Chapter 2

Current Guideline Recommendations on Different Classes of Antihypertensive Agents

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This chapter reviews recommendations in current guidelines that relate to the five major classes of antihypertensive therapy (angiotensin converting enzyme inhibitors [ACEI], angiotensin II receptor blockers [ARB], β-blockers, calcium channel blockers [CCB] and thiazide-like diuretics). European guidelines recommend that most patients with hypertension begin with a combination of an ACEI or ARB with a CCB or a diuretic. However, other comorbidities often influence the prescribing decision: for example, β-blockers and CCBs are evidence-based treatments for heart failure with reduced ejection fraction and stable coronary artery disease, post-myocardial infarction (MI), and are also useful for ameliorating the symptoms of angina.

Introduction

There are many antihypertensive agents available currently for therapeutic use. For this reason, guidelines for the management of hypertension consider the therapeutic evidence base for five major classes of antihypertensive agents, as well as for individual agents within those classes. This chapter considers current recommendations from major guidelines relating to the use of antihypertensive classes for the management of arterial hypertension in adults. Table 1 provides a list of the guidelines reviewed in this chapter [1–7], and Table 2 gives an overview of the five antihypertensive drug classes, with examples of the more commonly used individual drugs within them [8]. In each case, these tables define the commonly used acronyms for these drug classes and the guidelines that will be used throughout this chapter.

Table 1 Hypertension guidelines summarised in this chapter with names of their sponsoring organisations.

Guideline	Year of publication
Guideline for the management of arterial hypertension from the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) [1]	2018
Guideline on the prevention of cardiovascular disease from the ESC and 12 additional expert societies [2]	2021
Guideline on the management of high BP in adults from the American College of Cardiology (ACC), the American Heart Association (AHA) and 9 other expert societies [3]	2018
International Society of Hypertension (ISH) global hypertension practice guideline [4]	2020
National Institute for Health and Care Excellence (NICE) guideline on hypertension management in adults [5]	2022
ESC guideline for the management of heart failure [6]	2021
ESC guideline for the management of chronic coronary syndromes [7]	2019

BP: blood pressure.

Table 2 Major classes of antihypertensive agents [2].

Antihypertensive class	Examples of commonly used individual drugs within each class[d]
ACEI	Captopril, enalapril, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, trandolapril
ARB	Azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan
β-blocker	*β_1-selective*: acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol[a] *Not β_1-selective*: carvedilol,[b] labetolol,[b] levobunolol, nadolol, pindolol, propranolol, sotalol, timolol
CCB	*Dihydropyridine*: amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine *Non-dihydropyridine*: verapamil, diltiazem
Diuretic[c]	Bendroflumethiazide, chlorthalidone, hydrochlorothiazide, indapamide

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker.
[a]Also inhibits phosphodiesterase-5.
[b]Also blocks α_1-adrenoceptors.
[c]Particularly thiazide and thiazide-like diuretics, listed here.
[d]The lists of drugs of each class serves to provide examples only, and are not intended to be exhaustive. Compiled from information presented in reference [2].

General recommendations on the use of antihypertensive therapy

Importance of lifestyle interventions

Adverse lifestyle behaviours, such as physical inactivity and poor diet leading to weight gain are associated with higher levels of blood pressure (BP) [9]. Conversely, lifestyle intervention—improving the diet and undertaking increased levels of physical activity—improves multiple cardiovascular risk factors, including reducing BP in people with hypertension [10–12]. A recent large, observational study from the United Kingdom (UK) showed that a healthier lifestyle (compared with a very unhealthy lifestyle) was associated with increased life expectancy of up to about 6 years in men and about 8 years in women [13]. All guidelines agree on the central importance of encouraging patients with hypertension to improve their lifestyle. It is important to note that all guideline recommendations on the pharmacological management of hypertension discussed here are considered in addition to lifestyle modification.

Initiation of antihypertensive pharmacotherapy

Table 3 summarises the main recommendations relating to the initiation of antihypertensive pharmacotherapy from major guidelines for the management of hypertension. It should be noted that lifestyle improvement should be undertaken by all patients, as described above.

