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Hypertension management in patients with cardiovascular comorbidities

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Abstract

Arterial hypertension is a leading cause of death globally. Due to ageing, the rising incidence of obesity, and socioeconomic and environmental changes, its incidence increases worldwide. Hypertension commonly coexists with Type 2 diabetes, obesity, dyslipidaemia, sedentary lifestyle, and smoking leading to risk amplification. Blood pressure lowering by lifestyle modifications and antihypertensive drugs reduce cardiovascular (CV) morbidity and mortality. Guidelines recommend dual- and triple-combination therapies using renin–angiotensin system blockers, calcium channel blockers, and/or a diuretic. Comorbidities often complicate management. New drugs such as angiotensin receptor–neprilysin inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists improve CV and renal outcomes. Catheter-based renal denervation could offer an alternative treatment option in comorbid hypertension associated with increased sympathetic nerve activity. This review summarises the latest clinical evidence for managing hypertension with CV comorbidities.

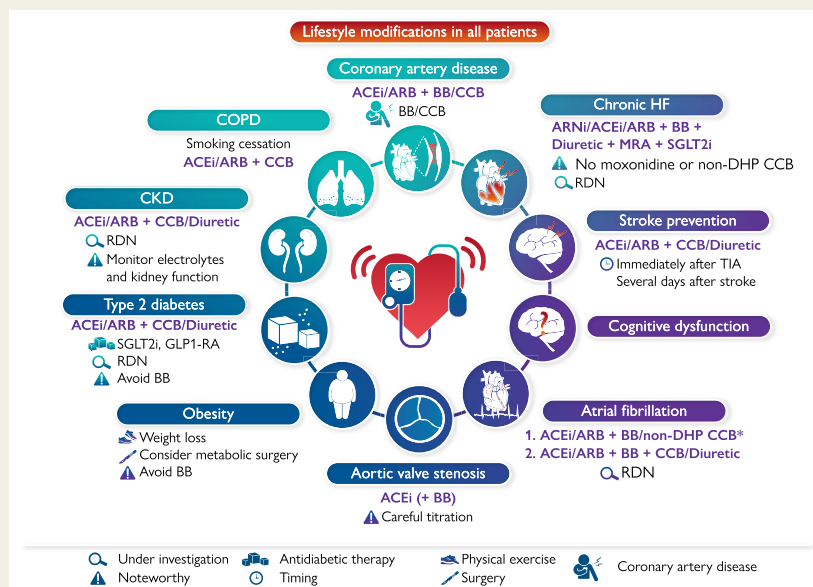
Keywords

Hypertension • Cardiovascular comorbidities • Heart failure • Chronic kidney disease • Atrial fibrillation • Chronic obstructive pulmonary disease • Obesity • Diabetes mellitus • Stroke • Transient ischemic attack • Aortic valve stenosis

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Graphical Abstract



Dependent on comorbidities, some medications should be preferred while others are contraindicated. Catheter-based renal denervation is under investigation (indicated by the magnifying glass) for patients with hypertension and comorbidities associated with increased sympathetic nervous system activity. *Combination of beta-blockers with non-dihydropyridine calcium channel blockers (e.g. verapamil or diltiazem) is not recommended due to a potential risk of heart block or bradycardia. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; GLP1-RA, glucagon-like peptide 1 receptor agonist; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RDN, renal denervation; SGLT2i, sodium–glucose cotransporter 2 inhibitor; TIA, transient ischaemic attack.

Epidemiology

High systolic blood pressure (SBP) is the most prevalent modifiable cardiovascular (CV) risk factor and a leading cause of death,¹ accounting for 10.8 million deaths globally.¹ While high SBP is the leading cause of death in females, it is second to tobacco consumption in males.¹ Both systolic and diastolic hypertension are independently associated with CV events.² While SBP increases linearly with increasing age, diastolic blood pressure (DBP) typically falls from mid-life (>50–60 years) due to arterial stiffening.³ The prevalence of raised blood pressure (BP) increased from 594 million in 1975 to 1.13 billion in 2015.⁴ Although the incidence has shifted from high- to low-income countries, incident hypertension remains high in Europe and the USA⁴ with a lifetime risk of >75%.⁵ Its prevalence is higher in the black than in the non-black population.^{6,7} Blood pressure lowering reduces the risk for CV morbidity and all-cause mortality, irrespective of sex and ethnicity.^{8–10} Disease awareness and BP control rates remain poor worldwide^{11,12} since only 47% of women and 38% of men with hypertension received antihypertensive therapy.¹² Of these, 23% of women and 18% of men achieved BP control.¹² Control rates are particularly low in racial and ethnic minorities.⁷

Hypertension-mediated organ damage

High BP causes CV end-organ damage¹³ and elevates the risk for chronic kidney disease (CKD) and stroke in concert with other CV risk factors.^{14,15} This risk association is higher in black than non-black adults.¹⁶ The risk of death increases starting at an SBP and DBP as low as 90/75 mmHg^{14,15,17} and more steeply at lower BP in women than in men before midlife.¹⁸ The coexistence of other CV risk factors additional to high BP^{19,20} exponentially increases the risk of CV events, such as myocardial infarction, and CV death.^{21,22} Blood pressure lowering results in greater absolute risk reductions when baseline risk is high.²³

Treatment targets

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) hypertension guidelines recommend targeting an office BP <140/90 mmHg. If tolerated, office SBP should be reduced to 120–129 mmHg. These targets are based on meta-analyses^{8,24} and the Systolic Blood Pressure Intervention Trial (SPRINT), showing at high

CV risk without diabetes that intensive BP lowering (treatment goal office SBP <120 mmHg unattended) reduced major CV events and all-cause death by ~25% compared with a lenient BP target (office SBP <140 mmHg unattended).^{25,26} These effects were maintained after including the data of the observational post-intervention period.²⁶ The rate of acute decompensated heart failure (HF) was higher in the intensive treatment group during the post-intervention period.²⁶ A network meta-analysis showed a linear association between mean achieved SBP and risk of CV disease with the lowest risk at 120–124 mmHg.⁹ Of note, in Action to Control Cardiovascular Risk in Diabetes targeting an SBP <120 mmHg in patients with Type 2 diabetes and high CV risk did not reduce the composite outcome of non-fatal myocardial infarction, non-fatal stroke, or CV death compared with an SBP target of <140 mmHg.²⁷ The target for office DBP is <80 mmHg.²⁸

Office SBP should not be lowered to <120 mmHg, and office DBP should not be lowered to <70 mmHg. Low BP (e.g. office SBP <110 mmHg) has been associated with adverse CV outcomes in patients with stable coronary artery disease²⁹ and high CV risk.³⁰ The phenomenon in which BP below and above a nadir is associated with increased risk is called the *J-curve phenomenon*.³¹ It has been speculated that the risk associated with too low BP levels rises more steeply at low BP in patients with micro- and macrovascular events (but not stroke).³² Patients with diabetes had consistently higher risks over the whole BP range, and relative risks for CV events did not differ between those with and without diabetes.³² The risk of too low on-treatment BP has often been attributed to reverse causation.³³ Reverse causation refers to a phenomenon in which the pre-morbid condition alters the risk factor, for example, the increase in risk at low BP because of progressing disease, comorbidities, or frailty.^{33,34} Particularly, the causal relationship between lower DBP and stiffening of the aorta and large arteries contributes to increased CV risk.^{35,36} The risk associated with low DBP was eliminated by reperfusion or revascularization therapies suggesting a relevant relationship between low DBP, low coronary perfusion pressure, and increased risk.^{37,38} Both very low and very high on-treatment BP may reflect advanced disease associated with high CV risk.

