiovascular disease mortality compared with normal blood pressure.[77] The JNC 8 had provided a weak recommendation for pharmacological therapy to lower diastolic BP to <90 mm

Hg in people 18-29 years.[19] However, more recent data indicated that antihypertensive medication reduces the risk of cardiovascular disease in patients 18-55 years old as in older individuals.[78] Compared with older antihypertensive drugs, newer agents (ARBs, ACE inhibitors, calcium antagonists and vasodilating beta-blockers) have neutral or even beneficial effects on erectile function. Phospho-diesterase-5 inhibitors may be safely administered to hypertensives, even those on multiple drug regimens (with the possible exception of alpha-blockers and in the absence of nitrate administration). Recommendations are provided in Table 8.

Women

Recommendations for therapy of hypertension in women as well as during pregnancy are discussed below (Hypertension in pregnancy). Use of oral contraceptives is associated with some small but significant increases in BP.

Ethinc Groups

In black patients thiazide diuretics are more effective in lowering BP, but monotherapy is not usually enough (Table 9).

Drugs

Specific recommendations and criteria for drug choice and doses are presented in Tables 10 and 11 and Figure 6. The choice of the antihypertensive agent (s) depends on the patients' age and comorbidities. Overall, however, an ACC/AHA review had found no evidence that any class of medications (i.e., angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), calcium channel blockers, or beta blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome.[79] Adherence to medication is better with ARB, followed by ACEI, CCB, diuretics, and beta blockers in descending order.[80] Dosing timing for medications does not appear to be important.[81]

For *monotherapy* of patients without comorbidities, thiazide or thiazide-like diuretics are superior to angiotensin-converting enzyme inhibitors, whereas non-dihydropyridine calcium channel blockers are inferior to other drugs.[82] However, a satisfactory blood pressure response is rarely reached with *monotherapy* alone, and a drug combination therapy is more effective than monotherapy.[83,84] Useful combinations are: ACE Inhibitor or ARB with a diuretic or a CCB, and a beta blocker with a diuretic or a dihydropyridine.[85] Combination of multiple drugs at substantially reduced doses may also be beneficial.[86] In black patients in sub-Sahara Africa, amlodipine combined with either an ACE inhibitor (perindopril) or a thiazide diuretic (hydrochlorothiazide) was found superior to perindopril plus hydrochlorothiazide in lowering both ambulatory and office blood pressures.[87] A subanalysis of the ACCOMPLISH trial suggested that diuretic-based regimens are beneficial in *obese patients* in whom there is usually an excess volume. In *lean patients* calcium channel blockers may be preferable.[88]

Renin-Angiotensin Inhibitors

ARB and ACEI are first choice therapy in most instances, and especially in young people, who generally have a more active renin-angiotensin system. In a large-scale observational study of over 3 million patients worldwide, there was no statistically significant difference in the primary outcomes of acute myocardial infarction, heart failure, stroke, or composite cardiovascular events. Patients on ARBs had significantly lower risk of angioedema, cough, pancreatitis, and GI bleeding.[89] ***Angioedema*** induced by treatment with ACEI is estimated to occur in up to 0.68% of patients, and symptoms can take years to appear. *Icatibant*, a selective bradykinin B2–receptor antagonist (FDA approved for treating patients with hereditary angioedema but very expensive drug) may resolve oedema much quicker (8 vs 27 h) than corticosteroids and antihistamines that are typically directed at mast cell–mediated angioedema.[90] ARB also have a considerably less incidence of ***cough***.[91] In the ALLHAT, *lisinopril* (but not amlodipine) was associated with a significantly lower incidence of ***conduction system disease*** compared to chlothalidone.[92] ARB may prevent ***stroke and development of dementia*** in hypertensives better than ACEI, due to angiotensin II type 1 (AT1) receptor blockade and AT2 stimulation by increased production of angiotensin II and IV.[93] AT2 receptors reduce focal cerebral ischemia by vasodilation and antioxidant activities. Such an advantage of ARB over ACE inhibitors, however, has not been apparent in clinical trials.[94] In ***diabetics***, a meta-analysis has suggested that ACEI may be preferable,[95] but this was not verified in the largest comparative study so far.[89] In an individual data meta-analysis, both ARB and ACEI reduced the risk of new-onset type 2 diabetes.[96] Case reports and observational studies have suggested that ACEI may increase the risk of lung cancer and pancreatitis through the accumulation of bradykinin and substance P in the lung and pancreatic duct, respectively.[89,97] There have also been initial suggestions that ARBs (mainly *telmisartan*) are associated with a modestly increased risk of new cancer diagnosis, [98] but were subsequently refuted.[99-101] Generic preparations of valsartan containing the potential carcinogen *N-nitrosodimethymelamine (NDMA)* have been recalled due to reported cases of cancer, but the association is considered rather biologically implausible.[102] The combined use of ACEI and ARB is not recommended for the treatment of hypertension.[103,104] They are not contraindicated in hospitalized patients with Covid-19.[105]

