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REVIEW ARTICLE

Tolerability of Antihypertensive Medications in Older Adults

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Abstract Several guidelines for hypertension have recently undergone revisions to incorporate an approach providing choices of medications based on age, race, and specific situations where hypertension may co-exist with disorders such as diabetes, coronary artery disease, heart failure and chronic kidney disease. Initial recommendations include diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers; beta blockers are favored in some guidelines and are a choice in specific settings. Within the classes of drugs, several antihypertensive agents provide options. This review discusses antihypertensive drugs by class, including adverse effects and tolerability, with preferences in older adults and specific settings. Adverse drug events from antihypertensive medications are discussed by class and where applicable for specific agents. Data from select studies pertinent to tolerability and adverse effects are presented in tables for several classes of drugs. The rationale for nonadherence to medication is reviewed, including the roles played by tolerability and adverse drug effects. Antihypertensive therapy in typical settings in older adults is discussed; they include hypertension in association with impaired cognition, depression, diabetes, sexual dysfunction, and falls. The key to successful therapy and tolerability is to promote a healthy lifestyle in conjunction with medications as the approach, thereby also lowering the adverse drug effects. The eventual choice of the specific drug(s) is based on risks, benefits, and patient preferences, and is best tailored for each older adult.

Key Points

The risk for adverse drug events relates to age-related physiological changes, comorbidity, dosing, and drug interactions.

Adverse drug events can be significantly minimized by careful drug selection, appropriate dosing, and addressing polypharmacy.

Tolerability to antihypertensive agents relates to a host of factors and may play a significant role in nonadherence.

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1 Introduction

Hypertension, a worldwide public health concern, is estimated to account for 12.8 % of all deaths; the World Health Organization estimates the prevalence in adults aged 25 years and over to be around 40 % and the number with

uncontrolled hypertension close to a billion [1]. The crude prevalence of hypertension exceeds 25 % in men and women in the USA, Canada, most European countries, China, India, and the Middle East; many remain uncontrolled and inadequately treated [2]. Concerted coordinated efforts have the potential to reduce the prevalence of hypertension [2]. US data from 2007 to 2010 indicate the prevalence was highest in the age group ≥65 years (71.6 %), among non-Hispanic Blacks, and specifically in patients with diabetes mellitus (DM), and the obese [3]. The majority of adults were aware of their hypertension, and 76 % were receiving medication to lower blood pressure (BP) [4].

Guidelines for the management of hypertension have been in place for decades, with several updated recently: The Eighth Joint National Committee (JNC 8) guideline for the management of high BP in adults [5]; the American Society of Hypertension (ASH) and International Society of Hypertension (ISH) *Clinical Practice Guidelines for the Management of Hypertension in the Community* [6]; and the 2013 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) *Guidelines for the Management of Arterial Hypertension* [7]. Although each guideline provides a basic approach to the drug management of hypertension, the recommendations do not concur, resulting in unanswered questions and controversies [8].

All guidelines on hypertension focus on implementing lifestyle intervention, with a focus on dietary sodium restriction, the performance of aerobic exercise most days a week, maintenance of a healthy body weight, consideration for stress management in some, and a need to continue the lifestyle measures irrespective of pharmacological management [5–9]. Adherence to lifestyle measures deserve emphasis, especially since adverse effects are seldom an issue with this approach. Further, a healthy lifestyle helps reduce the dose or number of antihypertensive medications, with consequently fewer adverse drug events (ADEs) and perhaps better tolerability. Although concerns have been raised regarding the long-term safety of several antihypertensive agents, the lowering of BP through the use of medications is largely considered safe and beneficial [9]. On the other hand, poor control of hypertension leads to vascular damage, with consequences in the heart, brain, kidney, and other organs, emphasizing the importance of good control, achievable in the majority. Central to the process of controlling hypertension are processes such as tolerability to antihypertensive agents and adherence to drug therapy.

2 Relevant Terminology

'Tolerability' refers to the degree to which ADEs are tolerated by an individual; the term must be considered in the context for which the medication is used [10]. In the case of hypertension, the tolerability of an antihypertensive agent must be factored in conjunction with the severity and manifestations of the hypertensive disorder [10]. Tolerability to a drug must be distinguished from the term 'drug tolerance', which may develop following medication use. Drug tolerance refers to the progressively diminishing effect in an individual for a specific drug dose and concentration, necessitating an increase in the dosage to produce the same effect; tolerance may also result from disease progression or alteration in drug efficacy due to several factors.

