

Hypertension management in patients with cardiovascular comorbidities

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Received 4 February 2022; revised 23 June 2022; accepted 8 July 2022



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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.

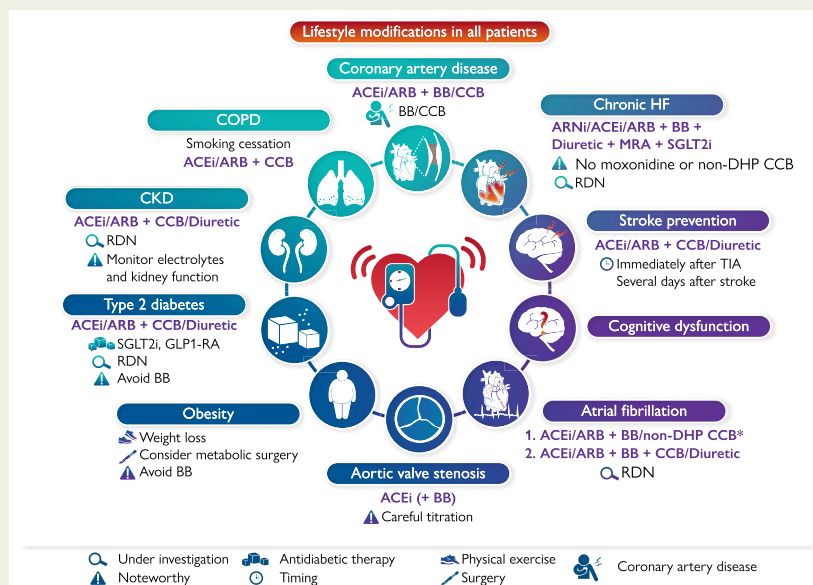
Keywords

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 (≥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

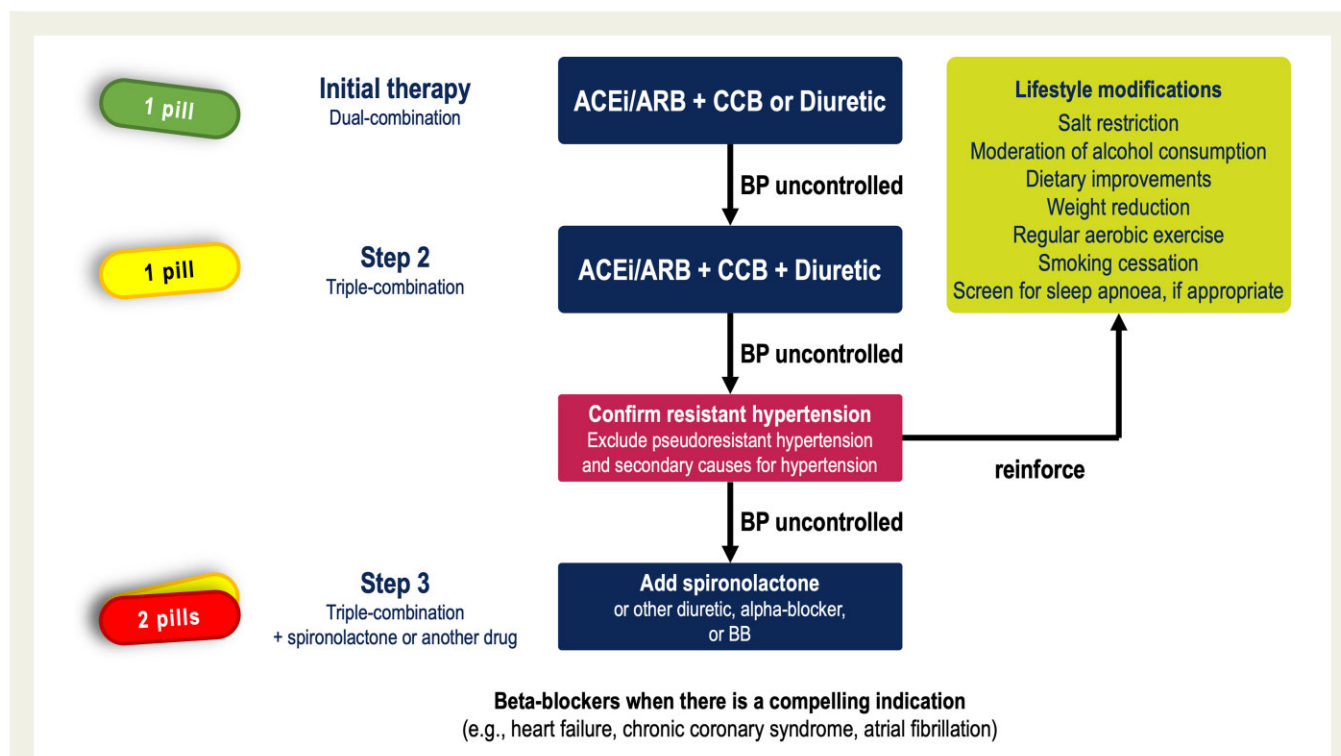


Figure 1 General treatment algorithm for arterial hypertension.²⁸ In general, single-pill dual combination therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with a calcium channel blocker or thiazide/thiazide-like diuretic should be initiated. If treatment targets 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}

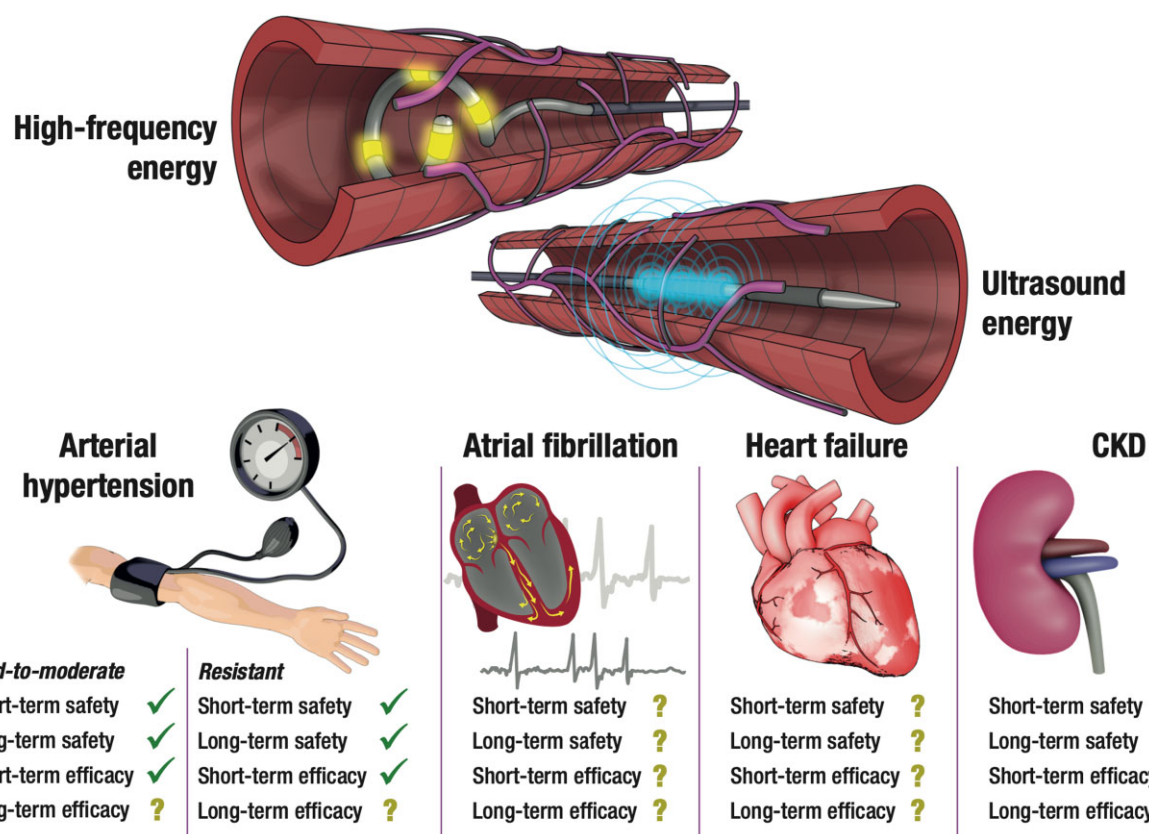


Figure 2 Possible indications for renal denervation. Evidence (✓) and gaps in evidence (?) for the treatment of hypertensive patients with atrial fibrillation, heart failure, and chronic kidney disease with ultrasound- and radiofrequency-based atrial fibrillation. There are ongoing trials for atrial 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 A1c, 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 euvoalaemia, 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