Since ARB and ACEI both increase plasma renin activity, the direct renin inhibitor *aliskiren* (150-300 mg od) has the potential to be more beneficial. It has been shown to have comparable efficacy and side effects with ARBs.[106] Combinations of aliskiren with valsartan or amlodipine have been more effective than either drug alone.[107,108] However, aliskiren should not be used with an ACEI or ARB in patients with type 2 diabetes and renal impairment. The ALTITUDE trial was stopped due to an increased incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension with this combination.[109]

Calcium Channel Blockers

Both long-acting dihydropyridines and non-dihydropyridine calcium channel blockers have been studied in hypertension and are now considered first choice drugs together with ACEI/ARB.

However, as monotherapy, CCB are inferior to ACEI, ARB, and diuretics for reducing the risk of acute myocardial infarction, congestive heart failure, and major cardiovascular events.[110]

CCB may offer protection against ***dementia*** due to reduction of excess intracellular free calcium in neurons, which seems to happen in patients with dementia of the Alzheimer's type,[57,93] and are superior to other drugs for the prevention of ***stroke***.[111] *Diltiazem* and *verapamil* cause less peripheral edema than dihydropyridines and no tachycardia, and are better tolerated (particularly diltiazem, since verapamil may cause constipation). They can be added to a scheme containing a dihydropyridine in resistant cases. They are especially useful in patients with ***chronic renal disease***, and renal transplantation,[112,113] but care is needed because diltiazem may interfere with cyclosporine levels. The combination of CCB with renin-angiotensin system blockers reduce the risk of CCB-associated ***peripheral edema*** and ACEI might be more efficacious than ARB in this respect.[114] However, there is evidence that patients with hypertension, and especially diabetics, treated with CCB have increased incident HF.[115] All CCB are contraindicated in ***heart failure***, and diltiazem and verapamil in ***sick sinus syndrome***, ***AV nodal conduction disease*** and concomitant use of high doses of beta blockers. An association of CCB, and possibly diuretics, with ***chronic eczematous eruptions*** in patients older than 50 years has been reported.[116] In the elderly, concurrent use of *clarithromycin* a CYP3A4 inhibitor has been associated with increased levels of CCB, hypotensive episodes, and a greater 30-day risk of hospitalization with acute kidney injury.[73]

Third generation CCB such as *lercanidipine, lacidipine* and *manidipine* may induce less peripheral oedema than other digydropyridines.[117] In case of CCB poisoning, charcoal decontamination may be considered up to 1 hour after ingestion. For symptomatic patients, IV calcium, high-dose insulin therapy (1 unit/kg bolus followed by 1 unit/kg/hour with dextrose and close potassium monitoring), and norepinephrine or epinephrine are used. Lipid emulsion and temporary pacing may also be needed in refractory cases.[118]

Thiazide diuretics

Thiazides and thiazide-like diuretics are still considered as a first-line therapy for hypertension.[79] Thiazides exert their action by reducing extracellular fluid and plasma volume, leading to deceased cardiac preload. They also reduce systemic vascular resistance but the exact mechanisms are unclear. Secondary activation of the rennin-aldosterone-axis makes their combination with ACEI/ARB attractive. They are particularly indicated in low-renin or salt-sensitive hypertension (elderly, obese, blacks), and in resistant hypertension. They are superior to other drugs for the prevention of heart failure,[111] and are associated with a lower rate of hip and pelvic fracture compared to ACEI and, probably, CCB.[70]

Thiazides effectively reduce blood pressure and the risk of cardiovascular events but at a risk of an excess of 3-4% of new cases of ***diabetes*** over several years compared to other antihypertensive medications.[119] Patients with hypertension have a higher risk of developing new-onset diabetes in general, and that risk, although relatively small, is higher with diuretics in patients with impaired