In fit patients aged >65 years, the ESC/ESH hypertension guidelines recommend office SBP targets between 130 and 139 mmHg if tolerated.²⁸ STEP showed that in Chinese patients aged 60–80 years, an intensive treatment target of 110–129 mmHg was associated with lower CV event incidence than at 130–149 mmHg.³⁹ Intensive treatment was well tolerated but associated with higher rates of hypotension.³⁹ Lowering SBP <130 mmHg in fit older patients might be effective and safe, but BP treatment targets should be individualized for very old and frail patients.

Treatment algorithm

Lifestyle modifications should precede and accompany antihypertensive drug therapy.²⁸ Interventional therapies, including catheter-based renal denervation (RDN), have emerged as an adjunctive treatment option for uncontrolled and resistant hypertension.⁴⁰

Lifestyle

Lifestyle changes include avoidance of BP-increasing medications (e.g. non-steroidal anti-inflammatory drugs^{41,42}), restriction of high sodium

intake (<2 g sodium/day), reduction of alcohol (<100g/week), weight loss, smoking cessation, and regular aerobic exercise.^{28,43} Regular exercise reduces incident hypertension.⁴⁴ In hypertensives, exercise lowers BP^{45,46} and reduces mortality.⁴⁷ Substituting salt using low-sodium, potassium-enriched salts reduced BP⁴⁸ and stroke rates.⁴⁹ Potassium-enriched diets carry the risk of hyperkalaemia, especially on mineralocorticoid receptor antagonists (MRAs).⁵⁰ Comorbidities like HF, CKD, or frailty can limit lifestyle interventions.

Pharmacotherapy

Pharmacotherapy should be initiated swiftly. Only in grade 1 hypertension (office BP 140–159/90–99 mmHg) at low-to-moderate CV risk, lifestyle interventions without pharmacotherapy can be considered for 3–6 months.²⁸ In general, dual single-pill combination therapy with a renin–angiotensin system (RAS) blocker [angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)] with a calcium channel blocker (CCB) or thiazide/thiazide-like diuretic should be initiated (*Figure 1*).²⁸ If treatment targets are not achieved with a dual-drug combination, a triple-drug combination of a RAS blocker, CCB, and thiazide/thiazide-like diuretic in a single pill is recommended.²⁸ In black patients, thiazide/thiazide-like diuretics and CCB are more effective than RAS blockers.^{51,52} The risk of angioedema is elevated in black patients taking ACE inhibitors.^{51,52} The ESC/ESH hypertension guidelines recommend a diuretic or CCB, either in combination or with an ARB in black patients.²⁸ While females report more adverse effects associated with antihypertensive drugs (except for MRA),⁵³ studies designed to assess sex-specific differences in BP-lowering efficacy are scarce. A meta-analysis found comparable BP reductions and protection in men and women.⁵⁴ The optimal choice should consider comorbidities, frailty, and contraindications.

Single-pill combinations result in greater BP reductions than free combinations, probably due to improved medication adherence and targeting of different mechanisms.^{55,56} Monotherapy should be considered in patients with uncomplicated hypertension and an office SBP <150 mmHg, in very old (>80 years) or frail patients.²⁸

Resistant hypertension is defined as elevated office BP ($\geq 140/90$ mmHg) despite appropriate lifestyle changes and the confirmed intake of a triple combination of recommended drugs at maximally tolerated doses.²⁸ Pseudo-resistant hypertension and secondary hypertension causes, such as primary hyperaldosteronism, renovascular disease, CKD, and sleep apnoea, should be excluded.²⁸ Targeted measures, including diuretics in excessive volume-overload, salt restriction, and treatment of secondary causes of hypertension, are pivotal. Medications (e.g. oestrogen-containing contraceptives, non-steroidal anti-inflammatory drugs) and other substances, including alcohol, are associated with BP elevation and should be discontinued.²⁸ Based on PATHWAY-2⁵⁷ and meta-analyses,^{58–61} spironolactone (25–50 mg daily) should be added to triple-drug therapy in resistant hypertension. If not tolerated, eplerenone, amiloride, or higher doses of diuretics, beta-blockers (BBs) or doxazosin should be considered.²⁸

BB were less protective against stroke than other antihypertensives.^{62,63} They are not recommended as first-line therapy and are reserved for conditions such as HF, rate control in atrial fibrillation (AF), or chronic coronary syndrome.²⁸

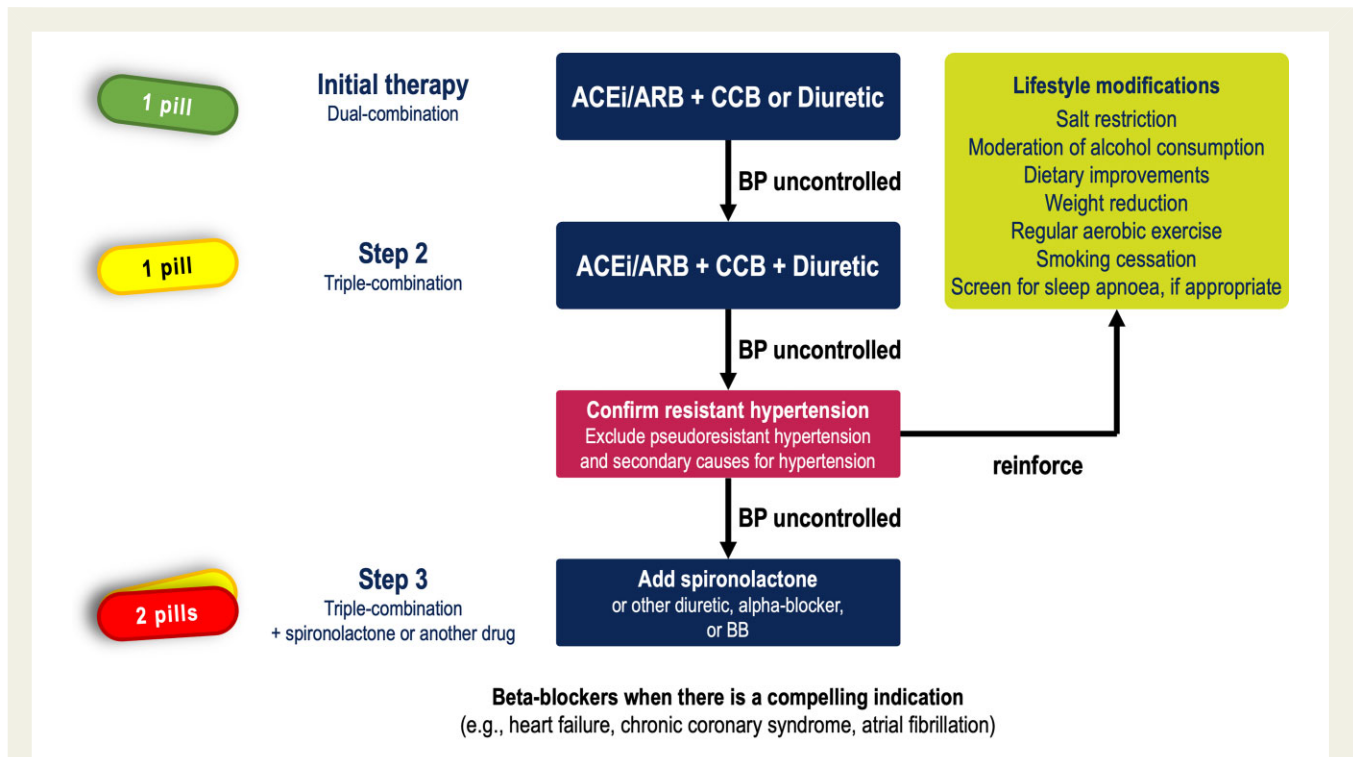


Figure 1 General treatment algorithm for arterial hypertension.²⁸ In general, single-pill dual combination therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with a calcium channel blocker or thiazide/thiazide-like diuretic should be initiated. If treatment targets are not achieved with a two-drug combination, a single-pill triple-drug combination of a renin-angiotensin system blocker, calcium channel blocker, and thiazide/thiazide-like diuretic is recommended. Single-pill combination therapies are associated with improved adherence and more pronounced blood pressure reductions by simultaneously targeting different mechanisms. In patients with resistant hypertension, spironolactone should be utilized. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CCB, calcium channel blocker.