ADEs are a basis for much drug-related morbidity and mortality, often escaping attention [11]. Simply stated, an ADE is harm caused by the use of a drug or the inappropriate use of a drug (inclusive of dose reduction and discontinuation) [11]. Adverse drug reaction (ADR) is harm caused by a drug administered in normal doses [12]. Broadly, ADRs fall under the umbrella of ADEs [11]. In this review, the term ADEs is largely used, to be inclusive of ADRs. The term 'side effect' appears to minimize drug injury and is not a preferred term.

'Nonadherence' with reference to medication intake is preferred over the older term 'non-compliance'. Adherence refers to the patient's conforming to the recommendations with respect to the correct administration of the drug, including timing, dosage, and frequency during the prescribed duration of time. Nonadherence results from several factors, including failure to understand instructions, adverse effects, socioeconomic reasons, perceived lack of efficacy, and comorbidity (e.g., depression or dementia) in the individual. Nonadherence is more common than believed and may be of the order of 30–50 %; among the many causes of nonadherence, drug tolerability could be one significant factor.

In summary, tolerability to a drug, ADEs, and nonadherence may be associated or linked in complex ways and, in conjunction with additional factors, determine the degree of hypertension control. Drug tolerance plays little if any role in the development of resistant hypertension, which largely results from nonadherence to lifestyle and medication regimen or from unidentified secondary causes of hypertension [13].

3 Age-Related Physiology and Pharmacology

Aging is associated with several changes in the body. These may be physiological or pathological and may impact both pharmacokinetics (drug handling by the body) and pharmacodynamics (what the drug does to the body) [14, 15]. Pharmacokinetics refers to the path or course of a drug within the body, including absorption, bioavailability, metabolism, protein binding, distribution, and elimination

Table 1 Factors influencing pharmacokinetics and pharmacodynamics of drugs in older adults [14–22]

Factor	Effect
Age-related physiological changes	Alterations in body weight resulting from changes in muscle, bone, lipid, and water compartments
	Decline in body water with age, more pronounced in females
	Relative increase in body fat (vs. water), more pronounced in females
	Decline in muscle mass (sarcopenia), and resultant misinterpretation of renal function based on lower than expected SCr levels
	Alterations in GI function are minimal, absorption largely preserved
	Alterations in hepatic function and the CYP450 system impact drug metabolism
	Decline in renal function, including a decline in eGFR and tubular secretion alter drug kinetics
Pathological disorders	GI disease (resection, motility disorders, mucosal disease) can influence drug absorption
	Disorders of body compartments: edema, dehydration, obesity, muscle wasting
	Altered hepatic function due to liver disease or drug-induced liver injury
	Acute kidney failure and CKD impact drug kinetics and dynamics, influencing the choice of medication and dosing
	HF alters pharmacokinetics and can influence the choice of antihypertensive
Interactions that influence drug kinetics and dynamics	Drug interactions (e.g., NSAIDs blunt the effect of diuretics and ACEIs)
	Disease interactions (e.g., ACEIs or ARBs may worsen pre-existing renal impairment and cause hyperkalemia)
	Diet (nutrient) interactions (e.g., dietary salt or K^+ may nullify or predispose to ADEs of antihypertensives such as edema, resistant hypertension, hyperkalemia)
	Polypharmacy (e.g., medications and supplements may worsen hypertension through drug interaction or organ dysfunction such as hepatic or renal impairment)

ADE adverse drug event, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CKD* chronic kidney disease, *CYP450* cytochrome P450, *eGFR* estimated glomerular filtration rate, *GI* gastrointestinal, *HF* heart failure, *NSAID* nonsteroidal anti-inflammatory drug, SCr serum creatinine

through any route. Pharmacodynamics refers to the action of a drug at cellular, molecular, sub-molecular, and tissue levels; the effects may be therapeutic (beneficial) or undesired (adverse effects or toxicity).

Physiological changes with age include a decline in body water and bone and muscle mass, and an increase in the fat compartment. The changes are not precise for a given age, but are individualized and vary with sex. Comorbidity involving renal, hepatic, cardiac, or thyroid function further influences drug kinetics and dynamics. Relevant to the causation and management of hypertension is the fact that the activity of the renin-angiotensin-aldosterone system (RAAS) demonstrates a decline in renin and aldosterone levels with aging.