glucose tolerance and cardiovascular risk factors.[120] However, as discussed, their use in diabetes is not precluded. The odds ratio of developing it with diuretics almost doubles compared to ARB (odds ratio for ARB 0.57, ACEI 0.67, CCB 0.75, placebo 0.77, beta blocker 0.90, with diuretics as reference).[121] In the ALLHAT study, the largest randomized trial performed to date, *chlorthalidone* (12.5-25 mg daily) was more effective in reducing systolic blood pressure and cardiovascular complications than lisinopril (10-40 mg daily) or amlodipine (2.5-10 mg daily), but at an increased risk of diabetes.[122] Chlorthalidone is a thiazide-like diuretic that binds to erythrocyte carbonic hydrase and has a longer half-life than hydrochlorothiazide. It is twice as potent as hydrochlorothiazide,[123] but produces more pronounced hypokalemia, without any differences in major cardiovascular outcome events or non–cancer-related deaths.[124,125] It seems that the difference in antihypertensive efficacy of various thiazides is mainly due to their potency.[126] It seems that *hydrochlorothiazide* in doses 12.5-25 mg is significantly less effective as monotherapy in reducing blood pressure compared to ARB, ACEI, beta blockers and CCB.[127] and may not be ideal as a monotherapy drug.[128] Thiazides are a reasonable choice in obese patients with excess volume, but they are less protective than calcium channel blockers against cardiovascular events in lean patients.[88] *Indapamide* is a non-thiazide sulphonamide that has vasodilation activity, and is more potent than hydrochlorothiazide at commonly prescribed doses without evidence for greater adverse metabolic effects in a recent systematic review.[129] In general, thiazide use is a risk factor for hyponatremia and hypokalemia, and the effect appears to be dose-dependent and highly variable depending on the substance. Syncope and falls seem to be causally related to thiazide use especially in the elderly.[130]

Thiazides are considered ineffective when the ***glomerular filtration rate*** decreases below 30-40 ml/min/1.73 m^2 of BSA, since the reduced glomerular filtration rate limits the overall filtered sodium load reaching the distal tubule, and reabsorption in the distal tubule is only modestly effective as compared with that in the thick ascending limb, although direct evidence is lacking. Traditionally, they are usually replaced by loop diuretics when serum creatinine levels exceed roughly 2mg/dl. However in a small RCT, among patients with advanced chronic kidney disease and poorly controlled hypertension, chlorthalidone therapy improved blood-pressure control at 12 weeks as compared with placebo.[131]

Hypokalemia and ***hypomagnesemia*** are common, especially in the elderly and with hydroxyclorothiazide or chlorthalidone doses exceeding 25 mg daily. Hydrochlorothiazide appears safer than chlorothalidone in the elderly, in this respect.[124] Hypokalemia is managed by salt restriction, hypomagnesemia correction, and addition of an ARB/ACEI or a potassium-sparing diuretic (preferred to supplemental KCl). These should be also considered from the beginning of therapy if baseline potassium levels are <3.8 mmol/L. Potassium homoestasis is important in view of the evidence that potassium levels outside the interval of 4.1–4.7 mmol/L are associated with increased mortality risk in patients with hypertension.[132] Hypokalemia (<3.5 mmol/L) reduces repolarization reserve by inhibiting K+ channel and suppressing Na+-K+ ATPase with consequent

intracellular Na+ and Ca+ loading and early and delayed afterdepolarization-mediated arrhythmogenocity.[133] In addition, hypokalemia is implicated in thiazide-induced dysglecemia, and the development of coronary events.[134] ***Dilutional hyponatremia*** may also occur especially with combinations with loop diuretics. SSRIs and excessive water intake should be avoided. Hyponatraemia (serum sodium concentration <135 mmol/l), is the most common disorder of body fluid and electrolyte balance encountered in clinical practice. Guidelines for its treatment have been published.[135] Correction of hypokalemia and hypomagnesemia may also reduce night ***muscle cramps***. Alternatively, vitamin B complex, calcium channel blockers such as diltiazem, and naftidrofuryl oxalate (a drug that may enhance utilization of oxygen and glucose in peripheral vascular disease and protection of brain parenchyma during anoxia), may be tried.[136] Quinine derivatives are better avoided for routine use because of the potential of toxicity. PPIs may also promote hypomagnesemia.[137] ***Hypercalcaemia*** may also occur with thiazides, especially in elderly females, but it is usually mild unless there is underlying primary hyperparathyroidism (34% of these patients).[138]

Thiazides reduce the excretion of calcium and uric acid and exacerbations of ***gout*** may require discontinuation of the thiazide during the acute attack if uric acid levels are significantly elevated.[139] Reduced uric acid excretion is also accentuated by low dose aspirin administration. Uricosuric prophylaxis may be needed in the long-term.

Thiazides may increase total ***cholesterol and LDL*** by 5-7% in the first year of therapy.[119]

Concerns have been raised about the long-term use of thiazides with ***squamous cell carcinoma and melanoma***.[140]

Loop diuretics

Loop diuretics are less effective in reducing blood pressure than thiazides.[119] Usually frusemide is used in diuretic tolerance (see Chapter 33), or renal failure (glomerular filtration rate <40 ml/min/1.73 m^2 of BSA, usually but not invariably corresponding to a creatinine>2.5 mg/dl). Bumetanide and torsemide may be used in patients not responsive to furosemide.