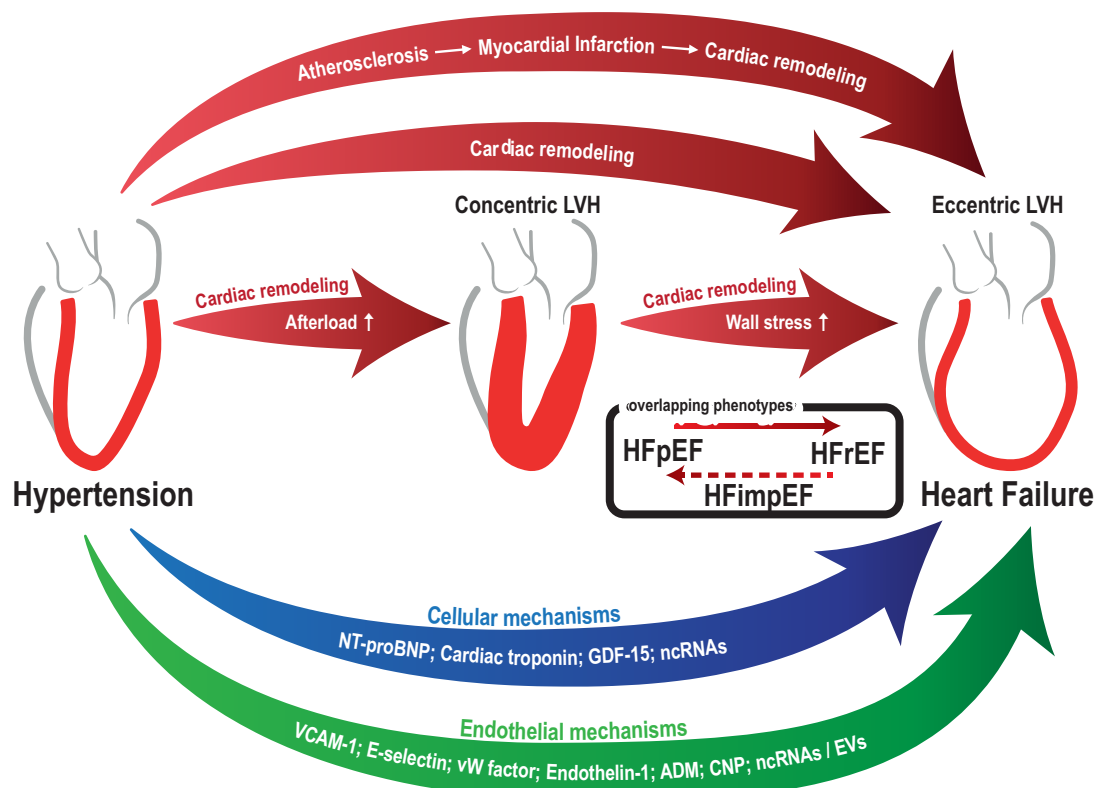


Figure 3 From hypertension to heart failure. Hypertension initiates concentric left ventricular hypertrophy with subsequent diastolic dysfunction. Although left ventricular ejection fraction is initially typically preserved (heart failure with preserved ejection fraction), it represents a precursor of 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.

Acknowledgements

The authors are grateful to Armin Schweitzer for graphical artwork.

Conflict of interest: L.L. reports speaker honoraria from Medtronic and ReCor Medical. F.M. is supported by Deutsche Gesellschaft für Kardiologie and Deutsche Forschungsgemeinschaft (SFB TRR219) and has received scientific support and speaker honoraria from Bayer, Boehringer Ingelheim, Inari, Medtronic, and ReCor Medical. M.A. has received research grants from the French Ministry of Health, the European Horizon 2020 programme, and Quantum Genomics; has received grant support and non-financial support from ReCor Medical and Idorsia; and has received personal fees from AstraZeneca, Alnylam Pharmaceutical, Medtronic, and Poxel Pharma. D.L.B. discloses the following relationships—Advisory Board: Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, DRS.LINQ (stock options), Society of Cardiovascular Patient Care, TobeSoft; Chair:

Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME, Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St Jude Medical (now Abbott), Philips, Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda. S.E. has received scientific support and speaker honoraria from Medtronic, ReCor Medical, AstraZeneca, Daiichi Sankyo, Bayer, and Novartis. K.K. has received research grants from Asteras Pharma, Taisho Pharmaceutical, and Boehringer Ingelheim Japan, and honoraria from AstraZeneca, Kowa, Sanofi, Mitsubishi Tanabe Pharma, and Boehringer Ingelheim Japan outside

the submitted work. G.P. reports speaker honoraria from Omron Healthcare, Bayer, and Servier. P.R. reports consulting for Bayer, CinCor, G3P, Idorsia, and KBP; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer Ingelheim, Corvidia, CVRx, Fresenius, Novartis, Novo Nordisk, Relypsa Inc., a Vifor Pharma Group Company, Roche, Sanofi, Sequana Medical, Servier, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal, a company developing potassium and creatinine sensors for home monitoring. M.P.S. is supported by an NHMRC Research Fellowship and has received consulting fees, and/or travel and research support from Medtronic, Abbott, Novartis, Servier, Pfizer, and Boehringer Ingelheim. K.K.T. has nothing to declare. R.R.T. Consultant to Medtronic, BD, AXIO, and Jansen, Royalty from UpToDate; grants from NIH. C.T. has received speaker honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Servier, Sanofi, Medtronic, Novartis, and ReCor Medical. M.A.W. reports consulting and research payments from Medtronic, ReCor Medical, Ablative Solutions, Johnson & Johnson, and Urovant. T.W. reports speaker honoraria from Astra Zeneca, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Merck, Novartis, Pfizer, and Servier and research support from Medtronic. M.B. reports personal fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Vifor, Servier, Medtronic, and Novartis; and grants from Deutsche Forschungsgemeinschaft and AstraZeneca, all outside the submitted work.

Data availability

No new data were generated or analysed in support of this review.

References

- Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**: 1223–1249.
- Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019;**381**: 243–251.
- Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. *Circulation* 1997;**96**:308–315.
- NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;**389**:37–55.
- Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, et al. Residual lifetime risk for developing hypertension in middle-aged women and men. *JAMA* 2002;**287**:1003–1010.
- Modesti PA, Reboldi G, Cappuccio FP, Agyemang C, Remuzzi G, Rapi S, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. *PLoS One* 2016;**11**:e0147601.
- Aggarwal R, Chiu N, Wadhwa RK, Moran AE, Raber I, Shen C, et al. Racial/ethnic disparities in hypertension prevalence, awareness, treatment, and control in the United States, 2013 to 2018. *Hypertension* 2021;**78**:1719–1726.
- Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–967.
- Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality. *JAMA Cardiol* 2017;**2**:775.
- Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Wamil M, et al. Age-stratified and blood-pressure-stratified effects of blood-pressure-lowering pharmacotherapy for the prevention of cardiovascular disease and death: an individual participant-level data meta-analysis. *Lancet* 2021;**398**:1053–1064.
- Egan BM, Li J, Sutherland SE, Rakotz MK, Wozniak GD. Hypertension control in the United States 2009 to 2018: factors underlying falling control rates during 2015 to 2018 across age- and race-ethnicity groups. *Hypertension* 2021;**78**:578–587.
- Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021;**398**:957–980.
- Dzaou V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. *Am Heart J* 1991;**121**:1244–1263.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
- Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet* 2014;**383**:1899–1911.
- Whelton PK, Einhorn PT, Muntner P, Appel LJ, Cushman WC, Diez Roux AV, et al. Research needs to improve hypertension treatment and control in African Americans. *Hypertension* 2016;**68**:1066–1072. doi:10.1161/HYPERTENSIONAHA.116.07905
- Whelton SP, McEvoy JW, Shaw L, Psaty BM, Lima JAC, Budoff M, et al. Association of normal systolic blood pressure level with cardiovascular disease in the absence of risk factors. *JAMA Cardiol* 2020;**5**:1011–1018.
- Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, et al. Sex differences in blood pressure associations with cardiovascular outcomes. *Circulation* 2021;**143**: 761–763.
- Power C, Atherton K, Manor O. Co-occurrence of risk factors for cardiovascular disease by social class: 1958 British birth cohort. *J Epidemiol Community Heal* 2008;**62**:1030–1035.
- Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019. *J Am Coll Cardiol* 2020;**76**:2982–3021.
- Yusuf S, Hawken S, Öunpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:937–952.
- Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;**366**:321–329.
- Sundström J, Arima H, Woodward M, Jackson R, Karmali K, Lloyd-Jones D, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. *Lancet* 2014;**384**:591–598.
- Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. Less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. *J Hypertens* 2016;**34**:613–622.
- The SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
- The SPRINT Research Group, Lewis CE, Fine LJ, Beddhu S, Cheung AK, Cushman WC, et al. Final report of a trial of intensive versus standard blood-pressure control. *N Engl J Med* 2021;**384**:1921–1930.
- Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–1585.
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
- Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016;**388**:2142–2152.
- Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet* 2017;**389**:2226–2237.
- Stewart IMG. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet* 1979;**313**:861–865.
- Böhm M, Schumacher H, Teo KK, Lonn EM, Mahfoud F, Mann JFE, et al. Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. *Eur Heart J* 2019;**40**:2032–2043.
- Böhm M, Ewen S. Blood pressure risk associations in heart failure. *JACC Heart Fail* 2017;**5**:820–822.
- Sattar N, Preiss D. Reverse causality in cardiovascular epidemiological research. *Circulation* 2017;**135**:2369–2372.
- Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction. *J Am Coll Cardiol* 2014;**63**:636–646.
- Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? *Circulation* 2001;**103**:1245–1249.