The classical approach to the pharmacological management of hypertension has been to start with monotherapy, followed by sequential addition of other drugs if BP is not controlled adequately. Observations of a high prevalence of uncontrolled hypertension and high rates of non-adherence in drug-treated patients have prompted reconsideration of this approach. For example, one study from the United States (US) found that 38% of patients taking antihypertensive monotherapy had BP >140/90 mmHg [14]. Accordingly, guidelines proposed by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) recommends starting pharmacological antihypertensive treatment with a 2-drug combination for most patients (possible exceptions being patients with SBP <150 mmHg and low cardiovascular risk, the very elderly and frail patients) [3]. A blocker of the renin-angiotensin system (RAS), such as an ACEI or ARB, given with a CCB or diuretic is preferred. A more recent guideline on cardiovascular disease (CVD) prevention from the ESC and 12 other expert societies provide similar recommendations on the initiation of antihypertensive pharmacotherapy, but also state that a combination of any of the five classes of antihypertensive therapies can be used instead of the preferred ACEI/ARB + CCB or diuretic combination [2].

The 2018 ESC guideline for the management of hypertension [2] (but not the 2021 guideline for cardiovascular risk reduction [3]) provides support for pharmacological management of high-normal BP, especially in very high-risk patients with coronary artery disease. The US guideline from 2018 (proposed by the American College of Cardiology [ACC] and American Heart Association [AHA]) also supports pharmacological intervention to prevent recurrent CVD in patients with BP ≥130/80 mmHg and either prior CVD or 10-year CVD risk ≥10%. Antihypertensive medication is proposed for patients at lower cardiovascular risk if their BP is

Table 3 Overview of recommendations on initiation of antihypertensive pharmacotherapy.

Sponsor(s)	Summary of recommendations[c]
ESC/ESH (2018) [1][a]	Initiate pharmacotherapy for patients with Grade I hypertension at low-to-moderate CV risk if a 3–6-month trial of lifestyle intervention is unsuccessful Initiate pharmacotherapy immediately for patients with Grade I hypertension and high or very high CV risk (with CV or renal disease or target organ damage) and for all patients with Grade 2 or 3 hypertension Start with a 2-drug combination for most patients (ACEI/ARB + CCB or diuretic preferred)
ESC (2021) [2][b]	Similar recommendations as above for initiation of antihypertensive pharmacotherapy, including preference for ACEI/ARB + CCB or diuretic Support for alternative combination of any two drugs from the five major classes
ACC/AHA (2018) [3]	Prescribe antihypertensive therapy if BP is ≥130/80 mmHg and CVD is already present or 10-year CV risk is ≥10% Prescribe antihypertensive therapy if BP is ≥140/90 mmHg for patients at lower risk Consider initial combination of drugs with complementary mechanisms of action for patients with BP ≥140/90 mmHg
ISH (2020) [4]	Initiate pharmacotherapy for patients with Grade I hypertension at low-to-moderate CV risk if a 3–6-month trial of lifestyle intervention is unsuccessful Initiate pharmacotherapy immediately for patients with Grade I hypertension and high or very high CV risk (with CV or renal disease, target organ damage or diabetes) and for all patients with Grade 2 or 3 hypertension Use ACEI/ARB + CCB or diuretic initially ("optimal" recommendation) or use whatever drugs are available if they have as many of the following characteristics as possible: evidence-based improvement in outcomes, effective given once daily, affordable and cost effective, well tolerated, and shown to be effective in the population in which they are to be used ("essential" recommendation)
NICE (2022) [5]	"Discuss" pharmacological antihypertensive therapy for patients with Stage 1 hypertension if they have one or more target organs with damage, established CV or renal disease, diabetes, or 10-year CV risk ≥10% "Consider" pharmacological antihypertensive therapy for patients with Stage 1 hypertension and lower CV risk Initiate pharmacological antihypertensive therapy for patients with Stage 2 hypertension Use clinical judgement with regards to patient issues such as comorbidities, frailty, etc. ACEI/ARB favoured for patients with type 2 diabetes or age <55 years who are not of African-Caribbean heritage CCB favoured for age >55 years without diabetes or patients of African-Caribbean heritage

BP: blood pressure; CV: cardiovascular; CVD: cardiovascular disease. See Table 1 for definitions of acronyms for expert societies.
[a]Guideline for the management of arterial hypertension.
[b]Guideline for CV risk reduction.
[c]All recommendations for pharmacological therapy are in addition to lifestyle interventions. Applies to patients without contraindications of compelling indications for a particular class of therapy (see text).