Aldosterone antagonists

The use of thiazide diuretics can provoke hypokalemia, especially when there is unrecognized primary aldosteronism pathophysiology, and thiazide diuretics increase insulin resistance and sympathetic nervous system activity, which can be abrogated by early mineralocorticoid receptor antagonist therapy.[141] Eplerenone is a selective aldosterone antagonist that combined with enalapril decreases proteinuria and LVH beyond what is achieved by either drug alone.[142,143] Renal function and serum potassium levels must be closely monitored due to the risk of hyperkalemia especially when these agents are used together with an ACE or ARB. Spironolactone is also effective but may cause painful gynecomastia in men (antagonist of aldosterone and androgen and progesterone receptors). Aldosterone antagonists have been found particularly effective in patients who are obese or have sleep apnea.[144] and may also be useful in resistant hypertension.[145] They should not be used in

the presence of hyperkalemia (K >5 mmol/l), or creatinine>2.5 mg/dl. Baxdrostat, a highly selective aldosterone synthase inhibitor is under study.[146]

Potassium-sparing agents

Potassium-sparing agents are amiloride and triamterene**.** Amiloride is an epithelial sodium channel blocker that is more effective than spironolactone in blacks with drug-resistant hypertension.[147] It is combined with thiazides for correction of hypokalemia. Concerns have also been raised about a possible association between all diuretics and ***renal carcinoma,*** although hypertension itself increases the risk of malignant disease.[148]

Beta blockers

In patients with uncomplicated hypertension beta blockers exert no effect in reducing stroke, and do not have any protective effect with regard to coronary artery disease. They may increase the risk for new-onset diabetes,[149-152] although this finding is not consistent.[120] In contrast to what occurs patients with myocardial infarction and heart failure, beta-blocker-associated reduction in heart rate may increase the risk of cardiovascular events and death in hypertensive patients.[150,153] These effects has been attributed to suboptimal effect in lowering blood pressure compared to other drugs, their "pseudoantihypertensive" efficacy (failure to lower central aortic pressure), lack of an effect on regression of left ventricular hypertrophy and endothelial dysfunction, and unfavorable metabolic effects such as an increased risk of diabetes.[96] However, much of the unfavorable data were collected from studies involving traditional β blockers, such as atenolol. Vasodilatory third generation β blockers (i.e., carvedilol and nebivolol) reduce blood pressure in large part through reducing systemic vascular resistance rather than by decreasing cardiac output, and have less effects on metabolic and lipid parameters. In addition, blockade of the β-adrenergic receptor ADRB1 boosts killer T cell ($CD8^+$ T) function by preventing its terminal exhaustion and inducing effective anti-tumour T cell responses.[154] ***Carvedilol*** is a very slightly β_1 -selective beta blocker that becomes non-selective at higher doses. In addition, it possesses alpha 1-blocking (vasodilatory) and antioxidant properties.[155] ***Nebivolol*** is the most β_1 -selective beta blocker (3-fold that of bisoprolol and more than 4-fold that of metoprolol) at doses <10 mg. It does not have sympathomimetic activity but it is an agonist of β_2 and β_3 receptors and can cause relatively less bronchoconstriction or sexual dysfunction. It also improves endothelial dysfunction and may via stimulation of endothelial nitric oxide synthase and antioxidant properties.[156] According to published evidence, beta blockers, in general, are indicated in hypertensive patients with ***prior myocardial infarction*** (*metoprolol*), ***heart failure*** (*carvedilol, metoprolol, bisoprolol*, and *nebivolol* in the elderly), ***arrhythmias*** (*carvedilol, metoprolol, bisoprolol*), patients <60 years old with ***increased sympathetic activity*** (*metoprolol, bisoprolol, carvedilol, nebivol*ol). In ***pheochromocytoma***, *labetalol*, a beta and alpha blocker is preferred to avoid unopposed a-mediated vasoconstriction. ***COPD*** is not a contraindication for their use.[157,158] In patients with mild to moderate ***asthma*** (not in the acute phase) cardioselective beta blockers may be used in minimum doses.[159]

In case of beta blocker poisoning, charcoal decontamination may be considered up to 1 hour after ingestion. For symptomatic patients, high-dose insulin therapy (1 unit/kg bolus followed by 1 unit/kg/hour with dextrose and close potassium monitoring) or high-dose glucagon infusion, and norepinephrine or epinephrine are used. Lipid emulsion and temporary pacing may also be needed.[160]

Adherence to Medication

Recommenadtiosn are provided in Table 12 and Figure 7. Recommendatuons for **orthostatic hypotension** are provided in Table 13.