37. Böhm M, Ferreira JP, Mahfoud F, Duarte K, Pitt B, Zannad F, et al. Myocardial reperfusion reverses the J-curve association of cardiovascular risk and diastolic blood pressure in patients with left ventricular dysfunction and heart failure after myocardial infarction: insights from the EPHEsus trial. *Eur Heart J* 2020;**41**:1673–1683.
38. Bhatt DL. Troponin and the J-curve of diastolic blood pressure: when lower is not better. *J Am Coll Cardiol* 2016;**68**:1723–1726.
39. Zhang W, Zhang S, Deng Y, Wu S, Ren J, Sun G, et al. Trial of intensive blood-pressure control in older patients with hypertension. *N Engl J Med* 2021;**385**:1268–1279.
40. Schmieder RE, Mahfoud F, Mancia G, Azizi M, Böhm M, Dimitriadis K, et al. European Society of hypertension position paper on renal denervation 2021. *J Hypertens* 2021;**39**:1733–1741.
41. Ruschitzka F, Borer JS, Krum H, Flammer AJ, Yeomans ND, Libby P, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement). *Eur Heart J* 2017;**38**:3282–3292.
42. Hwang AY, Dave CV, Smith SM. Use of prescription medications that potentially interfere with blood pressure control in new-onset hypertension and treatment-resistant hypertension. *Am J Hypertens* 2018;**31**:1324–1331.
43. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Böck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337.
44. Diaz KM, Booth JN, Seals SR, Abdalla M, Dubbert PM, Sims M, et al. Physical activity and incident hypertension in African Americans. *Hypertension* 2017;**69**:421–427.
45. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2002;**136**:493–503.
46. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004473.
47. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure. *J Hypertens* 2012;**30**:1277–1288.
48. Bernabe-Ortiz A, Saly Rosas VG, Ponce-Lucero V, Cárdenas MK, Carrillo-Larco RM, Diez-Canseco F, et al. Effect of salt substitution on community-wide blood pressure and hypertension incidence. *Nat Med* 2020;**26**:374–378.
49. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, et al. Effect of salt substitution on cardiovascular events and death. *N Engl J Med* 2021;**385**:1067–1077.
50. Greer RC, Marklund M, Anderson CAM, Cobb LK, Dalcin AT, Henry M, et al. Potassium-enriched salt substitutes as a means to lower blood pressure. *Hypertension* 2020;**75**:266–274.
51. Wright JT, Harris-Haywood S, Pressel S, Barzilay J, Baimbridge C, Bareis CJ, et al. Clinical outcomes by race in hypertensive patients with and without the metabolic syndrome: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2008;**168**:207–217.
52. Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. *Ann Intern Med* 2004;**141**:614–627.
53. Kalibala J, Pechère-Bertschi A, Desmeules J. Gender differences in cardiovascular pharmacotherapy—the example of hypertension: a mini review. *Front Pharmacol* 2020;**11**:564.
54. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J* 2008;**29**:2669–2680.
55. Webster R, Salam A, de Silva HA, Selak V, Stepien S, Rajapakse S, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA* 2018;**320**:566–579.
56. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. *Lancet* 2021;**398**:1043–1052.
57. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;**386**:2059–2068.
58. Zhao D, Liu H, Dong P, Zhao J. A meta-analysis of add-on use of spironolactone in patients with resistant hypertension. *Int J Cardiol* 2017;**233**:113–117.
59. Wang C, Xiong B, Huang J. Efficacy and safety of spironolactone in patients with resistant hypertension: a meta-analysis of randomised controlled trials. *Heart Lung Circ* 2016;**25**:1021–1030.
60. Liu L, Xu B, Ju Y. Addition of spironolactone in patients with resistant hypertension: a meta-analysis of randomized controlled trials. *Clin Exp Hypertens* 2017;**39**:257–263.
61. Chen C, Zhu XY, Li D, Lin Q, Zhou K. Clinical efficacy and safety of spironolactone in patients with resistant hypertension. *Medicine (Baltimore)* 2020;**99**:e21694.
62. Thomopoulos C, Bazoukis G, Tsioufis C, Mancia G. Beta-blockers in hypertension: overview and meta-analysis of randomized outcome trials. *J Hypertens* 2020;**38**:1669–1681.
63. DeCarolis DD, Gravelly A, Olney CM, Ishani A. Impact of antihypertensive drug class on outcomes in SPRINT. *Hypertension* 2022;**79**:1112–1121.
64. Lauder L, Azizi M, Kirtane AJ, Böhm M, Mahfoud F. Device-based therapies for arterial hypertension. *Nat Rev Cardiol* 2020;**17**:614–628.
65. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;**391**:2346–2355.
66. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;**391**:2335–2345.
67. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE, et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020;**395**:1444–1451.
68. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T, et al. Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. *Lancet* 2021;**397**:2476–2486.
69. Mahfoud F, Kandzari DE, Kario K, Townsend RR, Weber MA, Schmieder RE, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet* 2022;**399**:1401–1410.
70. Townsend RR, Walton A, Hettrick DA, Hickey GL, Weil J, Sharp ASP, et al. Review and meta-analysis of renal artery damage following percutaneous renal denervation with radiofrequency renal artery ablation. *EuroIntervention* 2020;**16**:89–96.
71. The GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017;**377**:13–27.
72. Jones DW, Kim JS, Andrew ME, Kim SJ, Hong YP. Body mass index and blood pressure in Korean men and women. *J Hypertens* 1994;**12**:1433–1437.
73. Doll S, Paccaud F, Bovet P, Burnier M, Wietlisbach V. Body mass index, abdominal adiposity and blood pressure: consistency of their association across developing and developed countries. *Int J Obes* 2002;**26**:48–57.
74. Hall JE, Do Carmo JM, Da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. *Circ Res* 2015;**116**:991–1006.
75. Wolk R, Shamsuzzaman ASM, Somers VK. Obesity, sleep apnea, and hypertension. *Hypertension* 2003;**42**:1067–1074.
76. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, et al. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med* 2014;**370**:2276–2285.
77. Wilsaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences. *Arch Intern Med* 2000;**160**:2847–2853.
78. Bramlage P, Pittrow D, Wittchen HU, Kirch W, Boehler S, Lehnert H, et al. Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. *Am J Hypertens* 2004;**17**:904–910.
79. Gudmundsdottir H, Høiegggen A, Stenehjem A, Waldum B, Os I. Hypertension in women: latest findings and clinical implications. *Ther Adv Chronic Dis* 2012;**3**:137–146.
80. Kim JK, Alley D, Seeman T, Karlamangla A, Crimmins E. Recent changes in cardiovascular risk factors among women and men. *J Womens Health (Larchmt)* 2006;**15**:734–746.
81. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure. *Hypertension* 2003;**42**:878–884.
82. Blumenthal JA, Hinderliter AL, Smith PJ, Mabe S, Watkins LL, Craighead L, et al. Effects of lifestyle modification on patients with resistant hypertension: results of the TRIUMPH randomized clinical trial. *Circulation* 2021;**144**:1212–1226.
83. Shi Q, Wang Y, Hao Q, Vandvik PO, Guyatt G, Li J, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet* 2022;**399**:259–269.
84. Giugliano D, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol* 2021;**20**:189.
85. Ferdinand KC, White WB, Calhoun DA, Lonn EM, Sager PT, Brunelle R, et al. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. *Hypertension* 2014;**64**:731–737.
86. Maringwa J, Sardu ML, Hang Y, Czerniak R, Vishnubhotla M, Vakilynejad M, et al. Characterizing effects of antidiabetic drugs on heart rate, systolic and diastolic blood pressure. *Clin Pharmacol Ther* 2021;**109**:1583–1592.

87. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**: 2117–2128.
88. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors. *J Am Coll Cardiol* 2020;**75**:422–434.
89. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ* 2021;**372**:m4573.
90. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *Circulation* 2014;**129**:102–138.
91. Di Lorenzo N, Antoniou SA, Batterham RL, Busetto L, Godoroja D, Iossa A, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surg Endosc* 2020;**34**:2332–2358.
92. American Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes—2021. *Diabetes Care* 2021;**44**: S100–S110.
93. Yoshino M, Kayser BD, Yoshino J, Stein RI, Reeds D, Eagon JC, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. *N Engl J Med* 2020;**383**: 721–732.
94. Schiavon CA, Bersch-Ferreira AC, Santucci EV, Oliveira JD, Torreglosa CR, Bueno PT, et al. Effects of bariatric surgery in obese patients with hypertension. *Circulation* 2018;**137**:1132–1142.
95. Schiavon CA, Bhatt DL, Ikeoka D, Santucci E V, Santos RN, Damiani LP, et al. Three-year outcomes of bariatric surgery in patients with obesity and hypertension. *Ann Intern Med* 2020;**173**:685–693.
96. Hallersund P, Sjöström L, Olbers T, Lönroth H, Jacobson P, Wallenius V, et al. Gastric bypass surgery is followed by lowered blood pressure and increased diuresis—long term results from the Swedish obese subjects (SOS) study. *PLoS One* 2012;**7**:e49696.
97. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* 2012;**366**:1567–1576.
98. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med* 2017;**376**:641–651.
99. Piché ME, Tchernof A, Després JP. Obesity phenotypes, diabetes, and cardiovascular diseases. *Circ Res* 2020;**126**:1477–1500.
100. Pareek M, Bhatt DL, Schiavon CA, Schauer PR. Metabolic surgery for hypertension in patients with obesity. *Circ Res* 2019;**124**:1009–1024.
101. Seravalle G, Colombo M, Perego P, Giardini V, Volpe M, Dell'Oro R, et al. Long-term sympathoinhibitory effects of surgically induced weight loss in severe obese patients. *Hypertension* 2014;**64**:431–437. doi:10.1161/HYPERTENSION.AHA.113.02988
102. Ahmed AR, Rickards G, Coniglio D, Xia Y, Johnson J, Boss T, et al. Laparoscopic Roux-en-Y gastric bypass and its early effect on blood pressure. *Obes Surg* 2009;**19**:845–849.
103. Adams ST, Salhab M, Hussain ZI, Miller G V, Leveson SH. Obesity-related hypertension and its remission following gastric bypass surgery - a review of the mechanisms and predictive factors. *Blood Press* 2013;**22**:131–137.
104. Zhou X, Yu J, Li L, Gloy VL, Nordmann A, Tiboni M, et al. Effects of bariatric surgery on mortality, cardiovascular events, and cancer outcomes in obese patients: systematic review and meta-analysis. *Obes Surg* 2016;**26**:2590–2601.
105. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: a systematic review and meta-analysis. *Diabetes Obes Metab* 2017;**19**:1223–1232.
106. Nathan DM, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin JM, et al. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. *Diabetes* 2013;**62**:3976–3986.
107. Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, Ferrannini E. Hypertension and diabetes mellitus. *Hypertension* 2018;**71**:422–428. doi:10.1161/HYPERTENSION.117.10546
108. Wijkman M, Länne T, Engvall J, Lindström T, Östgren CJ, Nystrom FH. Masked nocturnal hypertension—a novel marker of risk in type 2 diabetes. *Diabetologia* 2009;**52**:1258–1264.
109. Nakano S, Fukuda M, Hotta F, Ito T, Ishii T, Kitazawa M, et al. Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. *Diabetes* 1998;**47**:1501–1506.
110. Lemmer B, Oster H. The role of circadian rhythms in the hypertension of diabetes mellitus and the metabolic syndrome. *Curr Hypertens Rep* 2018;**20**:43.
111. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ* 2016;**352**:i717.
112. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10—should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens* 2017;**33**:922–944.
113. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;**313**: 603–615.
114. Nazarzadeh M, Bidel Z, Canoy D, Copland E, Wamil M, Majert J, et al. Blood pressure lowering and risk of new-onset type 2 diabetes: an individual participant data meta-analysis. *Lancet* 2021;**398**:1803–1810.
115. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.
116. ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–840.
117. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;**371**: 1392–1406.
118. Oxlund CS, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus. *J Hypertens* 2013;**31**:2094–2102.
119. Takahashi S, Katada J, Daïda H, Kitamura F, Yokoyama K. Effects of mineralocorticoid receptor antagonists in patients with hypertension and diabetes mellitus: a systematic review and meta-analysis. *J Hum Hypertens* 2016;**30**:534–542.
120. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:2219–2229.
121. Pitt B, Filippatos G, Agarwal R, Anker SD, Bakris GL, Rossing P, et al. Cardiovascular events with finerenone in kidney disease and type 2 diabetes. *N Engl J Med* 2021;**385**:2252–2263.
122. Agarwal R, Filippatos G, Pitt B, Anker SD, Rossing P, Joseph A, et al. Cardiovascular and kidney outcomes with finerenone in patients with type 2 diabetes and chronic kidney disease: the FIDELITY pooled analysis. *Eur Heart J* 2022;**43**:474–484.
123. Agarwal R, Joseph A, Anker SD, Filippatos G, Rossing P, Ruilope LM, et al. Hyperkalemia risk with finerenone: results from the FIDELIO-DKD trial. *J Am Soc Nephrol* 2022;**33**:225–237.
124. Messerli FH, Suter T, Bangalore S. What ever happened to cardioprotection with β -blockers? *Mayo Clin Proc* 2018;**93**:401–403.
125. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension. *JAMA* 2004;**292**:2227–2236.
126. Ayers K, Byrne LM, DeMatteo A, Brown NJ. Differential effects of nebivolol and metoprolol on insulin sensitivity and plasminogen activator inhibitor in the metabolic syndrome. *Hypertension* 2012;**59**:893–898. doi:10.1161/HYPERTENSION.111.189589
127. Tsujimoto T, Sugiyama T, Shapiro MF, Noda M, Kajio H. Risk of cardiovascular events in patients with diabetes mellitus on β -blockers. *Hypertension* 2017;**70**: 103–110.
128. Tsujimoto T, Kajio H, Shapiro MF, Sugiyama T. Risk of all-cause mortality in diabetic patients taking β -blockers. *Mayo Clin Proc* 2018;**93**:409–418.
129. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**: 311–322.
130. Zhao D, Liu H, Dong P. Liraglutide reduces systolic blood pressure in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *Clin Exp Hypertens* 2020;**42**:393–400.
131. Zhao X, Huang K, Zheng M, Duan J. Effect of liraglutide on blood pressure: a meta-analysis of liraglutide randomized controlled trials. *BMC Endocr Disord* 2019;**19**:4.
132. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, et al. Twenty-four-hour blood pressure-lowering effect of a sodium-glucose cotransporter 2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension. *Circulation* 2019;**139**:2089–2097.
133. Goud A, Zhong J, Peters M, Brook RD, Rajagopalan S. GLP-1 agonists and blood pressure: a review of the evidence. *Curr Hypertens Rep* 2016;**18**:16.
134. Kario K, Ferdinand KC, Vongpatanasin W. Are SGLT2 inhibitors new hypertension drugs? *Circulation* 2021;**143**:1750–1753.
135. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George J, et al. Empagliflozin and clinical outcomes in patients with type 2 diabetes mellitus,