≥140/90 mmHg, which is consistent with the ESC recommendations, described above. Physicians are invited to consider the use of a combination of antihypertensive agents with complementary mechanisms of action as initial antihypertensive pharmacotherapy for patients with BP ≥140/90 mmHg; it should be noted that the US guideline identifies this level of BP as "Stage 2 hypertension", which differs from the European approach summarised in Box 1.

With regard to other guidelines, the approach of the International Society of Hypertension (ISH) towards initiation of antihypertensive pharmacotherapy is broadly similar to that of the ESC, with combination treatment preferred in all but the lowest-risk and very elderly patients. "Optimal" recommendations favour the use of an ACEI/ARB + CCB or diuretic at therapy initiation, but "essential" recommendations for areas with limited access to healthcare support the use of any available combination, which ideally satisfies five criteria. The most recent (2022) guideline considered here, from the National Institute for Health and Care Excellence (NICE) in the UK, takes a very different approach to that of other expert groups [7]. There is no absolute recommendation for the use of antihypertensive drug treatment for patients with Grade 1 hypertension, even those at high risk. The choice of initial drug treatment is based on a patient's medical history or ethnicity, with either ACEI/ARB or CCB preferred as initial therapy. There is no focus on the application of antihypertensive combination therapy at diagnosis in this guideline.

Box 1. Grading of severity of hypertension (European definition).

Grade	Systolic BP (mmHg)	Diastolic BP (mmHg)
High normal	130–139	85–89
Grade 1	140–159	90–99
Grade 2	160–179	100–109
Grade 3	≥180	≥110

BP: blood pressure. Compiled from information presented in reference [3].

Elderly patients

The ESC/ESH guideline supports the use of antihypertensive pharmacotherapy for patients with Grade I hypertension who are aged between 65 and 80 years. Older patients may receive antihypertensive pharmacotherapy if their SBP is ≥160 mmHg. Other guidelines take a broadly similar approach.

Further intensification of antihypertensive therapy

Approximately one-third of patients with hypertension will remain sub-optimally controlled despite treatment with two antihypertensive agents [15]. The ESC/ESH guideline favours a triple combination of ACEI/ARB + diuretic + CCB as the usual mode of treatment for these patients [2, 3]. Addition of spironolactone is recommended if not contraindicated, or other classes of diuretic, β-blocker, α-blocker or centrally acting agents for patients unable to receive spironolactone. The ACC/AHA guideline acknowledges the need for a third antihypertensive for some patients, and notes the existence of single-tablet combinations containing ACEI/ARB/CCB [3]. NICE and the ISH also favour the use of this triple combination, followed where required by addition of low-dose spironolactone (where not contraindicated) [5, 6].

Antihypertensive therapy for special populations

Hypertension often appears alongside other long-term, non-communicable diseases that may influence the choice of antihypertensive therapy. Table 4 summarises European guideline recommendations on the management of hypertension in patients with comorbidities. In some cases, the recommendations cited are a synthesis of those given in guidelines for hypertension and the specific comorbidity, e.g. heart failure or chronic coronary syndrome.

Table 4 Use of classes of antihypertensive agents in populations with a comorbidity.

Comorbidity	Include in the regimen
Heart failure with reduced ejection fraction	ACEI/ARB (or sacubitril/valsartan) β-blocker MRA SGLT2 inhibitor Loop diuretic (for fluid retention) Consider CCB if BP target not achieved
Heart failure with preserved ejection fraction	SGLT2 inhibitor Consider β-blocker, long-acting nitrates, CCB, ivabradine, ranolazine, trimetazidine, nicorandil (alone or in combination) for angina relief but there is no evidence base for improved outcomes
CCS (post-MI)	ACEI and β-blocker or CCB (history of myocardial infarction) β-blocker and/or CCB (for symptomatic angina)
Diabetes	ACEI/ARB + CCB or diuretic
Chronic kidney disease	ACEI/ARB + CCB or diuretic SGLT2 inhibitor
Atrial fibrillation	β-blocker or non-dihydropyridine CCB if rate control is needed
Prior ischaemic stroke or TIA	ACEI/ARB + CCB or diuretic
COPD	ACEI/ARB + CCB Consider β_1-selective β-blocker or diuretic if BP goal not met

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BP: blood pressure; CCB: calcium channel blocker; CCS: chronic coronary syndrome; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; SGLT2: sodium glucose co-transporter 2; TIA: transient ischaemic attack.
Compiled from information presented in European guidelines for the management of hypertension, heart failure or chronic coronary syndromes [2, 6, 7].