Specific conditions

Diabetes mellitus

In patients with ***diabetes mellitus***, recommended target values are < 130/80 mm Hg (Table 14). In the ACCORD trial, in patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. However strokes were significantly reduced in the intensive therapy group.[161] A benefit of intensive therapy has been shown in the ADVANCE trial.[162] In the BROAD RCT, the incidence of major cardiovascular events has also been found significantly lower with intensive treatment targeting a systolic blood pressure of < 120 mm Hg than with a systolic blood pressure of <140 mm Hg.[163]

In patients with type 2 diabetes an ACE inhibitor or ARB is necessary, particularly in diabetic nephropathy with proteinuria. In a recent meta-analysis ACE inhibitors were associated with a 13% to 17% risk reduction in all-cause mortality, cardiovascular mortality, and major cardiovascular events, while ARBs did not show a similar benefit, with the exception of heart failure.[95] ACE inhibitors should also be ideally combined with calcium channel blockers in diabetics.[164] Thiazides are associated with increased risk for new-onset diabetes,[120-122] but their use is not precluded since they are usually necessary in combination therapies for control of hypertension in diabetics. Treatment strategies should consider intervention against all cardiovascular risk factors, including a statin. Because of the greater chance of postural hypotension, blood pressure should also be measured in the erect posture. In patients with the ***metabolic syndrome*** (visceral obesity, impaired glucose metabolism, hyperlipidemia and hypertension), drug treatment should start with a blocker of the renin-angiotensin system followed, if needed, by the addition of a calcium antagonist or a low-dose thiazide diuretic. ***Statins*** should be most probably given to all diabetics with hypertension especially those above the age of 40.[165] The Canadian Diabetes Association recommend that all diabetics should take statins when >40 years, and antihypertensive drugs when >55 years even in the absence of hypertension or other risk factors.[166]

Coronary artery disease

Hypertension is a major risk factor for coronary artery disease. Therapy is mandatory, but systolic blood pressure < 120 mm Hg and diastolic < 70 mm Hg were each associated with should be

avoided.[37,40,41] Recommendations for patients with coronary artery disease are provided in Figure 6 and Table 15.

Heart failure

Recommendations for patients with heart failure or reduced LVEF are presented in the relevant Chapter on Heart Failure.

Cerebrovascular disease

In patients with a history of stroke or TIAs, antihypertensive treatment has markedly reduced the incidence of stroke recurrence in almost all large RCTs, using different drug regimens. Although target values <130/80 mmHg have been recommended, hard evidence on this issue is lacking, and, as discussed, diastolic values <70 mm Hg should be avoided, especially in the elderly and in patients with coronary artery disease.[39] [37,40,41,43,54] Calcium channel blockers may have a slightly greater efficacy in stroke prevention (see below), but in clinical practice, all regimens are acceptable for stroke prevention. Recommendations for patients with cerebrovascular disease and embolic or haemorrhagic stroke are provided in Table 16.

Chronic Kidney Disease

In patients with renal impairment, BP control is mandatory. In patients with proteinuria (>3 g /24h), a BP <130/80 results in lower decline of renal function.[167] An angiotensin receptor blocker or an ACE inhibitor (but not the combination of both), often with loop diuretics are required (Table 17). An ARB combined with a calcium channel blocker slows progression of nephropathy to a greater extent than when combined with a thiazide.[168] All antihypertensive drugs except diuretics can be used in the haemodialysis patients, with doses determined by the haemodynamic instability and the ability of the drug to be dialysed. An integrated therapeutic intervention (antihypertensive, statin and antiplatelet therapy) has to be considered in patients with renal damage. When NSAIDs are prescribed, concomitant administration of an ACE (or ARB) and a diuretic may be associated with increased risk of kidney injury.[169]

Peripheral arterial disease

Patients with peripheral artery disease and atherosclerosis, should be treated as patients without peripheral arterial disease (Table 18).

Cancer

Several chemotherapy agents may cause arterial hypertension (e.g. VEGFi, second- and third-generation BCR-ABL TKI, brigatinib, ibrutinib, fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide). Recommendations are presented in Table 19, and Figures 8 and 9.

Non-cardiac surgery

Non-cardiac surgery may not be deferred with BP <180/110 mmHg (Table 20).

Treatment of cardiovascular risk factors and follow-up

Titration to BP control requires regular visits followed by 6-month follow-up after establishment of

normal values. Therapy is usually needed for life unless if life-style modifications are successful. Several strategies may improve hypertension control and modify cardiovascular risk factors (Table 21, and Figure 10).