- established cardiovascular disease, and chronic kidney disease. *Circulation* 2018; **137**:119–129.
136. Packer M, Butler J, Zannad F, Pocock SJ, Filippatos G, Ferreira JP, et al. Empagliflozin and major renal outcomes in heart failure. *N Engl J Med* 2021; **385**:1531–1533.
 137. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385**:1451–1461.
 138. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **380**:2295–2306.
 139. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**:644–657.
 140. Tikkanen I, Narko K, Zeller C, Green A, Salsali A, Broedl UC, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015; **38**:420–428.
 141. Böhm M, Fitchett D, Ofstad AP, Brueckmann M, Kaspers S, George JT, et al. Heart failure and renal outcomes according to baseline and achieved blood pressure in patients with type 2 diabetes: results from EMPA-REG OUTCOME. *J Hypertens* 2020; **38**:1829–1840.
 142. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart J* 2020; **41**:3402–3418.
 143. Böhm M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Empagliflozin improves cardiovascular and renal outcomes in heart failure irrespective of systolic blood pressure. *J Am Coll Cardiol* 2021; **78**:1337–1348.
 144. Ye N, Jardine MJ, Oshima M, Hockham C, Heerspink HJL, Agarwal R, et al. Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease. *Circulation* 2021; **143**:1735–1749. doi:10.1161/CIRCULATIONAHA.120.048740
 145. Striepe K, Jumar A, Ott C, Karg MV, Schneider MP, Kannenkeril D, et al. Effects of the selective sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function and central hemodynamics in patients with type 2 diabetes mellitus. *Circulation* 2017; **136**:1167–1169.
 146. Schlaich M, Straznicki N, Lambert E, Lambert G. Metabolic syndrome: a sympathetic disease? *Lancet Diabetes Endocrinol* 2015; **3**:148–157.
 147. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DASG. Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation* 2003; **108**:3097–3101.
 148. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; **123**:1940–1946.
 149. Ott C, Schmid A, Mahfoud F, Akarca E, Kistner I, Ditting T, et al. Secretory capacity of pancreatic beta-cells is enhanced 6 months after renal denervation in hypertensive patients. *J Am Coll Cardiol* 2018; **72**:3372–3374.
 150. Witkowski A, Prejbisz A, Florkacz EE, Kądziela J, Śliwiński P, Bieleń P, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension* 2011; **58**:559–565.
 151. Verloop WL, Spiering W, Vink EE, Beeftink MMA, Blankestijn PJ, Doevendans PA, et al. Denervation of the renal arteries in metabolic syndrome. *Hypertension* 2015; **65**:751–757.
 152. Tsioufis C, Dimitriadis K, Kasiakogias A, Kalos T, Liatakas I, Koutra E, et al. Effects of multielectrode renal denervation on elevated sympathetic nerve activity and insulin resistance in metabolic syndrome. *J Hypertens* 2017; **35**:1100–1108.
 153. O'Seaghdha CM, Perkovic V, Lam TH, McGinn S, Barzi F, Gu DF, et al. Blood pressure is a major risk factor for renal death. *Hypertension* 2009; **54**:509–515.
 154. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; **139**:244–252.
 155. Converse RL, Jacobsen TN, Toto RD, Jost CMT, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**:1912–1918.
 156. Grassi G, Quarti-Trevano F, Seravalle G, Arenare F, Volpe M, Furiani S, et al. Early sympathetic activation in the initial clinical stages of chronic renal failure. *Hypertension* 2011; **57**:846–851.
 157. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S. Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003; **41**:1341–1345.
 158. Muiesan ML, Ambrosioni E, Costa FV, Leonetti G, Pessina AC, Salvetti M, et al. Sex differences in hypertension-related renal and cardiovascular diseases in Italy. *J Hypertens* 2012; **30**:2378–2386.
 159. Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016; **11**:642–652.
 160. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, et al. The double challenge of resistant hypertension and chronic kidney disease. *Lancet* 2015; **386**:1588–1598.
 161. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* 2012; **380**:1649–1661.
 162. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994; **330**:877–884.
 163. Cheung AK, Chang TI, Cushman WC, Furth SL, Hou FF, Ix JH, et al. KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021; **99**:S1–S87.
 164. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. *Can Med Assoc J* 2013; **185**:949–957.
 165. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**:2073–2081.
 166. Zannad F, Rossignol P. Cardiorenal syndrome revisited. *Circulation* 2018; **138**:929–944.
 167. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 2011; **154**:541–548.
 168. Lambert T, Gammer V, Nahler A, Blessberger H, Kammler J, Grund M, et al. Individual-patient visit-by-visit office and ambulatory blood pressure measurements over 24 months in patients undergoing renal denervation for hypertension. *Int J Cardiol* 2015; **181**:96–101.
 169. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017; **28**:2812–2823.
 170. Hung SC, Kuo KL, Peng CH, Wu CH, Lien YC, Wang YC, et al. Volume overload correlates with cardiovascular risk factors in patients with chronic kidney disease. *Kidney Int* 2014; **85**:703–709.
 171. McMahon EJ, Bauer JD, Hawley CM, Isbel NM, Stowasser M, Johnson DW, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 2013; **24**:2096–2103.
 172. Agarwal R, Sinha AD, Cramer AE, Balmes-Fenwick M, Dickinson JH, Ouyang F, et al. Chlorthalidone for hypertension in advanced chronic kidney disease. *N Engl J Med* 2021; **385**:2507–2519.
 173. Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro CJ, et al. Hypertension in dialysis patients: a consensus document by the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and the hypertension and the kidney working group of the European Society of Hypertension (ESH). *Nephrol Dial Transplant* 2017; **32**:620–640.
 174. Agarwal R, Sinha AD. Cardiovascular protection with antihypertensive drugs in dialysis patients. *Hypertension* 2009; **53**:860–866.
 175. Heerspink HJL, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, et al. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; **373**:1009–1015.
 176. Denker MG, Cohen DL. Antihypertensive medications in end-stage renal disease. *Semin Dial* 2015; **28**:330–336.
 177. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; **383**:1436–1446.
 178. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, et al. Sympathetic nerve activity in end-stage renal disease. *Circulation* 2002; **106**:1974–1979.
 179. Mauriello A, Rovella V, Anemona L, Servadei F, Giannini E, Bove P, et al. Increased sympathetic renal innervation in hemodialysis patients is the anatomical substrate of sympathetic hyperactivity in end-stage renal disease. *J Am Heart Assoc* 2015; **4**:e002426.
 180. Campese VM, Kogosov E, Koss M. Renal afferent denervation prevents the progression of renal disease in the renal ablation model of chronic renal failure in the rat. *Am J Kidney Dis* 1995; **26**:861–865.
 181. Ott C, Mahfoud F, Mancia G, Narkiewicz K, Kuilope LM, Fahy M, et al. Renal denervation in patients with versus without chronic kidney disease: results from the Global SYMPPLICITY Registry with follow-up data of 3 years. *Nephrol Dial Transplant* 2022; **37**:304–310.
 182. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012; **23**:1250–1257.