In particular, an estimate of kidney function helps determine proper dosing of medications excreted by the kidney [16]. In older adults, the serum creatinine level is not a reliable measure of renal function. Age-related decline in muscle mass (sarcopenia) is associated with a lower than expected serum creatinine level, providing an inaccurate estimate of renal function in older adults. In fact, serum creatinine may remain within the laboratory normal range in the elderly, in spite of a decline in renal function. While glomerular filtration rate (GFR) is an overall index of renal function, it is not measured directly; a derived estimated GFR (eGFR) is accepted as the standard measure of function. Clinicians may opt to use the Cockcroft-Gault (C-G) equation or the Modification of Diet in Renal Disease (MDRD) Study equation to derive the eGFR, the latter method easily generated electronically. An idea of the eGFR is useful in older adults, particularly to determine kinetics and dosage of medications, including several antihypertensive agents [14–22].

Nutritional factors and medications may interact to enhance or diminish drug effects [23]. Antihypertensive agents may require dosing alterations, following a review of dietary intake, in the presence of system dysfunction. Examples include the presence of hypertension along with heart failure (HF), chronic kidney disease (CKD), hepatic impairment, and thyroid dysfunction. Table 1 summarizes the essentials [14–22].

4 Antihypertensives and Tolerability by Class

This review looks at the tolerability of medications by class, focusing predominantly on those drugs recommended in the recent hypertension guidelines [5–7]. The

classes used as first-line agents in the management of hypertension include diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Of note, the different guidelines do not concur on choice of drug therapy. Age, race, and compelling indications (such as HF, coronary artery disease [CAD], CKD, and DM) significantly influence decision making [5–7]. Older antihypertensive agents and potassium-sparing diuretics (which are not primarily used for hypertension management) are discussed only briefly in this narrative.

4.1 Diuretics

Diuretics have stood the test of time and are consistently favored in the guidelines. A comparison of health outcomes in 192,478 patients randomized to seven treatment strategies involving various antihypertensive agents as first-line therapy suggested low-dose diuretics were most effective in reducing cardiovascular morbidity and mortality [24].

Thiazides and thiazide-like diuretics have been prescribed for hypertension for decades and remain effective therapy, with their added ability to increase the efficacy of most classes of antihypertensive agents [25]. Thiazides can be combined with virtually every class of antihypertensive agents for synergetic effect. In most hypertension trials, although diuretics were effective in management, their adverse effect profile has raised questions regarding their long-term use. The mechanisms of action whereby diuretics lower BP are poorly understood. They may relate to endothelial- or vascular smooth muscle-mediated vasodilatation, decrease in sodium absorption from the distal tubule, and a decrease in extracellular volume; a decline in volume results in diminished venous return and eventually reduced cardiac output and lower BP [26].

For the treatment of hypertension, thiazides such as hydrochlorothiazide and thiazide-like diuretics chlorthalidone and indapamide are generally recommended [27]. Chlorthalidone and hydrochlorothiazide are structurally similar, but differ in pharmacokinetics, volume of distribution, and elimination, with chlorthalidone having a much longer half-life [28]. Chlorthalidone in a smaller dose is more potent than a larger dose of hydrochlorothiazide with respect to drop in BP [28]. Loop diuretics are not first-line antihypertensives, but are indicated in hypertension coexisting with significant volume overload states.

Although effective for the management of hypertension, diuretics are associated with numerous ADEs. Some ADEs result from inappropriate and overzealous use, excessive dosing to treat HF or edema, and use in combination with other diuretics. Adverse effects include electrolyte imbalance, glucose intolerance, hyperlipidemia, hyperuricemia, sexual dysfunction, and rarer consequences such as rash, thrombocytopenia, interstitial nephritis, and acute pancreatitis [29, 30].

Hypokalemia is common with diuretic use and tends to get worse with higher doses. Mechanisms include excessive sodium intake, renal loss from the distal tubules, secondary aldosteronism, and transcellular shift due to metabolic alkalosis. In a large study comparing hydrochlorothiazide with chlorthalidone, a far longer-acting diuretic, the latter was associated with a higher likelihood of hospitalization due to hypokalemia and hyponatremia; this was irrespective of whether the dose of chlorthalidone was 12.5, 25, or 50 mg per day [31]. The shorter half-life of hydrochlorothiazide may be a disadvantage for hypertension management but better for electrolyte balance [31]. These effects may be exaggerated in older adults, in whom a thiazide is generally considered safe. The risk of hypokalemia with thiazides appears higher in men and increases with age and dosage [32]. In ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), although incident hypokalemia was high with chlorthalidone, increased mortality was not specifically attributed to the drug [33]. Of interest, the same paper relates the clinical implication of incident hyperkalemia to a higher risk of cardiovascular disease (CVD) but hypokalemia to a higher risk of death [33]. The effect of hypokalemia on the development of glucose tolerance has been a concern; data suggest that potassium levels may be independently associated with prediabetes and newly diagnosed DM in hypertensive adults [34].