Resistant Hypertension

Resistant hypertension is defined as BP remaining above goal despite three or more BP-lowering drugs of different classes at maximally tolerated doses, of which one is a diuretic (Tables 22 and 23).[19,20] However, there is no consensus on a uniform definition for resistant hypertension, and its exact prevalence is not known, with reported values in the real world ranging from 12 to 18%.[170] A higher prevalence (up to 40%) has been reported among treated hypertensive adults in clinical trials (REGARDS, CRIC, INVEST, NHANES, ALLHAT, and others) but this is likely explained by the selection of patients with demographic and comorbidity characteristics that place them at high risk for cardiovascular disease.[170,171] Refractory hypertension can be either true or apparent ie pseudohypertension, due to bad measuring technique or non-adherence to treatment. Since volume overload is the commonest cause of resistant hypertension, diuretics are essential.[172] Hyperaldosteronism is also common in patients with resistant hypertension, including those with low renin activity,[173] and a mineralocorticoid receptor antagonists may be useful in resistant cases despite the use of an ACEI/ARB, diuretic and calcium channel blocker.[145]

The management of resistant hypertension (Tables 24 and 25, and Figure 11) can be improved by evaluating whether the failure of blood pressure control results from sodium-volume excess (*low plasma renin activity*), insufficiently blocked renin levels (*high plasma renin activity*), or a combination of both (*medium plasma renin activity*) and adjusting therapy accordingly.[174,175] Low plasma renin activity indicates a diuretic or an aldosterone inhibitor, since low-renin hypertensives have a high prevalence of adrenocortical adenomas and primary aldosteronism.[173] High plasma renin activity indicates an ACEI or ARB or a direct renin inhibitor such as aliskiren, and if this fails addition of a vasodilating beta blocker such as carvedilol or nebivolol. In patients with normal PRA who are already on triple therapy of ACEI/ARB, diuretic and calcium channel blockers, an aldosterone antagonist, especially if the patient is obese or has sleep apnea is beneficial. Patients with treatment-resistant hypertension usually have a good antihypertensive response to aldosterone antagonists.[69] Mineralocorticoid receptor antagonists (MRAs) can block the mineralocorticoid receptor-mediated pathophysiological effects of aldosterone but induce dose-related counter-regulatory increases in renin and circulating aldosterone concentrations that may stimulate MR-independent effects of aldosterone.[176] An alternative therapeutic approach is direct inhibition of aldosterone synthase, which catalyzes the final three steps in aldosterone biosynthesis. In the BaxHTN RCT, Baxdrostat, a highly selective, potent aldosterone synthase inhibitor added to

background therapy resulted in a reduction in seated-systolic BP at 12 weeks compared with placebo in patients with uncontrolled or resistant hypertension.[177]

If BP control is still not achieved with full doses of a 4-drug combination, use of other agents such as a-blockers (*doxazosin* 4-8 mg od),[178] the imidazoline I_1-receptor agonist *moxonidine* (0.2-0.4 mg od) that has favourable effects on the insulin resistance syndrome), drugs with central action on the sympathetic system (alpha-agonists such as *methyldopa* (250-750 mg bd) and *clonidine*, or vasodilators such as *hydralazine* may be needed. However, these agents are effective for lowering BP, but have poor tolerability and lack of positive outcome data. Moxonidine, clonidine, and hydralazine without a nitrate should be avoided in ischaemic heart failure.[40] Novel drugs such as endothelin-receptor antagonists (*darusentan*), and gene-therapies are under study.[179] Intensive lipid-lowering is also recommended in patients with treatment-resistant hypertension.[180]

Device-based Therapy

Renal denervation is now an adjunct treatment option for cases of resistant hypertension, and the efficacy and safety of the multi-electrode Symplicity Spyral RDN catheter system (Medtronic) and the Paradise ultrasound catheter system (ReCor) have been documented (Table 25).[20,181,182] Serious complications such as renal artery dissection or rupture are very rare. Following the initial conflicting results of the SYMPLICITY HTN-2 trial,[183] and SYMPLICITY HTN-3 trials,[184,185] results have been consistent in subsequent trials. In the DENERGTN trial, renal denervation plus standardized stepped-care antihypertensive treatment resulted in a greater decrease in blood pressure than standardized stepped-care antihypertensive treatment alone.[186] In the SPYRAL-HTN ON (OFF) MED RCTs in patients in the presence or the absence of medication, renal denervation in the main renal arteries and branches significantly reduced blood pressure compared with sham control with no major safety events.[187-189] In the RADIANCE-HTN SOLO RCT, it reduced ambulatory blood pressure at 2 months in patients with mild to moderate hypertension in the absence of medications,[190] and controlled hypertension with less medication in patients with resistant hypertension.[191,192] In the RADIANCE-HTN TRIO renal denervation reduced blood pressure at 2 months in patients resistant to three or more antihypertensive medications.[193] These results were maintained 6 months after the procedure.[194] In a subsequent meta-analysis on RCTs using radiofrequency denervation, there was also a significant reduction of blood pressure with intervention.[195] Long-term (3-year) data from the SPYRAL HTN-ON MED RCT,[189] the SYMPLICITY HTN-3 RCT,[196] and the SYMPLICITY Registry,[197] and a subsequent meta-analysis,[198] have also demonstrated the safety and efficacy of the procedure. Renal denervation appears more effective in patients with heart rates ≥70 beats/min, possibly caused by increased sympathetic tone.[199] Renal denervation is also under study for atrial fibrillation and heart failure.[182,200] Ultrasound renal denervation has also reduced daytime ambulatory systolic BP in the absence of antihypertensive medications without postprocedural major adverse events.[201] In the 2023 Guidelines of the European Society of Hypertension, renal denervation is considered as a treatment option in patients with an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of

antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.[202] The FDA in 2023 approved 2 renal denervation systems, the ultrasound-based uRDN Recor Paradise, and the multipolar radiofrequency Medtronic Spyral for the treatment of resistant hypertension.