Catheter-based therapies

The best evidence exists for RDN⁶⁴ to interrupt perivascular sympathetic nerves.⁶⁴ In sham-controlled trials, radiofrequency- and ultrasound-RDN lowered office and ambulatory BP in uncontrolled hypertension with and without medication.^{65–69} No severe periprocedural adverse events were observed.^{64,70} While reducing BP using antihypertensive drugs is associated with risk reductions of major CV events,⁸ it remains unclear whether RDN confers similar beneficial effects. RDN is under investigation for comorbidities associated with increased sympathetic nervous system (SNS) activity (Figure 2). Implementing RDN in practice requires appropriate procedural performance, patient selection, and should incorporate the patient's preference.⁴⁰

Comorbid conditions

Obesity

Obesity prevalence rapidly increased in children and adults, accounting for 4 million deaths globally.⁷¹ It is higher among women than men. The association between body mass index (BMI) and BP is almost linear, even at a BMI <25 kg/m².⁷² A gain of 1.7 kg/m² BMI or 4.5 cm waist circumference corresponded to a 1 mmHg SBP increase.⁷³ Weight gain causes a 65–75% risk increase for hypertension.⁷⁴ Renin-angiotensin system activation and increased SNS contribute to hypertension in obesity.⁷⁴ Obstructive sleep

apnoea contributes to hypertension in obesity, requiring screening and treatment.^{75,76} Obesity⁷¹ and obesity-associated hypertension⁷⁷ are more prevalent in women than men. Especially in obese women, BP control is often not achieved.^{74,78–80}

Antihypertensive treatment

The ESC/ESH hypertension guidelines recommend lifestyle modifications, including regular physical activity, to achieve normal weight (BMI of 20–25 kg/m², waist circumference <94 cm for men and <80 cm for women).²⁸ Weight loss can prevent hypertension and reduce BP (about 1 mmHg drop in SBP per kilogram weight loss).⁸¹ In Treating Resistant Hypertension Using Lifestyle Modification to Promote Health (TRIUMPH), diet and exercise lowered BP in obese patients with resistant hypertension.⁸² Severely obese patients (BMI >40 kg/m²) frequently require more antihypertensive drugs.⁷⁸

Other treatments

Glucagon-like peptide-1 receptor agonists (GLP1-RA) were shown to reduce body weight⁸³ and have pleiotropic CV effects,⁸⁴ including modest reductions in SBP^{85,86} and CV events in patients with diabetes with CV disease or at increased CV risk.⁸⁴ Treatment with sodium-glucose cotransporter 2 (SGLT2) inhibitors was associated with modest weight loss and reductions in waist circumference and BP.^{87–89}

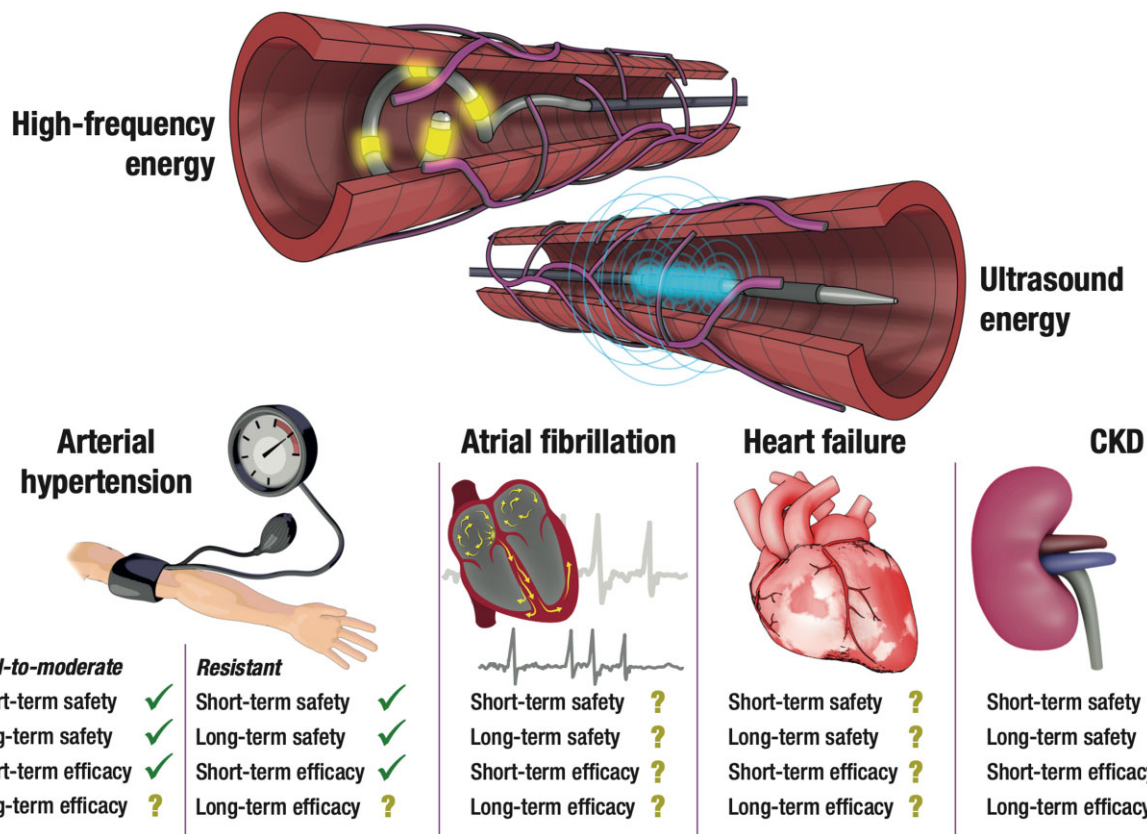


Figure 2 Possible indications for renal denervation. Evidence (✓) and gaps in evidence (?) for the treatment of hypertensive patients with atrial fibrillation, heart failure, and chronic kidney disease with ultrasound- and radiofrequency-based atrial fibrillation. There are ongoing trials for atrial fibrillation, heart failure, and chronic kidney disease. Pilot and proof of concept trials are not considered here.