Heart failure

Heart failure with reduced left ventricular ejection fraction (HFrEF)

ACEI/ARBs [16] (or sacubitril/valsartan [17]), β-blockers [18] and mineralocorticoid receptor antagonists (MRAs) [19] are evidence-based therapies for improving clinical outcomes in people with HFrEF, and guidelines recommend that they should be included in the therapeutic regimen of these patients. Sodium glucose co-transporter 2 inhibitors (SGLT2i) have shown large and consistent reductions in hospitalisations and mortality due to HFrEF, which led to guideline recommendations to include them in treatment regimens for heart failure [20]. Moreover, SGLT2i produce reductions in SBP of about 2–4 mmHg [21, 22], which may contribute to the overall management of BP in patients with hypertension and

HFrEF (or indeed, chronic kidney disease [CKD], see below). A recent meta-analysis found a combination of sacubitril/valsartan, β-blocker, mineralocorticoid receptor antagonists (MRA) and SGLT2i to be the most effective combination for reducing the risk of mortality in patients with heart failure [23]. Non-dihydropyridines should not be given to patients with decompensated heart failure.

Heart failure with preserved left ventricular ejection fraction (HFpEF)

HFpEF is usually defined as heart failure with a left ventricular ejection fraction (LVEF) >50%, although patients with LVEF 40–50% have been included in many studies [7]. As many as half of community-dwelling patients with heart failure have HFpEF [24]. Prognosis is poor, with one study reporting an average life expectancy of 2.1 years and 75% mortality over 5 years from diagnosis [25].

Blockers of the RAS or sacubitril/valsartan, which are effective in improving mortality outcomes in HFrEF (see above), have not been shown to reduce mortality in HFpEF [26, 27]. MRA appear to reduce hospitalisations for HFpEF, but not mortality [25]. Meta-analyses have reported that treatment with a β-blocker reduced the risk of cardiovascular mortality in patients with HFpEF [25, 26]. A further meta-analysis found a mortality benefit for β-blockade in patients with LVEF 40–49%, but not in a small group with LVEF ≥50% [17]. These findings are intriguing, and suggest the need for further research on the effects of β-blockers in HFpEF. However, the limited and *post-hoc* nature of this evidence does not support a role for the use of β-blockers in the management of HFpEF currently, in the absence of an additional reason for their use.

Guidelines for HFpEF recommend the use of diuretics to improve heart failure symptoms [7]. The Emperor-Preserved trial demonstrated recently that treatment with an SGLT2i (empagliflozin) significantly reduced the risk of hospitalisation for heart failure in patients with HFpEF [28]. A large meta-analysis, which included patients with LVEF >50%, added support to this finding [29]. In future, SGLT2i may become part of the standard management of HFpEF, with some implications for BP management, as for HFrEF.

Chronic coronary syndrome (post-MI)

As with HFrEF, RAS blockers and β-blockers are evidence-based therapy for improving clinical outcomes in patients with a prior history of MI [30, 31]. Patients with symptomatic angina pectoris may benefit from a combination of a β-blocker with a CCB.

Other comorbidities and contraindications

The recommended initial pharmacotherapy for a patient with hypertension and diabetes, CKD, prior stroke or transient ischaemic attack, or chronic obstructive pulmonary disease (COPD), is a blocker of the RAS combined with a CCB or a thiazide-like diuretic. An exception is atrial fibrillation, where a β-blocker or non-dihydropyridine CCB may be useful in controlling both BP and the ventricular rate.

SGLT2i have been shown to improve clinical outcomes in patients with CKD, and some agents now have an indication for this condition. Future guidelines for the management of hypertension may include a compelling indication for these agents in the management of patients with CKD and hypertension.