Renal denervation mediated by dehydrated alcohol delivered into the perivascular space surrounding the renal artery is a new promising therapeutic modality (TARGET BP I RCT).[203] Other methods for therapeutic intervention such as modulation of the sympathetic nervous system, central iliac arteriovenous anastomosis, and other targets, are under study.[204-206]

Hypertensive Emergencies

Hypertensive emergencies are defined as large elevations in BP (systolic >180 mmHg or >diastolic >120 mmHg associated with impending or progressive organ damage such as major neurological changes, hypertensive encephalopathy, cerebral infarction, intracranial haemorrhage, acute LV failure, acute pulmonary oedema, aortic dissection, renal failure, or eclampsia. [207] Nonadherence to the antihypertensive regimen remains the most common cause for malignant hypertension, although antiangiogenic and immunosuppressant therapy can also trigger hypertensive emergencies.[208] Severe acute arterial hypertension without obvious organ damage is usually defined as hypertensive crisis.[209] Hypertension with a diastolic BP>140 mm Hg consists an emergency. Care should be taken that extremely rapid falls in blood pressure may not be associated with complications such as underperfusion of the brain and cerebral infarction or damage to the myocardium and kidneys. Excessive or rapid reductions in blood pressure should be avoided in acute stroke. A reasonable approach is to lower her blood pressure by approximately 20 to 25% in the first hour and aim for a blood pressure of approximately 160/100 mm Hg by 6 hours.[210] Therapeutic schemes and drugs are presented in Tables 26 and 27, and Figure 11. [207]

Nitroprusside is the most effective agent but it lowers venous return and cardiac output and may increase intracranial pressure. Potential complications are nausea, vomiting, muscle twitching, sweating, thiocynate and cyanide intoxication. *Fenoldopam* is useful for most hypertensive emergencies but caution is required with glaucoma. Liquid or sublingual *nifedipine* results in ischemic complications due to too rapid reduction of blood pressure and is no longer recommended. Treatment of preeclampsia and phechromocytoma are discussed in the relevant sections.

Hypertension in Pregnancy

In pregnancy, BP initially declines (Tables 28 and 29, and Figure 12), following which systolic and diastolic BP progressively increase by an average of ≈8 mm Hg by the time of delivery.[211] Hypertension in pregnancy is typically defined as systolic BP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg, measured using repeated BP readings in the office or hospital on two separate occasions

or ≥15 min apart in severe hypertension (≥160/110 mmHg) (Table 30). Hypertension complicates 5% to 10% of all pregnancies and is a leading cause of maternal and fetal morbidity and mortality globally.[211,212] Elevated blood pressure during pregnancy, regardless of type and even without known risk factors, indicates high risk of later cardiovascular disease, chronic kidney disease, and diabetes mellitus.[213 214] Hypertensive disorders of pregnancy were associated with a nearly 2-fold higher risk of premature cardiovascular disease within the first decade postpartum.[215]

Gestational hypertension is defined as a systolic BP 140 mm Hg or more or a diastolic BP of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure pregnancy-induced hypertension, and complicates 6–7% of pregnancies. Gestational hypertension is considered severe when the systolic level reaches 160 mm Hg or the diastolic level reaches 110 mm Hg, or both. On occasion, especially when faced with severe hypertension, the diagnosis may need to be confirmed within a shorter interval (minutes) than 4 hours to facilitate timely antihypertensive therapy.[216,217]

Preeclampsia is a disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term (Figures 13 and 14).[216] Preeclampsia complicates 2 to 4% of pregnancies globally, and is associated with approximately 46,000 maternal deaths and approximately 500,000 fetal and newborn deaths annually.[218] It has been traditionally defined by the de novo appearance of hypertension, accompanied by new-onset of significant proteinuria (≥0.3 g/day in a 24 h urine collection or ≥30 mg/mmol urinary creatinine in a spot random urine sample) (Table 31).[219] However, it may present in some women in the absence of proteinuria.[216] Pre-eclampsia increases to 25% in women with pre-existing hypertension, and occurs more frequently during the first pregnancy, in multiple fetuses, hydatidiform mole, or diabetes, and is one of the most common causes of prematurity.[220] Reliance on maternal symptoms may be occasionally problematic in clinical practice. Right upper quadrant or epigastric pain is thought to be due to periportal and focal parenchymal necrosis, hepatic cell edema, or Glisson's capsule distension, or a combination. However, there is not always a good correlation between the hepatic histopathology and laboratory abnormalities. Similarly, studies have found that using headache as a diagnostic criterion for preeclampsia with severe features is unreliable and nonspecific.[216]