Metabolic surgery

Guidelines recommend considering metabolic surgery in patients with class III (BMI ≥ 40 kg/m²) or class II obesity (BMI 35–39.9 kg/m²) with comorbidities.^{90–92} Roux-en-Y gastric bypass, sleeve gastrectomy, and adjustable gastric banding are effective treatments to reduce weight and achieve glycaemic control.⁹³ The GATEWAY trial randomized patients (76% female) with treated hypertension and a BMI of 30.0–39.9 kg/m² to Roux-en-Y gastric bypass plus medical therapy or medical therapy alone.⁹⁴ The primary endpoint of BP control while reducing $\geq 30\%$ of antihypertensive medications was achieved in 84% of the patients after surgery.⁹⁴ After 3 years, 35% from the gastric bypass group and 2% from the control group had controlled office BP without medications.⁹⁵ In Swedish Obese Subjects (SOS) study, gastric bypass reduced office SBP.⁹⁶ The Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial observed significant reductions in antihypertensive medications.^{97,98} Mechanisms involve improvements in SNS activity, baroreflex control, salt and water haemostasis, and inflammation.^{99–101} Blood pressure drops occur early before weight loss.¹⁰² Predictors of non-response were advanced age, black race, and diabetes.¹⁰³ Beyond meta-analyses, prospective randomised studies on CV morbidity and mortality reduction are lacking.^{104,105}

Diabetes mellitus

Hypertension and diabetes commonly coexist due to shared pathophysiological factors such as obesity and hyperinsulinaemia.^{74,106,107} Ambulatory BP measurements are recommended to identify masked and nocturnal hypertension occurring in 30% of patients with diabetes^{28,108} associated with frequent CV events.^{109,110} Several meta-analyses have shown that BP-lowering therapy reduces death and micro- and macrovascular complications, including CKD, retinopathy, and albuminuria.^{111–114} Care should be taken to prevent postural hypotension in patients with autonomic neuropathy.^{28,115}

Antihypertensive treatment

Combination therapies with RAS blockers, CCB, or diuretics are recommended.^{28,115} In an individual participant data meta-analysis including 145 939 participants, RAS blockers reduced the relative risk of new-onset diabetes by 16%,¹¹⁴ whereas CCB were neutral and BB and thiazide diuretics increased incident diabetes.¹¹⁴ In diabetes, RAS blockers were more effective than diuretics and CCB in reducing albuminuria and progression to diabetic nephropathy.¹¹² In Action in Diabetes and Vascular Disease—Preterax and Diamicron MR Controlled Evaluation (ADVANCE), perindopril combined with indapamide reduced mortality and microvascular events over a 6-year follow-up.^{116,117}

In resistant hypertension and diabetes, spironolactone (25–50 mg daily) reduces BP and albuminuria.^{118,119} In Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD), the non-steroidal MRA finerenone reduced CV and kidney outcomes despite only modest BP reduction in diabetes with CKD.^{120–122} Serum potassium should be monitored closely to prevent hyperkalaemia.¹²³

Beta-blockers should be avoided in pre-diabetes without a compelling CV indication as some affect insulin sensitivity and cause lipid changes and weight gain.^{115,124} Carvedilol and nebivolol did not affect insulin sensitivity.^{125,126} Beta-blockers were associated with an increased risk of severe hypoglycaemia and CV events¹²⁷ and, in patients with diabetes, might be associated with an increased risk of mortality.¹²⁸

Antihypertensive effects of glucose-lowering treatments

Compared with placebo, the GLP1-RA liraglutide reduced CV death, non-fatal myocardial infarction, or non-fatal stroke by 13%.¹²⁹ At 36 months, liraglutide reduced office SBP by –1.2 mmHg but slightly increased office DBP (+0.6 mmHg).¹²⁹ In meta-analyses, liraglutide reduced weight and SBP in diabetes.^{130–132} The mechanisms might involve natriuresis, improved insulin sensitivity, and endothelial function.¹³³ Sodium–glucose cotransporter 2 inhibitors reduced the rate of CV events and renal dysfunction in patients with and without diabetes.^{87,134–139} In Empagliflozin, CV Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) BP, empagliflozin reduced 24 h SBP and DBP in patients with type 2 diabetes and hypertension.¹⁴⁰ The BP-lowering effect depends on baseline BP¹⁴¹ and is minor in HF with reduced ejection fraction (HFrEF).^{142,143}

In SGLT2 Inhibitor and ARB Combination Therapy in Patients with Diabetes and Uncontrolled Nocturnal Hypertension (SACRA), empagliflozin reduced night-time ambulatory SBP compared with placebo.¹³² Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENDENCE) randomised patients with type 2 diabetes and CKD without MRA to treatment with canagliflozin or placebo.^{138,144} Canagliflozin reduced office SBP by 3.5 mmHg across all subgroups, including resistant hypertension.¹⁴⁴ Mechanistically, SGLT2 inhibitors increased natriuresis while decreasing SNS activity, inflammation effects, vascular stiffness, and BP variability.^{88,145}

Catheter-based therapies

Hypertension and diabetes result in greater SNS activity than either condition alone.^{146,147} Renal denervation reduced fasting glucose, haemoglobin A_{1c}, insulin, and C-peptide.^{148,149} In sleep apnoea with hypertension, RDN reduced BP and improved glucose tolerance.¹⁵⁰ In DREAMS, BP and SNS activity were significantly reduced and the response to oral glucose loading was restored in patients with metabolic syndrome or diabetes, whereas insulin sensitivity did not improve after RDN.^{151,152}

Chronic kidney disease

Hypertension may cause CKD and contribute to its progression,^{153,154} whereas CKD causes hypertension.^{155,156} Several studies showed a relationship between elevated BP and CKD risk.^{153,157}

While the overall CKD prevalence among hypertensive patients is similar across sexes, the prevalence of reduced glomerular filtration rate (GFR) is higher in women.¹⁵⁸ In CKD, masked and resistant hypertension are common and associated with a lower GFR and higher levels of albuminuria.^{159–161} Blood pressure lowering slows CKD progression in patients with albuminuria.^{162–164} Furthermore, CKD increases the risk for CV disease.^{165,166}

The ESC/ESH hypertension guidelines recommend lowering office SBP in CKD patients to 130–139 mmHg based on a systematic review¹⁶⁷ and meta-analysis.¹⁵⁴ Mortality and end-stage CKD were lowest for SBP between 130 and 139 mmHg and DBP between 60 and 79 mmHg.¹⁶⁸ Based on SPRINT, the Kidney Disease: Improving Global Outcomes (KDIGO) recommends a target office SBP of <120 mmHg for hypertension and CKD.¹⁶³ In SPRINT, patients at risk for CV disease were randomized to an intensive (unattended office SBP <120 mmHg) or standard treatment arm (unattended office SBP <140 mmHg).^{25,26} Compared with standard treatment, intensive treatment reduced the primary outcome, a composite of CV events and death (risk reduction of 25%) and all-cause mortality (27%).²⁵ In CKD, the primary outcome was also reduced following intensive treatment.¹⁶⁹ These BP targets do not apply to dialysis or kidney transplant patients, for whom the optimal BP target is unknown.¹⁶³

Antihypertensive treatment

Renin–angiotensin system blockers are more effective in reducing albuminuria and are recommended combined with a CCB or a diuretic. Volume overload is common in patients with CKD, especially in patients on dialysis, and contributes to resistant hypertension.¹⁷⁰ Reduction of sodium (100 mmol/day) improves BP control in patients with stages 3 and 4 CKD.¹⁷¹ Blood pressure control can be improved by using potent, long-acting thiazide-like diuretics, such as chlorthalidone and indapamide. Chlorthalidone showed efficacy in stage 4 CKD and poorly controlled hypertension (60% receiving loop diuretics) to reduce 24 h SBP by 10.5 mmHg.¹⁷² The lowest dose (12.5 mg daily) had the largest BP-lowering effect.¹⁷² When RAS blockers and MRA are combined, electrolytes and serum creatinine should be monitored. Hyperkalaemia can be managed by dietary potassium restriction, adding potassium-eliminating diuretics in volume overload, or oral potassium binders.¹⁶³ Renin–angiotensin system blockers decrease GFR by lowering renal filtration pressure.^{28,163} The current ESC/ESH and KDIGO guidelines recommend continuing treatment unless serum creatinine rises >30%.^{28,163}