The 2018 ESC/ESH guideline for the management of hypertension includes "compelling" and "possible" contraindications to the use of the five main classes of antihypertensive agents. These are discussed briefly here as they will impact on the use of these drugs in patients with specific comorbidities.

Diabetes or metabolic syndrome: These conditions are listed as "possible" contraindications for β-blockers and thiazide-like diuretics. Diuretics may also be considered contraindicated in patients who are athletes or physically active. It should be noted that β-blockers are a highly heterogeneous class of drugs, including individual agents with or without selectivity for the β_1-adrenoceptor, intrinsic sympathomimetic activity or additional vasodilator properties, among other attributes [32]. The potentially adverse metabolic effects of β-blockers are largely associated with blockade of β_2-adrenoceptors, and such effects have not been observed with highly selective β_1-adrenoceptor blockers (cardioselective agents), such as bisoprolol [33–36]. Metabolic disturbances

with thiazides are less marked at low dosages, consistent with those delivered in fixed-dose combinations with other antihypertensive agents [37].

COPD/asthma: Asthma is listed as a compelling contraindication for β-blockers. Again, β_2-adrenoceptor blockade accounts for most or all of the adverse effects on bronchial tone in people with asthma, or with interference with the action of β_2-agonists taken to manage an asthma attack [38]. Observational data have shown no increased risk of asthma exacerbations in patients receiving a selective β_1-adrenoceptor, compared with clearly increased risk with a non-selective agent, even at lower dosages [39]. The European Summary of Product Characteristics lists only "severe bronchial asthma" as a contraindication for bisoprolol (a highly selective β_1-adrenoceptor blocker), compared with "a history of bronchospasm or asthma" for the non–cardio-selective β-blocker, propranolol. These observations are important, as β-blockers may be underused in patients with airways disease [40].

Sinoatrial block or bradycardia: Neither β-blockers nor non-dihydropyridine CCBs should be used in patients with high-grade atrioventricular block or severe bradycardia.

Pregnancy: ACEI and ARBs should not be taken during pregnancy and being a "woman of childbearing potential without reliable contraception" is given as a contraindication for these agents. Pregnancy is also a contraindication for thiazide-like diuretics.

Other compelling contraindications: ACEI or ARB may cause hyperkalaemia [41]. Accordingly, hyperkalaemia (serum K^+ >5.5 mmol/L) is listed among the compelling contraindications to the use of these agents. ACEI or ARBs should not be used in patients with bilateral renal artery stenosis, as they may precipitate acute renal failure in this setting. This arises because the maintenance of glomerular pressure and filtration becomes dependent on angiotensin II-mediated constriction of the efferent arteriole when flow though the renal afferent arteriole is limited (as in renal artery stenosis). Removing the effect of angiotensin II collapses glomerular pressure and effectively switches off glomerular filtration [42]. ACEI use also rarely causes angioneurotic oedema, associated with accumulation of bradykinin, which would

normally be metabolised by ACE; this is another compelling contraindication for this class of antihypertensive [43]. Finally, gout is a compelling contraindication for thiazide-like diuretics, associated with increased circulating levels of uric acid [44].

Discussion

Perhaps the main take-home message from current major guidelines for the management of hypertension, especially those from Europe, is that almost all patients will need combination therapy with at least two drugs to achieve adequate control of BP. The most common recommendation for initial antihypertensive therapy in the guidelines is for a blocker of the RAS (ACEI or ARB), together with a CCB or thiazide-like diuretic, which fulfils the requirement of choosing two agents with different, and potentially complementary, mechanisms of action. The role of β-blockers has diminished in guidelines in recent years, due in part to concerns over adverse metabolic effects (likely attributable to lack of β_1-adrenoceptor selectivity of some β-blockers, as described above), or lower potential to reduce the risk of adverse coronary events than newer classes in some meta-analyses [45, 46], although this was not seen in a large meta-analysis that incorporated data from 464,000 patients [47]. These meta-analyses also suggested that CCBs tend to be more effective in preventing strokes than other antihypertensive classes. Combining a highly selective β-blocker with a CCB therefore remains a rational approach to the management of hypertension, especially for patients with HFrEF, prior MI or stroke, atrial fibrillation or hypertension driven by high sympathetic tone [48, 49]. Chapter 4 of this book will consider the mechanism of action of this combination.

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