183. Ott C, Schmid A, Ditting T, Veelken R, Uder M, Schmieder RE. Effects of renal denervation on blood pressure in hypertensive patients with end-stage renal disease: a single centre experience. *Clin Exp Nephrol* 2019;**23**:749–755.
184. Scalise F, Sole A, Singh G, Sorropago A, Sorropago G, Ballabeni C, et al. Renal denervation in patients with end-stage renal disease and resistant hypertension on long-term haemodialysis. *J Hypertens* 2020;**38**:936–942.
185. Crisafulli E, Costi S, Luppi F, Cirelli G, Cilione C, Coletti O, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. *Thorax* 2008;**63**:487–492.
186. Feary JR, Rodrigues LC, Smith CJ, Hubbard RB, Gibson JE. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax* 2010;**65**:956–962.
187. Loth DW, Brusselle GG, Lahousse L, Hofman A, Leufkens HGM, Stricker BH. β -Adrenoceptor blockers and pulmonary function in the general population: the Rotterdam Study. *Br J Clin Pharmacol* 2014;**77**:190–200.
188. Morales DR, Jackson C, Lipworth BJ, Donnan PT, Guthrie B. Adverse respiratory effect of acute β -blocker exposure in asthma. *Chest* 2014;**145**:779–786.
189. Coiro S, Girerd N, Rossignol P, Ferreira JP, Maggioni A, Pitt B, et al. Association of beta-blocker treatment with mortality following myocardial infarction in patients with chronic obstructive pulmonary disease and heart failure or left ventricular dysfunction: a propensity matched-cohort analysis from the high-risk myocardi. *Eur J Heart Fail* 2017;**19**:271–279.
190. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005;**2005**:CD003566.
191. Kotlyar E, Keogh AM, Macdonald PS, Arnold RH, McCaffrey DJ, Glanville AR. Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. *J Heart Lung Transplant* 2002;**21**:1290–1295.
192. Andersson B, She L, Tan R-S, Jeemon P, Mokrzycki K, Siepe M, et al. The association between blood pressure and long-term outcomes of patients with ischaemic cardiomyopathy with and without surgical revascularization: an analysis of the STICH trial. *Eur Heart J* 2018;**39**:3464–3471.
193. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
194. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
195. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.
196. The SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
197. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) study investigators. *Lancet* 1993;**342**:821–828.
198. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;**327**:669–677.
199. Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliassen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;**333**:1670–1676.
200. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1994;**343**:1115–1122.
201. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995;**345**:669–685.
202. The Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
203. Fox KM, The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–788.
204. Ferrari R, Fox K. Insight into the mode of action of ACE inhibition in coronary artery disease. *Drugs* 2009;**69**:265–277.
205. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;**368**:581–588.
206. Pitt B, Poole-Wilson P, Segal R, Martinez FA, Dickstein K, John Camm A, et al. Effects of losartan versus captopril on mortality in patients with symptomatic heart failure: rationale, design, and baseline characteristics of patients in the losartan heart failure survival study-ELITE II. *J Card Fail* 1999;**5**:146–154.
207. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–1675.
208. Pfeffer MA, McMurray JJV, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
209. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;**360**:752–760.
210. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2022–2031.
211. Teo KK, Pogue J, Dyal L, Copland I, Health P, Sciences HHH, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
212. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:1004–1010.
213. Sawada T, Yamada H, Dahlöf B, Matsubara H. Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART study. *Eur Heart J* 2009;**30**:2461–2469.
214. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895–906.
215. Schieffer B, Bunte C, Witte J, Hoepfer K, Böger RH, Schwedhelm E, et al. Comparative effects of AT1-antagonism and angiotensin-converting enzyme inhibition on markers of inflammation and platelet aggregation in patients with coronary artery disease. *J Am Coll Cardiol* 2004;**44**:362–368.
216. Montalescot G, Drexler H, Gallo R, Pearson T, Thoenes M, Bhatt DL. Effect of irbesartan and enalapril in non-ST elevation acute coronary syndrome: results of the randomized, double-blind ARCHIPELAGO study. *Eur Heart J* 2009;**30**:2733–2741.
217. Ceconi C, Fox K, Remme WJ, Simoons ML, Bertrand M, Parrinello G, et al. ACE Inhibition with perindopril and endothelial function. Results of a substudy of the EUROPA study: PERTINENT. *Cardiovasc Res* 2007;**73**:237–246.
218. Ferrari R, Perindopril and Remodeling in Elderly with Acute Myocardial Infarction Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized perindopril and remodeling in elderly with acute myocardial infarction (PREAMI) study. *Arch Intern Med* 2006;**166**:659–666.
219. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? *Lancet* 2004;**364**:1684–1689.
220. Belsey J, Savellieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;**22**:837–848.
221. Ezekowitz MD, Hossack K, Mehta JL, Thadani U, Weidler DJ, Kostuk WJ, et al. Amlodipine in chronic stable angina: results of a multicenter double-blind crossover trial. *Am Heart J* 1995;**129**:527–535.
222. Hjemdahl P, Eriksson SV, Held C, Forslund L, Näsman P, Rehnqvist N. Favourable long term prognosis in stable angina pectoris: an extended follow up of the angina prognosis study in Stockholm (APSYS). *Heart* 2006;**92**:177–182.
223. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;**290**:2805–2816.
224. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;**275**:1557–1562.
225. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. *N Engl J Med* 1972;**287**:781–787.
226. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;**106**:3068–3072.
227. Weber T, Chirinos JA. Pulsatile arterial haemodynamics in heart failure. *Eur Heart J* 2018;**39**:3847–3854.

228. Drazner MH. The progression of hypertensive heart disease. *Circulation* 2011;**123**: 327–334.
229. Rame JE, Ramilo M, Spencer N, Blewett C, Mehta SK, Dries DL, et al. Development of a depressed left ventricular ejection fraction in patients with left ventricular hypertrophy and a normal ejection fraction. *Am J Cardiol* 2004;**93**:234–237.
230. Krishnamoorthy A, Brown T, Ayers CR, Gupta S, Rame JE, Patel PC, et al. Progression from normal to reduced left ventricular ejection fraction in patients with concentric left ventricular hypertrophy after long-term follow-up. *Am J Cardiol* 2011;**108**:997–1001.
231. Lauer MS, Evans JC, Levy D. Prognostic implications of subclinical left ventricular dilatation and systolic dysfunction in men free of overt cardiovascular disease (the Framingham Heart Study). *Am J Cardiol* 1992;**70**:1180–1184.
232. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
233. Redfield MM. Heart failure with preserved ejection fraction. *N Engl J Med* 2016;**375**: 1868–1877.
234. de Simone G, Devereux RB, Izzo R, Giffoglio D, Lee ET, Howard B V, et al. Lack of reduction of left ventricular mass in treated hypertension: the Strong Heart Study. *J Am Heart Assoc* 2013;**2**:e000144.
235. Turnbull F, Neal B, Algert C, Chalmers J, Woodward M, MacMahon S, et al. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;**362**: 1527–1535.
236. Dahlöf B, Hansson L, Lindholm LH, Scherstén B, Ekblom T, Wester PO, et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;**338**:1281–1285.
237. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;**265**:3255–3264.
238. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses and meta regression analyses of randomized trials. *J Hypertens* 2015;**33**:195–211.
239. Vaduganathan M, Pareek M, Kristensen AMD, Biering-Sørensen T, Byrne C, Almarzooq Z, et al. Prevention of heart failure events with intensive versus standard blood pressure lowering across the spectrum of kidney function and albuminuria: a SPRINT substudy. *Eur J Heart Fail* 2021;**23**:384–392.
240. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering treatment. 6. Prevention of heart failure and new-onset heart failure—meta-analyses of randomized trials. *J Hypertens* 2016;**34**:373–384.
241. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Arch Intern Med* 2011;**171**:384–394.
242. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003;**289**:2534–2544.
243. Filippatos G, Anker SD, Agarwal R, Ruilope LM, Rossing P, Bakris GL, et al. Finerenone reduces risk of incident heart failure in patients with chronic kidney disease and type 2 diabetes: analyses from the FIGARO-DKD trial. *Circulation* 2022; **145**:437–447.
244. Bangalore S, Wild D, Parkar S, Kukin M, Messerli FH. Beta-blockers for primary prevention of heart failure in patients with hypertension. *J Am Coll Cardiol* 2008;**52**: 1062–1072.
245. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Collaborative Research Group. *JAMA* 2000;**283**:1967–1975.
246. Davis BR, Kostis JB, Simpson LM, Black HR, Cushman WC, Einhorn PT, et al. Heart failure with preserved and reduced left ventricular ejection fraction in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* 2008;**118**:2259–2267.
247. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by anti-hypertensive treatment. *Hypertension* 2009;**54**:1084–1091.
248. Schmieder RE, Wagner F, Mayr K, Delles C, Ott C, Keicher C, et al. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. *Eur Heart J* 2017;**38**:3308–3317.
249. Williams B, Cockcroft JR, Kario K, Zappe DH, Brunel PC, Wang Q, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension. *Hypertension* 2017;**69**:411–420. doi:10.1161/HYPERTENSION.116.08556
250. Chua SK, Lai WT, Chen LC, Hung HF. The antihypertensive effects and safety of LCZ696 in patients with hypertension: a systematic review and meta-analysis of randomized controlled trials. *J Clin Med* 2021;**10**:2824.
251. Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation* 2016;**134**: e535–e578.
252. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726.
253. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
254. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin–neprilysin inhibition in heart failure. *JACC Heart Fail* 2018;**6**:489–498.
255. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-reduced and DAPA-HF trials. *Lancet* 2020;**396**:819–829.
256. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;**335**:1107–1114.
257. Udelson JE, DeAbate CA, Berk M, Neuberg G, Packer M, Vijay NK, et al. Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *Am Heart J* 2000; **139**:503–510.
258. Packer M, Carson P, Elkayam U, Konstam MA, Moe G, O'Connor C, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy. *JACC Heart Fail* 2013;**1**:308–314.
259. Cohn JN, Ziesche S, Smith R, Anand I, Dunkman WB, Loeb H, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril. *Circulation* 1997;**96**:856–863.
260. Cohn JN, Pfeffer MA, Rouleau J, Sharpe N, Swedberg K, Straub M, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 2003;**5**:659–667.
261. Hummel SL, Seymour EM, Brook RD, Sheth SS, Ghosh E, Zhu S, et al. Low-sodium DASH diet improves diastolic function and ventricular–arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail* 2013;**6**: 1165–1171.
262. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-preserved trial. *Lancet* 2003;**362**:777–781.
263. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. *Lancet* 2019;**393**:1034–1044.
264. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;**369**:2079–2087.
265. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction $\geq 40\%$ treated with diuretics plus angiot. *Am J Cardiol* 1997;**80**:207–209.
266. Jackson AM, Jhund PS, Anand IS, Düngen HD, Lam CSP, Lefkowitz MP, et al. Sacubitril–valsartan as a treatment for apparent resistant hypertension in patients with heart failure and preserved ejection fraction. *Eur Heart J* 2021;**42**:3741–3752.
267. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014;**370**:1383–1392.
268. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. *Circulation* 2015;**131**: 34–42.
269. de Denus S, O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G, et al. Spironolactone metabolites in TOPCAT—new insights into regional variation. *N Engl J Med* 2017;**376**:1690–1692.
270. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;**79**:e263–e421.
271. Grassi G, Quarti-Trevano F, Esler MD. Sympathetic activation in congestive heart failure: an updated overview. *Heart Fail Rev* 2021;**26**:173–182.
272. Polhemus DJ, Trivedi RK, Gao J, Li Z, Scarborough AL, Goodchild TT, et al. Renal sympathetic denervation protects the failing heart via inhibition of neprilysin activity in the kidney. *J Am Coll Cardiol* 2017;**70**:2139–2153.