In patients on dialysis, non-pharmacological strategies include the achievement of euvoemia, sodium restriction, and avoidance of short dialysis duration.¹⁷³ Pharmacological antihypertensive treatment reduces CV morbidity and mortality on dialysis.^{174,175} It is recommended to take comorbidities and dialysability of antihypertensives into account.^{173,176} In patients with hypotension during dialysis, dialyzable antihypertensive agents are advised.^{173,176} Direct vasodilators such as hydralazine or minoxidil should be avoided as they induce fluid retention and tachycardia.^{28,163}

Dapagliflozin reduced the risk of estimated GFR (eGFR) decline, end-stage CKD, or death from renal or CV causes in patients with CKD (eGFR 25–75 mL/min/1.73 m² and urinary albumin-to-creatinine ratio of 200–5000 mg/g) regardless of the presence of diabetes.¹⁷⁷ In

CREDENCE, canagliflozin lowered SBP and the need for additional BP-lowering agents in CKD and type 2 diabetes.¹⁴⁴

The non-steroidal MRA finerenone reduced CV and kidney outcomes despite only modest BP reduction in diabetes with CKD.^{120–122}

Catheter-based therapies

Sympathetic nervous system activity contributes to hypertension in end-stage CKD. Thus, RDN might offer a promising treatment approach.^{156,178,179} Surgical ablation of renal sympathetic nerves reduced SNS activity, prevented hypertension, and slowed CKD progression.¹⁸⁰ Because patients with an eGFR <40 mL/min/1.73 m² were excluded from recent sham-controlled RDN trials, the evidence for CKD is based on pilot studies and registries.¹⁸¹ A small study of 15 patients with stages 3 and 4 CKD and resistant hypertension suggested BP lowering with preserved kidney function over 1 year.¹⁸² Two single-centre studies support data on renal safety of RDN.^{183,184} The prospective sham-controlled RDN-CKD trial investigating RDN in stage 3 CKD patients with diabetic or non-diabetic nephropathy is currently recruiting (NCT04264403, ClinicalTrials.gov).

Chronic obstructive pulmonary disease

Hypertension and chronic obstructive pulmonary disease (COPD) commonly coexist. Hypertension is most prevalent in COPD (27%).¹⁸⁵ Patients with COPD are at increased risk of CV disease [odds ratio (OR) 4.98], stroke (OR 3.34), and diabetes (OR 2.04).¹⁸⁶

Antihypertensive treatment

Smoking cessation and physical exercise play an important role in hypertension with COPD. Both cardio-selective and non-cardio-selective BB reduce forced expiratory volume (FEV₁), but only non-selective BB reduce the ratio of FEV₁ to forced vital capacity.¹⁸⁷ In asthma, FEV₁ decreased by 6.9% using cardio-selective BB and 10.2% with non-selective BB, while symptoms only worsened with non-selective BB.¹⁸⁸ Beta-1-selective BBs are well tolerated and safe in COPD.^{189–191}

Diuretics may decrease the plasma level of potassium combined with beta-adrenergic agonists, worsen carbon dioxide retention, and deteriorate mucus secretion.²⁸

Coronary artery disease

INTERHEART suggested that 20% of myocardial infarctions are attributable to hypertension.²¹ A meta-analysis reported that every 10 mmHg reduction in office SBP reduced the risk by 17%.⁸ Guidelines recommend targets of 120–140 mmHg for office SBP and 70–80 mmHg for DBP.^{29,30} It remains unknown if a J-curve phenomenon persists in patients with revascularized coronary artery disease.^{37,192}

Antihypertensive treatment

In coronary artery disease, RAS blockers, BB, and CCB are the cornerstone of antihypertensive therapy.^{28,193,194} Angiotensin-converting enzyme inhibitors became indispensable in HFrEF.^{195–199} Their benefits in reducing myocardial infarction and mortality were subsequently demonstrated in patients with preserved ejection fraction (EF) within 24 h after acute myocardial infarction^{200,201} and for preventing myocardial infarction in patients with atherosclerosis without HF.^{116,202–205} Trials investigating ARB strengthened these findings.^{206–213} Anglo-Scandinavian

Cardiac Outcomes Trial—BP Lowering Arm (ASCOT-BPLA) was terminated prematurely as amlodipine combined with perindopril was superior to atenolol plus bendroflumethiazide in reducing CV events.²¹⁴ Renin-angiotensin system blockers protect the endothelium through anti-inflammatory and anti-apoptotic effects and reduce left ventricular (LV) remodelling following myocardial ischaemia.^{204,212,215–218} After myocardial infarction, BB¹⁹⁴ except atenolol²¹⁹ reduced the risk of recurrent coronary artery disease events by 31%. The ESC guidelines recommend treatment with BB and long-acting CCB for symptom relief.^{193,220–223}

Chronic heart failure

Hypertension is among the most important risk factors for the occurrence of HF.^{224,225} After a 20-year follow-up, hypertension preceded incident HF in 91% of the cases.²²⁴ Compared with normotensives, the hazards for HF were two-fold higher in men and three-fold higher in women.²²⁴ The incremental risk of incident HF was two-fold higher at an office BP ≥160/100 than <140/90 mmHg.²²⁶ Pathological changes in afterload involving both its resistive (peripheral resistance determined by systemic microvascular resistance) and pulsatile components (aortic stiffness and magnitude of arterial wave reflections) affecting ventricular-arterial coupling play a major role in the development of HF.²²⁷

Eccentric hypertrophy occurs *de novo* or develops from concentric LV hypertrophy (Figure 3).^{228–230} Hypertension causes ischaemic heart disease with eccentric remodelling and reduced EF.^{228–230} In HF with preserved EF (HFpEF), a high prevalence of hypertension occurs,²³² initiating further concentric LV hypertrophy with subsequent diastolic dysfunction.²³³ The prevalence of LV hypertrophy is higher in females than in males.²³⁴ Although EF is typically preserved (≥50%) at rest in hypertensive LV hypertrophy, it represents a precursor of LV systolic dysfunction,²³¹ indicating a continuum from LV hypertrophy to deterioration of EF.²²⁸

Antihypertensive therapy reduces the risk for HF events.^{235–238} Patients with hypertension at increased CV risk receiving intensive treatment to <120 mmHg had a 38% lower HF risk than a lenient office SBP target of <140 mmHg.²⁵ Kidney function and albuminuria were both independent additive HF risk markers but did not modify the effects of intensive BP control.²³⁹ In a meta-analysis including 123 studies with 613 815 patients, a 10 mmHg reduction in office SBP was associated with a decrease in relative risk of HF by 28%.⁸ Consistently, the relative risk of new-onset HF was substantially reduced by 42%.²⁴⁰