Several antihypertensive medications can cause hyperkalemia through differing mechanisms, including impaired trans-cellular shift though beta blockade, aldosterone blockade, or impaired potassium secretion in the distal tubule. Major drugs include ACEIs, ARBs, direct renin inhibitors (DRIs), aldosterone antagonists, and potassium-sparing diuretics [35–37]. The combination of ACEIs or ARBs with aldosterone antagonists is particularly noteworthy and calls for monitoring of potassium levels, particularly in older adults and in the presence of CKD [36]. Other drug–drug interactions also accentuate the tendency; examples include co-administration of non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim, or heparin. However, when interacting medications are discontinued, it is essential that potassium levels, which may still remain high, continue to be monitored [38]. A study concluded that four variables were significantly related to hyperkalemia: creatinine levels (creatinine >1.25 mg/dL and eGFR <60 mL/min), spironolactone, ACEIs, and β-blockers [37]. Hyperkalemia induced by medications may cause disturbances of intraventricular conduction and asystole besides morphological changes in the electrocardiogram [39]. Concern about potassium levels should not be a major influence for clinical decisions on initiating low- to moderate-dose thiazides [40].

In a study, about one-third of patients receiving thiazides for hypertension developed hyponatremia, indicating thiazides pose significant risk for the electrolyte disorder; there appeared no difference in the risk of mortality associated with the hyponatremia [41]. Hyponatremia, which results from a multitude of causes besides medications, can manifest as delirium, falls, lethargy, stupor, and even seizures, based on the severity and acuity of development. Predisposing factors include increasing age, female sex, larger dose of thiazide or thiazide-like diuretics, presence of hypokalemia, and lower body mass index; different studies suggest the influence of ACEIs to be a predisposition and otherwise [28, 42–49]. In a given individual, besides diuretics, there may well exist other causes for hyponatremia, such as water retention caused by excessive water intake, psychogenic polydipsia, heavy beer intake, and impaired water-excreting ability [50]. Hospitalizations were more likely to occur from diuretic-induced hyponatremia if the patient was a female and older [51]. A study has suggested that risks included home institutionalization and physical immobility; duration of thiazide use; concomitant use of loop diuretics; body weight (increased mass decreased the odds); while the use of ACEIs and NSAIDs and renal function bore no association [46]. While hyponatremia clearly occurs with thiazide use and increases with age, views on other predispositions vary or contradict based on a given study [47–49]. Indapamide use is associated with hyponatremia [52]. Thiazide-induced hyponatremia is also highly reproducible with thiazide rechallenge, suggesting possible genetic predisposition [53]. In summary, data regarding the etiology of hyponatremia are inconsistent. Predisposition appears clearly higher with chlorthalidone than with hydrochlorothiazide [31, 42], while it is similar between hydrochlorothiazide and indapamide [45]. Hyponatremia and hospitalization due to osteoporotic fractures may result from loop diuretics but not thiazides [54]; this observation may relate to the fact that thiazides induce positive calcium balance, unlike the loop diuretics.

A practical point worth noting is that thiazides are ineffective or less effective when renal function declines, in the setting of hypertension with CKD stage 4 and worse [55]. In a pilot study of subjects averaging 67.5 years with poorly controlled hypertension and advanced CKD (eGFR 26.8 ± 8.8 mL/min), chlorthalidone reduced BP, but adverse events seemed to occur (hypokalemia, hyponatremia, and hyperuricemia) [56]. A randomized trial appears to be underway to investigate the matter. Besides CKD, drug interactions with NSAIDs may blunt the effect of diuretics and cause fluid retention or worsening of electrolyte imbalance [28].