273. Wang H-J, Wang W, Cornish KG, Rozanski GJ, Zucker IH. Cardiac sympathetic afferent denervation attenuates cardiac remodeling and improves cardiovascular dysfunction in rats with heart failure. *Hypertension* 2014;**64**:745–755.
274. Sharp TE, Polhemus DJ, Li Z, Spaleta P, Jenkins JS, Reilly JP, et al. Renal denervation prevents heart failure progression via inhibition of the renin-angiotensin system. *J Am Coll Cardiol* 2018;**72**:2609–2621.
275. Liao SY, Zhen Z, Liu Y, Au KW, Lai W-H, Tsang A, et al. Improvement of myocardial function following catheter-based renal denervation in heart failure. *JACC Basic Transl Sci* 2017;**2**:270–281.
276. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol* 2013;**162**:189–192.
277. Almeida Mds, Gonçalves P da, Branco P, Mesquita J, Carvalho MS, Soares H, et al. Impact of renal sympathetic denervation on left ventricular structure and function at 1-year follow-up. *PLoS One* 2016;**11**:e0149855.
278. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* 2004;**62**:569–573.
279. Dhamoon MS, Tai VW, Boden-Albala B, Rundek T, Paik MC, Sacco RL, et al. Risk of myocardial infarction or vascular death after first ischemic stroke. *Stroke* 2007;**38**:1752–1758.
280. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res* 2017;**120**:439–448.
281. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;**376**:112–123.
282. Böhm M, Schumacher H, Teo KK, Lonn EM, Lauder L, Mancia G, et al. Cardiovascular outcomes in patients at high cardiovascular risk with previous myocardial infarction or stroke. *J Hypertens* 2021;**39**:1602–1610.
283. Katsanos AH, Filippatou A, Manios E, Deteoro S, Parissis J, Frogoudaki A, et al. Blood pressure reduction and secondary stroke prevention. *Hypertension* 2017;**69**:171–179.
284. Toschke AM, Gulliford MC, Wolfe CDA, Rudd AG, Heuschmann PU. Antihypertensive treatment after first stroke in primary care: results from the General Practitioner Research Database. *J Hypertens* 2011;**29**:154–160.
285. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. *Stroke* 2004;**35**:731–735.
286. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:e13–e115.
287. The SPS3 Study Group, Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;**382**:507–515.
288. Arima H, Chalmers J, Woodward M, Anderson C, Rodgers A, Davis S, et al. Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. *J Hypertens* 2006;**24**:1201–1208.
289. Park CS, Park JB, Kim Y, Yoon YE, Lee SP, Kim HK, et al. Left ventricular geometry determines prognosis and reverse J-shaped relation between blood pressure and mortality in ischemic stroke patients. *JACC Cardiovasc Imaging* 2018;**11**:373–382.
290. Gillebert TC, Chirinos JA. Left ventricular geometry, blood pressure, arterial hemodynamics, and mortality after ischemic stroke. *JACC Cardiovasc Imaging* 2018;**11**:383–385.
291. Collier DJ, Poulter NR, Dahlöf B, Sever PS, Wedel H, Buch J, et al. Impact of amlodipine-based therapy among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA). *J Hypertens* 2011;**29**:583–591. doi:10.1097/HJH.0b013e328342c845
292. Wang WT, You LK, Chiang CE, Sung SH, Chuang SY, Cheng HM, et al. Comparative effectiveness of blood pressure-lowering drugs in patients who have already suffered from stroke. *Medicine (Baltimore)* 2016;**95**:e3302.
293. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019;**50**:E344–E418.
294. Gottesman RF, Schneider ALC, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol* 2014;**71**:1218–1227.
295. Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology* 2001;**56**:1683–1689.
296. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid- to late life and risk of incident dementia. *Neurology* 2017;**89**:2447–2454.
297. Freitag MH, Peila R, Masaki K, Petrovitch H, Ross GW, White LR, et al. Midlife pulse pressure and incidence of dementia. *Stroke* 2006;**37**:33–37.
298. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurol* 2017;**74**:1246.
299. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 2014;**13**:788–794.
300. Walker KA, Sharrett AR, Wu A, Schneider ALC, Albert M, Lutsey PL, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA* 2019;**322**:535–545.
301. Benetos A, Rossignol P, Cherubini A, Joly L, Grodzicki T, Rajkumar C, et al. Polypharmacy in the aging patient: management of hypertension in octogenarians. *JAMA* 2015;**314**:170–180.
302. Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clin Exp Res* 2007;**19**:41–47.
303. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA* 1999;**281**:438–445.
304. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function. *Hypertension* 2005;**45**:374–379.
305. Kilander L, Nyman H, Bobberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment. *Hypertension* 1998;**31**:780–786.
306. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension. *Circ Res* 2019;**124**:1025–1044.
307. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia. *J Hypertens* 2013;**31**:1073–1082.
308. Godin O, Tzourio C, Maillard P, Mazoyer B, Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes. *Circulation* 2011;**123**:266–273.
309. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol* 2020;**19**:61–70.
310. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, et al. Effect of intensive vs standard blood pressure control on probable dementia. *JAMA* 2019;**321**:553–561.
311. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. *Hypertension* 2016;**68**:e67–e94.
312. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (syst- eur) study. *Arch Intern Med* 2002;**162**:2046–2052.
313. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;**163**:1069–1075.
314. van Middelaar T, van Vught LA, van Charante EPM, Eurelings LSM, Ligthart SA, van Dalen JW, et al. Lower dementia risk with different classes of antihypertensive medication in older patients. *J Hypertens* 2017;**35**:2095–2101.
315. Tully PJ, Hanon O, Cosh S, Tzourio C. Diuretic antihypertensive drugs and incident dementia risk. *J Hypertens* 2016;**34**:1027–1035. doi:10.1097/HJH.0000000000000868
316. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;**13**:321–332.
317. Deng H, Bai Y, Shantsila A, Fauchier L, Potpara TS, Lip GYH. Clinical scores for outcomes of rhythm control or arrhythmia progression in patients with atrial fibrillation: a systematic review. *Clin Res Cardiol* 2017;**106**:813–823.
318. Kannel WW, Wolf P, Benjamin E, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N–9N.
319. Sharashova E, Wilsgaard T, Ball J, Morseth B, Gerds E, Hopstock LA, et al. Long-term blood pressure trajectories and incident atrial fibrillation in women and men: the Tromsø Study. *Eur Heart J* 2020;**41**:1554–1562.
320. Dzeshka MS, Shantsila A, Shantsila E, Lip GYH. Atrial fibrillation and hypertension. *Hypertension* 2017;**70**:854–861.