Heart failure prevention

Blood pressure lowering with diuretics, ACE inhibitors, and ARB was more effective in preventing HF than antihypertensive therapy with CCB.^{240–242} In diabetic kidney disease, finerenone reduced the risk of incident HF.²⁴³ Beta-blockers did not significantly reduce the risk of HF beyond the beneficial effects associated with BP reduction.²⁴⁴ In Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), doxazosin was associated with a doubling of HF risk compared with chlorthalidone.²⁴⁵ Moreover, chlorthalidone was superior to lisinopril, amlodipine, and doxazosin for preventing HFpEF but not HFrEF.^{245,246} Blood pressure control can result in LV mass regression.²⁴⁷ Compared with ARB, ACE inhibitors, and CCB, BB were inferior in reducing LV mass.²⁴⁷ Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), reduced LV mass,²⁴⁸ N-terminal pro-B-type natriuretic peptide

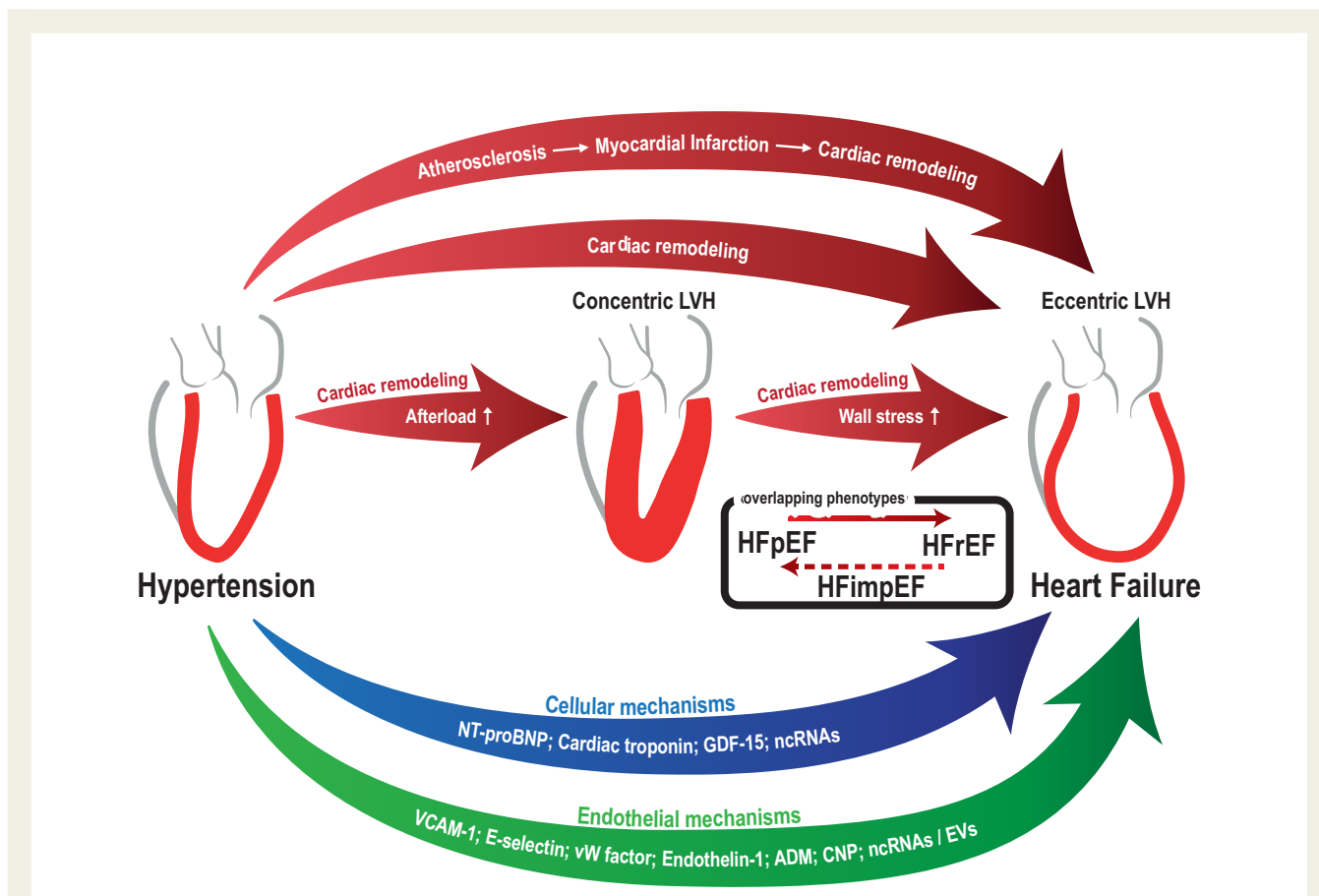


Figure 3 From hypertension to heart failure. Hypertension initiates concentric left ventricular hypertrophy with subsequent diastolic dysfunction. Although left ventricular ejection fraction is initially typically preserved (heart failure with preserved ejection fraction), it represents a precursor of left ventricular systolic dysfunction with eccentric hypertrophy,²³¹ indicating a continuum from left ventricular hypertrophy to deterioration of ejection fraction. Eccentric hypertrophy can also occur *de novo*. Hypertension increases the risk of ischaemic heart disease, resulting predominately in eccentric remodelling and reduced ejection fraction.^{228–230} Medical therapy can improve ejection fraction and reverse remodelling (heart failure with improved ejection fraction). Cardiac remodelling involves endothelial and cellular mechanisms, such as activation of the endothelial cells with expression of adhesion molecules (E-selectin, vascular cell adhesion molecule-1) and release of von Willebrand factor, C-type natriuretic peptide, endothelin-1, adrenomedullin, non-coding RNAs, and extracellular vesicles. Cardiomyocytes release natriuretic peptides in response to increased myocardial wall stress and cardiac troponins, growth differentiation factor-15, non-coding RNAs and EV upon cardiac injury and necrosis. ADM, adrenomedullin; CNP, C-type natriuretic peptide; EVs, extracellular vesicles; GDF-15, growth differentiation factor-15; HFimpEF, heart failure with improved ejection fraction; HFREF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VCAM-1, vascular cell adhesion molecule-1; vW, von Willebrand.

(NT-proBNP) levels and pulse pressure more pronounced than ARB.²⁴⁹ A meta-analysis of hypertension trials investigating sacubitril/valsartan showed that sacubitril/valsartan (200 or 400 mg daily) reduced SBP and DBP more pronounced than valsartan.²⁵⁰

Antihypertensive treatment in heart failure with reduced ejection fraction

No trials have specifically investigated antihypertensive therapy in patients with HF and hypertension.^{251,252} In HFREF, uncontrolled hypertension is rare.²⁵² Renin-angiotensin system blockers, MRA, and BB are recommended. Sacubitril/valsartan is superior to enalapril in reducing HF hospitalizations, CV mortality, and all-cause mortality in HFREF.²⁵³ Sacubitril/valsartan improves quality of life²⁵³ and attenuates eGFR decline.²⁵⁴ Sodium-glucose cotransporter 2 inhibitors reduced the risk of HF

hospitalization and death.^{252,255} In fluid retention, diuretics are effective. Calcium channel blockers such as amlodipine and felodipine were neutral on survival but safely reduced BP in HFREF.^{256–259} Importantly, non-dihydropyridine CCB (diltiazem and verapamil) were associated with worse outcomes.²⁵² MOXonidine CONgestive Heart Failure trial (MOXCON) investigated moxonidine, a selective imidazoline receptor agonist, in HFREF. Although moxonidine reduced plasma norepinephrine (−18.8% from baseline), MOXCON had to be terminated prematurely due to increased adverse events and death on moxonidine.²⁶⁰