Eclampsia is the convulsive manifestation of the hypertensive disorders of pregnancy and is among the more severe manifestations of the disease. Eclampsia is defined by new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use.[216]

Therapy

Low-dose aspirin (60-80 mg) beginning in the late first trimester may reduce preeclampsia in high-risk women.[216] Bed rest and salt restriction are not recommended any more. Non-pharmacological management (including close supervision and restriction of activities) is considered for pregnant women with systolic BP 140-149 mmHg or diastolic BP 90–95 mmHg (Table 30 and 31, and Figures

15 and 16). However, in the CHAP RCT, a strategy of targeting a blood pressure of less than 140/90 mm Hg was associated with better pregnancy outcomes than a strategy of reserving treatment only for severe hypertension.[221] Treatment within 30 to 60 min of confirmed severe hypertension (≥160/110 mm Hg and persistent for 15 minutes) should be initiated to reduce the risk of maternal heart failure, myocardial ischemia, stroke, or renal disease.[222] Antihypertensive therapy should be continued in postpartum patients with persistent hypertension (≥150/100 mm Hg).[222] In a multicenter RCT, tight control of mild-to-moderate nonproteinuric hypertension in pregnancy (diastolic blood-pressure targets, 100 mm Hg and 85 mm Hg, respectively) conferred no apparent benefits to the fetus, and only a moderate benefit (a lower rate of progression to severe hypertension) for the mother. However, tight control, as targeted in this study, did not carry major risks for the fetus or newborn.[223]

Labetalol, nifedipine, and methyldopa and hydralazine are the recommended drugs (Tables 32 and 33).[224] All *beta blockers* can cause bradycardia and hypoglycaemia in foetus. As beta-1 selective beta-blockers are less likely to affect uterine relaxation, they are preferred.[225] Maternal use of beta-blockers in the first trimester have not been associated with a large increase in the risk for overall malformations or cardiac malformations.[226,227] However, in the EUROmediCAT study an association between alpha/beta-adrenergic blocker use in the first trimester with multi-cystic renal dysplasia was reported.[228] There have been concerns about low weight for gestational age with *beta blockers* and especially atenolol,[229,230] although the effects reported may not be large enough to be of clinical importance. Exposure to atenolol has been associated with a higher risk of infants born small for gestational age compared with metoprolol and propranolol, consistent with this association not being a class effect.[231,232] *Diltiazem* has been found teratogenic in animals, with only limited human data, and its use is not generally recommended in pregnancy. *Verapamil* is considered safer than diltiazem and could be used as a second-line drug.[232] *Hydrochlorothiazide* may also be used since previous concerns about increased risk are not supported by recent data.[230] *ACEI and ARB* are contraindicated, especially in the second and third trimester.[230]

Systolic BP levels ≥170 or diastolic BP ≥110 mmHg should be considered an emergency requiring hospitalization. Oral *labetalol* (100-400 mg tds up to 1200 mg/d), oral *nifedipine* (long-acting 20-120 mg od), and oral *methyldopa* (250 -500 mg tds up to 2000 mg/d) are the drugs of choice.[220] In emergency, *IV labetalol*, *IV or IM hydralazine,* and *oral nifedipine* are indicated.[216] Induction of delivery is also recommended in gestational hypertension with proteinuria with adverse conditions such as visual disturbances, coagulation abnormalities, or fetal distress. *Calcium-channel blockers, diuretics*, and *ACEI*, pose little risk to ***breast-fed infants***. *Beta blockers*, especially those not secreted by the kidneys may be given under supervision of the baby.[233] Untreated hypertension, late initiation of treatment and non-selective beta blockers have been associated with an increased risk of hypospadias.[234] A detailed description of drug safety during pregnancy is presented in Appendix 6.

Currently, no disease-modifying therapy is available for established **preeclampsia.** However, *magnesium* may be helpful, and *steroids* may be indicated in selected patients. *Metformin* (3 g per

day) also shows particular promise and many trials are under way.[218] Anti-hypertensive treatment consists of *oral nifedipine* or *parenteral labetalol* or *hydralazine*. In preeclampsia with pulmonary oedema, *nitroglycerine* is the drug of choice; diuretic therapy is inappropriate because plasma volume is reduced. Patients who subsequently develop early-onset preeclampsia, exhibit depressed circulating Placental Growth Factor (PlGF) levels as early as late first or early second trimester, and the integration of PlGF testing and noninvasive hemodynamic monitoring may allow a phenotype-driven, tailored clinical care to high-risk pregnant patients.[235]

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