321. Dzeshka MS, Lip GYH, Snezhitskiy V, Shantsila E. Cardiac fibrosis in patients with atrial fibrillation. *J Am Coll Cardiol* 2015;**66**:943–959.
322. Wachtell K, Lehto M, Gerds E, Olsen MH, Hornestam B, Dahlöf B, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol. *J Am Coll Cardiol* 2005;**45**:712–719.
323. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;**154**:1449–1457.
324. Hart RG, Pearce LA, Albers GW, Connolly SJ, Friday GH, Gage BF, et al. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–554.
325. Esteve-Pastor M A, Rivera-Caravaca J M, Roldán V, Vicente V, Valdés M, Marín F, et al. Long-term bleeding risk prediction in 'real world' patients with atrial fibrillation: comparison of the HAS-BLED and ABC-bleeding risk scores. *Thromb Haemost* 2017;**117**:1848–1858.
326. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
327. Kim D, Yang PS, Kim TH, Jang E, Shin H, Kim HY, et al. Ideal blood pressure in patients with atrial fibrillation. *J Am Coll Cardiol* 2018;**72**:1233–1245.
328. Böhm M, Brueckmann M, Eikelboom JW, Ezekowitz M, Fräbörger M, Hijazi Z, et al. Cardiovascular outcomes, bleeding risk, and achieved blood pressure in patients on long-term anticoagulation with the thrombin antagonist dabigatran or warfarin: data from the RE-LY trial. *Eur Heart J* 2020;**41**:2848–2859.
329. Kim T-H, Yang P-S, Yu H-T, Jang E, Shin H, Kim H-Y, et al. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. *Eur Heart J* 2019;**40**:809–819.
330. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, et al. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–28.
331. Lafuente-Lafuente C, Valembois L, Bergmann JF, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2019;**9**:CD005049.
332. Capucci A, Botto G, Molon G, Spampinato A, Favale S, Proclemer A, et al. The Drug And Pace Health clinical Evaluation (DAPHNE) study: a randomized trial comparing sotalol versus β -blockers to treat symptomatic atrial fibrillation in patients with brady-tachycardia syndrome implanted with an antitachycardia pacemaker. *Am Heart J* 2008;**156**:373.e1–373.e8.
333. Nergårdh AK, Rosenqvist M, Nordlander R, Frick M. Maintenance of sinus rhythm with metoprolol CR initiated before cardioversion and repeated cardioversion of atrial fibrillation: a randomized double-blind placebo-controlled study. *Eur Heart J* 2007;**28**:1351–1357.
334. Schmieder RE, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. *J Hypertens* 2008;**26**:403–411.
335. Schaer BA, Schneider C, Jick SS, Conen D, Osswald S, Meier CR. Risk for incident atrial fibrillation in patients who receive antihypertensive drugs: a nested case-control study. *Ann Intern Med* 2010;**152**:78–84.
336. Reil JC, Hohl M, Selejan S, Lipp P, Drautz F, Kazakow A, et al. Aldosterone promotes atrial fibrillation. *Eur Heart J* 2012;**33**:2098–2108.
337. Reil JC, Tauchnitz M, Tian Q, Hohl M, Linz D, Oberhofer M, et al. Hyperaldosteronism induces left atrial systolic and diastolic dysfunction. *Am J Physiol Circ Physiol* 2016;**311**:H1014–H1023.
338. Shantsila E, Shahid F, Sun Y, Deeks J, Calvert M, Fisher JP, et al. Spironolactone in atrial fibrillation with preserved cardiac fraction: the IMPRESS-AF trial. *J Am Heart Assoc* 2020;**9**:e016239.
339. Böhm M, Linz D, Urban D, Mahfoud F, Ukena C. Renal sympathetic denervation: applications in hypertension and beyond. *Nat Rev Cardiol* 2013;**10**:465–476.
340. Böhm M, Linz D, Ukena C, Esler M, Mahfoud F. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? *Circ Res* 2014;**115**:400–409.
341. Castellà M, Kotecha D, van Laar C, Wintgens L, Castillo Y, Kelder J, et al. Thoracoscopic vs. Catheter ablation for atrial fibrillation: long-term follow-up of the FAST randomized trial. *Europace* 2019;**21**:746–753.
342. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol* 2012;**60**:1163–1170.
343. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020;**323**:248–255.
344. Ukena C, Becker N, Pavlicek V, Millenaar D, Ewen S, Linz D, et al. Catheter-based renal denervation as adjunct to pulmonary vein isolation for treatment of atrial fibrillation. *J Hypertens* 2020;**38**:783–790.
345. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–1011.
346. Linhartová K, Filipovský J, Čerbák R, Štěrbáková G, Hanišová I, Beránek V. Severe aortic stenosis and its association with hypertension: analysis of clinical and echocardiographic parameters. *Blood Press* 2007;**16**:122–128.
347. Bermejo J. The effects of hypertension on aortic valve stenosis. *Heart* 2005;**91**:280–282.
348. Lindman BR, Otto CM. Time to treat hypertension in patients with aortic stenosis. *Circulation* 2013;**128**:1281–1283.
349. Rahimi K, Mohseni H, Kiran A, Tran J, Nazarzadeh M, Rahimian F, et al. Elevated blood pressure and risk of aortic valve disease: a cohort analysis of 5.4 million UK adults. *Eur Heart J* 2018;**39**:3596–3603.
350. Tastet L, Capoulade R, Clavel MA, Larose É, Shen M, Dahou A, et al. Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis: results from the PROGRESSA study. *Eur Heart J Cardiovasc Imaging* 2017;**18**:70–78.
351. de Simone G, Izzo R, Aurigemma GP, De Marco M, Rozza F, Trimarco V, et al. Cardiovascular risk in relation to a new classification of hypertensive left ventricular geometric abnormalities. *J Hypertens* 2015;**33**:745–754.
352. Antonini-Canterin F, Huang G, Cervasato E, Faggiano P, Pavan D, Piazza R, et al. Symptomatic aortic stenosis. *Hypertension* 2003;**41**:1268–1272.
353. Rieck AE, Cramariuc D, Boman K, Gohlke-Bärwolf C, Staal EM, Lønnebakken MT, et al. Hypertension in aortic stenosis. *Hypertension* 2012;**60**:90–97.
354. Mancusi C, de Simone G, Brguljan Hitij J, Sudano I, Mahfoud F, Parati G, et al. Management of patients with combined arterial hypertension and aortic valve stenosis: a consensus document from the Council on Hypertension and Council on Valvular Heart Disease of the European Society of Cardiology, the European Association of Cardiovascular. *Eur Heart J Cardiovasc Pharmacother* 2021;**7**:242–250.
355. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632.
356. Nielsen OW, Sajadieh A, Sabbah M, Greve AM, Olsen MH, Boman K, et al. Assessing optimal blood pressure in patients with asymptomatic aortic valve stenosis: the Simvastatin Ezetimibe in Aortic Stenosis Study (SEAS). *Circulation* 2016;**134**:455–468.
357. Chockalingam A, Venkatesan S, Subramaniam T, Jagannathan V, Elangovan S, Alagesan R, et al. Safety and efficacy of angiotensin-converting enzyme inhibitors in symptomatic severe aortic stenosis: symptomatic cardiac obstruction-pilot study of enalapril in aortic stenosis (SCOPE-AS). *Am Heart J* 2004;**147**:E19.
358. Nadir MA, Wei L, Elder DHJ, Libianto R, Lim TK, Pauriah M, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol* 2011;**58**:570–576.
359. Bang CN, Greve AM, Køber L, Rossebø AB, Ray S, Boman K, et al. Renin-angiotensin system inhibition is not associated with increased sudden cardiac death, cardiovascular mortality or all-cause mortality in patients with aortic stenosis. *Int J Cardiol* 2014;**175**:492–498.
360. Bull S, Loudon M, Francis JM, Joseph J, Gerry S, Karamitsos TD, et al. A prospective, double-blind, randomized controlled trial of the angiotensin-converting enzyme inhibitor Ramipril in Aortic Stenosis (RIAS trial). *Eur Heart J Cardiovasc Imaging* 2015;**16**:834–841.
361. Rossi A, Temporelli PL, Cicciola M, Gaibazzi N, Cioffi G, Nistri S, et al. Beta-blockers can improve survival in medically-treated patients with severe symptomatic aortic stenosis. *Int J Cardiol* 2015;**190**:15–17.
362. Bang CN, Greve AM, Rossebø AB, Ray S, Egstrup K, Boman K, et al. Antihypertensive treatment with β -blockade in patients with asymptomatic aortic stenosis and association with cardiovascular events. *J Am Heart Assoc* 2017;**6**:e006709.