Antihypertensive treatment in heart failure with preserved ejection fraction

In HFpEF, the sodium-restricted dietary approaches to stop hypertension (DASH) diet was associated with favourable changes

in ventricular diastolic function, arterial elastance, and ventricular-arterial coupling.²⁶¹ Large clinical outcome trials confirmed the safety of RAS blockers, MRA, and diuretics in patients with HFpEF but did not consistently improve morbidity and mortality.^{262,263} Lowering BP improves diastolic dysfunction, irrespective of the type of antihypertensive treatment used.²⁶⁴ Even propranolol reduced mortality and non-fatal myocardial infarction compared with placebo in patients with previous myocardial infarction.²⁶⁵ In Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved, candesartan did not reduce mortality in patients with HFpEF (LVEF >40%) but reduced HF admissions.²⁶² Although sacubitril/valsartan did not lower the rate of total hospitalizations for HF and CV death in HFpEF in Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF),²³² a post-hoc analysis showed that sacubitril/valsartan effectively lowered BP in patients with resistant hypertension even in those receiving an MRA.²⁶⁶ In Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial (TOPCAT), spironolactone did not show benefit or the primary outcome and cardiac arrest in HFpEF.²⁶⁷ Excluding patients from Russia and Georgia, who had a lower number of events²⁶⁸ and in whom canrenone concentrations were undetectable in 30%,²⁶⁹ the risk for the primary outcome was reduced by 18%.²⁶⁸ American HF guidelines endorse spironolactone in selected patients with HFpEF (Class IIb, Level B recommendation).²⁷⁰

Catheter-based therapies

Renal denervation and baroreflex-activation therapy have shown encouraging but limited results in HFpEF and HFrEF.²⁷¹ Renal denervation reduced renal norepinephrine spillover, circulating angiotensin I and II, and renal neprilysin activity, caused less cardiac remodelling, and improved autonomic balance in several animal models of HF.^{272–275} In a first-in-man trial, including seven patients with HFrEF on guideline-recommended therapy with controlled BP, bilateral RDN improved symptoms, and submaximal exercise capacity (6 min walk distance increased by 27.1 ± 9.7 m, $P=0.03$) at 6 months.²⁷⁶ In HFpEF, RDN reduced LV mass.²⁷⁷ Prospective trials are evaluating the efficacy and safety of RDN in HF (e.g. NCT04947670).

Previous stroke or transient ischaemic attack

Hypertension is the most prevalent modifiable risk factor for haemorrhagic and ischaemic stroke.^{278–280} About 70% of patients with a stroke have a history of hypertension.^{278–280} In INTERSTROKE, the population-attributable risk for a patient-reported history of hypertension was 35% for all stroke types.²⁸¹ Despite declining stroke incidence, the absolute number of people affected by stroke has globally increased in men and women of all ages, demonstrating the need for stroke prevention.^{280,282} Hypertension predicts stroke recurrence, and BP reduction reduces risks for recurrent stroke.^{282–284} Secondary prevention is important as the mortality rate at 30 days increases from 22% after an initial stroke to 41% after a recurrent stroke.²⁸⁵ Optimal BP targets after stroke or transient ischaemic attack (TIA) are unclear.^{28,286} In Secondary Prevention

of Small Subcortical Strokes (SPS3) trial, the rate of intracerebral haemorrhage (–63%), but not the strokes, was significantly reduced at a target SBP <130 mmHg compared with 130–140 mmHg.²⁸⁷ Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia (PROGRESS) showed that patients with the lowest follow-up BP (median 112/72 mmHg) had the lowest recurrent stroke risk.²⁸⁸ Abnormal LV geometry was associated with increased risk for all-cause and CV mortality at both low and high SBP on admission, with the highest mortality risk for SBP <150 mmHg.²⁸⁹ Possibly, because, in patients with abnormal LV geometry, cerebral autoregulation is disturbed at lower SBP.²⁹⁰

Antihypertensive treatment

In randomized controlled trials investigating antihypertensive treatment^{212,291} and several meta-analyses,^{8,62} BB (mainly atenolol) were inferior to other antihypertensive drugs for stroke prevention. Therefore, antihypertensive treatment should not include BB unless there is a cardiac indication (e.g. rate control in AF).²⁸² Calcium channel blockers were superior to RAS blockers and diuretics for stroke prevention.⁸ In 39 329 patients after stroke, diuretics were superior to other agents for preventing cerebrovascular events.²⁹² Compared with placebo, only diuretics and ACE inhibitors significantly reduced recurrent stroke events.²⁹² The current guidelines recommend initiating or restarting BP lowering immediately in neurologically stable patients with TIA and within a few days in ischaemic stroke.^{28,286,293}

Cognitive dysfunction

Midlife hypertension is associated with cognitive decline,²⁹⁴ mild cognitive impairment,²⁹⁵ dementia,^{296–298} and Alzheimer's disease.²⁹⁹ In Atherosclerosis Risk In Communities (ARIC) neurocognitive study, patients with midlife hypertension and late-life hypotension had an increased risk for mild cognitive impairment and dementia.³⁰⁰ The increasing number of antihypertensive medications from mid-to-late life suggested overtreatment.³⁰¹ Other possible causes for BP decreases include cardiocirculatory dysfunction and impaired autonomic functioning.³⁰⁰ Data on whether or not a J-curve relationship exists between SBP and cognitive decline are conflicting.^{294,302} While in the ARIC, associations of midlife SBP with cognitive decline were continuous,²⁹⁴ U- or J-curved relationships were observed in older patients.^{302–304} In a cross-sectional study on 70-year-old men, the nocturnal non-dipping was associated with low cognitive function.³⁰⁵ The underlying mechanisms of hypertension and cognitive dysfunction are multifactorial, including neuronal loss by atrophy, microinfarcts and microbleeds, white matter lesions, neurovascular dysfunction, and enlarged perivascular space.³⁰⁶

Antihypertensive treatment reduced incident dementia,^{307–309} but the optimal BP target to prevent cognitive dysfunction is unclear. In SPRINT Memory and cognition IN Decreased hypertension (MIND), lowering unattended office SBP <120 mmHg compared with standard treatment reduced the risk of mild cognitive impairment but not of dementia.³¹⁰

Antihypertensive treatment

Data regarding the optimal antihypertensive treatment strategy to prevent dementia are conflicting.^{28,311} Most studies investigating specific antihypertensive agents were not designed to explore cognitive and dementia-associated endpoints.^{309,311} In Syst-Eur, in

hypertensive patients aged ≥ 60 years, treatment with nitrendipine reduced incident dementia.³¹² In PROGRESS, perindopril and indapamide prevented cognitive decline and reduced the risk of the composite of dementia with recurrent stroke by 34% after stroke or TIA.³¹³ In community-dwelling older people, CCB and ARB were associated with a decreased risk of dementia.³¹⁴

A meta-analysis investigating the effects of diuretics demonstrated a consistent reduction in dementia risk.³¹⁵ In a network meta-analysis, ARB were more effective than ACE inhibitors and diuretics in preventing overall cognition changes.³⁰⁷ A meta-analysis of six prospective community-based studies, including 31 090 adults without dementia, could not identify a specific antihypertensive drug class lowering the risk of dementia more effectively than others.³⁰⁹