Uric acid, the product of purine metabolism, is excreted by the kidneys; levels increase with a decline in uricosuria (as in renal failure), from volume contraction (following diuretic use), increased tubular absorption, or reduced secretion of uric acid [57, 58]. Hyperuricemia is not a strong contraindication for a thiazide [28]. While diuretics tend to increase uric acid levels through volume contraction, some antihypertensives such as ACEIs and ARBs actually increase uricosuria mildly [57]. Use of thiazides in doses over 25 mg/day is associated with a higher risk for initiation of anti-gout therapy [59]. Higher doses of thiazides are not necessarily more effective in BP control, but may be associated with more ADEs. A nested case-controlled study found the risk for gout also extended beyond diuretics to other drugs [60].

Overall, diuretics are effective antihypertensive agents, but their use is associated with electrolyte and metabolic effects; diuretics are among the drugs significantly associated with visits to the emergency department for ADEs [26, 29, 61–65]. The relationship of diuretic use to nocturia is discussed in the section on falls. Potassium-sparing agents are not primary antihypertensive agents and are not discussed in this narrative. Table 2 provides data on ADEs from select studies involving diuretics [31, 32, 37, 40–43, 45–48, 51, 54, 60–64].

4.2 Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

The clinical practice guidelines include ACEIs and ARBs among the approved classes of medications for treatment of hypertension. ACEIs act by inhibiting the angiotensin-converting enzyme (ACE) that converts angiotensin I to angiotensin II, a potent vaso-constrictor, with a resulting decrease in systematic blood vessel tension. There is no effect on blood volume. Angiotensin II also stimulates adrenal release of aldosterone, which in turn promotes sodium retention through the distal renal tubules. ARBs work through the antagonism of angiotensin II AT_1 (angiotensin II receptor subtype 1) receptors and are an option when certain adverse effects such as cough occur with the use of ACEIs [66]. Bradykinin is normally degraded by ACE; when ACEIs inhibit ACE, the half-life of bradykinin is prolonged and its concentration raised, contributing to some ADEs. Bradykinin degradation is not inhibited by ARBs.

The BP-lowering efficacy of ACEIs and ARBs are comparable [67]. The group of drugs are particularly beneficial in the presence of HF, DM, left ventricular hypertrophy, and kidney disease in the hypertensive patient. DRIs bind to the active site of renin, diminishing renin activity, and angiotensin II production [68]. DRIs may be as effective as ACEs and ARBs, with aliskiren shown to be beneficial in the lowering of systolic hypertension in geriatric patients [69]. However, renin inhibitors

Table 2 Diuretics: data on adverse effects [31, 32, 37, 40–43, 45–48, 51, 54, 60–64]

Study characteristics	Key results	References
Clinical emergency hospital, Bucharest: safety for HT in elderly 103 men, 94 women, mean age 72 ± 8 years, receiving diuretics	Incidence of hyponatremia was 24.87 %, most in aged >75 years; 73.46 % were related to a thiazide, rest due to loop diuretics	[61]
Risk of thiazide-induced hyponatremia in pts with HT Retrospective cohort study, multicenter, 2613 pts from teaching hospitals Newly treated hypertensives; 220 on thiazides vs. 2393 controls, over 10 years	3 in 10 pts exposed to thiazides developed hyponatremia; no difference in risk of hospitalizations associated with hyponatremia or mortality	[41]
Hospitalizations associated with thiazide-associated hyponatremia Retrospective case-controlled study, 10,805 pts from 91,802 cases	Overall: age, weight, hypokalemia, T2DM and ACEI use increase risk	[48]
Systematic review and meta-analysis of thiazide-induced hyponatremia Meta-analysis of 102 articles prior to October 2013 Mean age 75 years, 79 % women, mean body mass index 25	Hyponatremia occurred a mean of 19 days after treatment; mean trough serum Na^+ 116 nM, serum K^+ 3.3 nM Predisposition: advanced age, females, inappropriate saluresis, mild hypokalemia	[43]
Prevalence of hyponatremia among users of indapamide and HCTZ Single-center, retrospective study, Riyadh, Saudi Arabia 2000 pts, 1237 females (629 indapamide, 608 HCTZ); 762 males, (372 indapamide, 391 HCTZ); prevalence of T2DM 72.2 %	Prevalence of hyponatremia was higher with age; 37.3 % with indapamide; 38.7 % with HCTZ	[45]
Risk factors for thiazide-induced hyponatremia Retrospective case-control study; 223 cases, 216 controls; median 115 days of thiazide use, age 76 ± 9 years	Serum K^+ level, use of indapamide, home institutionalization, and physical immobility were risks but sex, duration of use, concomitant use of loop diuretics, ACEIs, NSAIDs, and renal function were not	[46]
Thiazide-induced hyponatremia, part of the Rotterdam Study Population-based cohort study, 13,325 individuals >45 years, suburb of Rotterdam 718 used thiazides at baseline, 2738 started on thiazide during study	522 developed hyponatremia, 32.4 % were on thiazides Exposure to thiazides increased the risk to 5 times higher Age and BMI influenced risk but sex did not	[47]
Diuretic-induced hyponatremia and fractures Retrospective case study, 10,823 adults ≥50 years from the ED	480 (5 %) had osteoporotic fractures; these pts were older (mean 73 years) Prevalence of hyponatremia increased with the number of diuretics taken Any diuretic other than thiazides was associated with osteoporotic fractures	[54]