Atrial fibrillation

Hypertension is highly prevalent in AF patients, even more in women than in men,³¹⁶ and represents an important risk factor for AF.^{317–319} Elevated BP causes LV hypertrophy, myocardial fibrosis, and diastolic dysfunction, resulting in atrial stretching and structural remodeling.^{320,321} The pathophysiology of left atrial remodelling involves inflammation, oxidative stress, and RAS activation.^{320,321} In Losartan Intervention For Endpoint reduction in hypertension trial (LIFE), new-onset AF had two-, three-, and five-fold increased rates of CV events, stroke, and HF hospitalizations.³²² Hypertension is the most important independent risk factor for stroke in patients with AF.^{323,324} Uncontrolled hypertension is associated with an increased intracerebral bleeding risk with therapeutic anticoagulation.³²⁵

The 2020 ESC guidelines for the management of AF have reinforced the importance of CV risk factors and comorbidities treatment by embracing them in the ABC pathway ('A = avoid stroke' and 'C = CV risk factors and concomitant diseases'). The recommended office SBP and DBP treatment targets in patients with AF are 120–129 and < 80 mmHg, respectively.³²⁶ An analysis of the Korean NHIS database demonstrated that office SBP of 130–139 mmHg and DBP of 80–89 mmHg was associated with greater risks of major CV events, ischaemic stroke and intracranial haemorrhage than controlled hypertension ($< 130 / < 80$ mmHg).³²⁷ Office SBP < 120 mmHg was associated with increased adverse CV outcomes suggesting a U-shaped relationship between BP and risk of major CV events.^{327,328} In patients on oral anticoagulation, there was also a J-curved association between SBP and DBP and all-cause death and any bleeding.³²⁸ However, only low achieved BP was associated with bleeding in patients on oral anticoagulation.³²⁸ The more prolonged hypertension endured, the higher was the risk of ischaemic stroke,³²⁹ but the increased risk was attenuated by SBP control.³²⁹

Antihypertensive treatment

Atrial fibrillation treatment includes weight and alcohol reduction. Alcohol abstinence in previous drinkers reduced arrhythmia recurrence beyond BP control.³³⁰ For rate control, the ESC/ESH hypertension guidelines recommend initial dual combination therapy with a BB and RAS blocker or dihydropyridine CCB.²⁸ Whether BB prevent AF recurrence or only transform symptomatic AF to silent AF due to rate control remains controversial.^{331–333} In normal EF, non-dihydropyridine CCB (e.g. verapamil or diltiazem) can be considered for BP and rate control if BBs are contraindicated or

not tolerated.²⁸ Compared with amlodipine, valsartan reduced the risk of new-onset AF in patients with at least one CV disease or risk factor, including LV hypertrophy.³³⁴ In LIFE, new-onset AF and stroke were reduced by losartan compared with atenolol.³²² Angiotensin-converting enzyme inhibitors [relative risk reduction (RRR) 25%], ARB (RRR 29%), and BB (RRR 22%) were associated with a lower risk for new-onset AF than CCB.³³⁵ Although aldosterone increases LV fibrosis,^{336,337} in the placebo-controlled Improved exercise tolerance in patients with Preserved Ejection fraction by Spironolactone on myocardial fibrosis in Atrial Fibrillation (IMPRESS-AF) trial, the MRA spironolactone did not improve exercise capacity, E/e' ratio, or quality of life in patients with AF and preserved EF.³³⁸

Catheter-based therapies

The autonomic nervous system plays an essential role in hypertension and AF.^{339,340} Therefore, RDN is under investigation as an adjunctive treatment for AF. Patients with hypertension undergoing pulmonary vein ablation are at a higher risk for AF recurrence.³⁴¹ In a randomized controlled trial, patients with symptomatic AF and resistant hypertension underwent pulmonary vein isolation with or without RDN.³⁴² Renal denervation reduced BP and the rate of AF recurrence at 3 and 12 months (29 vs. 69%; $P = 0.033$).³⁴² The randomized, controlled Evaluate Renal Denervation in Addition to Catheter Ablation to Eliminate Atrial Fibrillation (ERADICATE-AF) trial, including patients with paroxysmal AF and uncontrolled hypertension, supports these findings.³⁴³ A meta-analysis of six randomized controlled trials found that pulmonary vein isolation plus RDN reduced AF recurrence at 12 months compared with pulmonary vein isolation alone.³⁴⁴ The results of the randomized controlled Symplicity-AF trial (NCT02064764, ClinicalTrials.gov) investigating RDN for paroxysmal or permanent AF and hypertension are expected soon.

Aortic valve stenosis

Valvular heart disease affects approximately 2.5% of the population.³⁴⁵ Hypertension coexists in $\sim 70\%$ of the patients with aortic valve stenosis.³⁴⁶ Evidence exists that hypertension promotes the progression of aortic valve disease by applying abnormal tensile stress on leaflets causing endothelial injury.^{347,348} In 5.4 million patients without known CV disease, long-term exposure to elevated BP (median follow-up of 9.2 years) was associated with an increased risk of aortic valve stenosis and regurgitation. With a nadir at an SBP of 115 mmHg, each 20 mmHg increase in SBP was associated with a 41% higher risk of aortic valve stenosis.³⁴⁹ Each 10 mmHg increment in DBP was associated with a 24% higher risk of aortic valve stenosis.³⁴⁹ Furthermore, elevated SBP was associated with the progression of aortic valve calcification.³⁵⁰ High BP exposes the left ventricle to additional afterload increases.³⁵¹ Therefore, hypertension can exaggerate symptoms even in moderate aortic valve stenosis.³⁵² Hypertension was associated with a 56% higher rate of ischaemic CV events in patients with aortic valve stenosis.³⁵³

Current guidelines and a consensus document recommend avoiding grading aortic valve stenoses in uncontrolled hypertension as transaortic gradients are often underestimated at high BP.^{354,355} Based on SEAS, an office SBP of 130–139 mmHg and office DBP

of 70–90 mmHg are recommended in most patients with aortic valve stenosis and hypertension, if tolerated.³⁵⁶

Antihypertensive treatment

Careful drug titration is recommended in patients with symptomatic aortic valve stenosis and impaired systolic function to avoid hypotension.^{356,357} If indicated, significant valve disease should be treated to facilitate hypertension management. Renin–angiotensin system blockers are safe and effective in reducing BP, LV mass, and all-cause mortality.^{358,359} In Symptomatic Cardiac Obstruction–Pilot Study of Enalapril in Aortic Stenosis (SCOPE-AS), enalapril was well tolerated with low rates of hypotension, improved New York Heart Association functional class and 6 m walk test distance.³⁵⁷ In Ramipril In Aortic Stenosis (RIAS), ramipril modestly reduced LV mass in moderate-to-severe aortic valve stenosis.³⁶⁰ Beta-blockers might be considered in patients with concomitant coronary artery disease or AF to reduce myocardial oxygen consumption.³⁵⁴ Beta-blockers are safe and may improve survival in mild-to-moderate and high-grade aortic valve stenosis.^{361,362} Calcium channel blocker cannot be recommended in aortic valve stenosis as no studies exist on their long-term use.³⁵⁴ Alpha-blockers were associated with an increased risk of ischaemic CV events.³⁵³ Importantly, antihypertensive treatment should not delay surgical and transcatheter aortic valve implantation, if indicated.³⁵⁵

Conclusion

Management of hypertension should include lifestyle modifications and single-pill combination therapy with RAS inhibitors, CCB, and diuretics (*Graphical abstract*). Due to overlapping pathophysiology and shared risk factors, comorbidities often complicate hypertension. Hence, therapeutic concepts must be individualized according to patients' comorbidities. Renal denervation may offer a promising complementary therapeutic approach, especially for patients with comorbidities associated with increased SNS activity.

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