Table 2 continued

Study characteristics	Key results	References
Chlorthalidone vs. HCTZ for HT in older adults Observational cohort study, 29,873 adults age >66 years, 5-year follow-up 10,384 on chlorthalidone; doses of 12.5, 25, and 50 mg/day for both drugs	Chlorthalidone not associated with fewer adverse CV events or deaths, but associated with more electrolyte abnormalities, especially hypokalemia requiring hospitalization	[31]
Hyponatremia with diuretics: chlorthalidone vs. HCTZ Population-based case-control study with Dutch Integrated Primary Care Database	1033 cases of hyponatremia (Na <130 mm/L) in all subjects >18 years, 1996–2011 Hyponatremia more common with chlorthalidone than HCTZ at equal milligram dose/day, suggesting the need to consider a lower dose of chlorthalidone	[42]
Diuretic-induced hyponatremia in elderly hypertensive women General Practice Maccabi database, 180 hypertensive pts, 149 females, mean age 76.4 ± 9.2 years; pts hospitalized for hyponatremia	Odds ratio three times higher for women than men; both sexes over 65 years were 10 times more likely and if >75 years, 16 times more likely (vs. those <65 years)	[51]
Thiazides and risk of hypokalemia in the general population Population-based cohort study, within Rotterdam study	507 cases of hypokalemia occurred among 13,328 pts Thiazide use associated with a 11 times higher risk, more so in men Influenced by age and dosage; risk increased even if thiazide was used with triamterene	[32]
Current causes of hyperkalemia Retrospective study of pts presenting to ED with hyperkalemia	139 pts with hyperkalemia: 35 % mild (K^+ 5.2–5.8); 49 % moderate (K^+ 5.8–7.0); 16 % severe (K^+ >7.0) Renal failure (SCr >1.25 mg/dL or eGFR <60 mL/min) noted in 83 %, and K^+-increasing drugs (ACEIs, β-blockers, spironolactone) were used in 75 %	[37]
Significance of incident hypokalemia and hyperkalemia in treated HT Study looked at treated HT pts in the ALLHAT study	Overall mortality was higher with hypokalemia than hyperkalemia Hyperkalemia associated with an increased risk of CVD Hypokalemia associated with increased mortality, but unrelated to specific effects of chlorthalidone K^+ level by itself should not influence clinician's decision about initiating HT treatment with low to moderate doses of thiazides (12.5–25 mg) or chlorthalidone	[40]
Risk for T2DM in hypertensive pts receiving thiazide diuretics Multicenter, unblended, RCT, 2004–12 HT clinics at 106 sites in Japan, low-dose HCTZ (12.5 mg/day or equivalent); 1130 pts studied, 544 on diuretics	Antihypertensive treatment with low-dose thiazide was not associated with increased risk for new-onset T2DM, suggesting the safety of low doses	[62]
Low-dose thiazide diuretics on fasting glucose and serum potassium Meta-analysis of 10 RCTs, including sample of 17,636 subjects for K^+ and 17,947 for glucose	Magnitude of observed change in fasting glucose associated with low-dose thiazide was statistically significant, but not enough to place pts at significant risk Change in serum K^+ was statistically significant and may be clinically relevant in pts at risk for CAD or ventricular arrhythmias	[63]

Table 2 continued

Study characteristics	Key results	References
Diuretic use and risk of incident gout	91,530 cases of gout identified	[64]
General Practice Research Database in UK, 1990–2010	Combined loop and thiazide diuretics had highest incidence; loop, thiazides and thiazide-like diuretics increased risk of gout, while potassium-sparing drugs did not	
	CCBs and losartan slightly attenuated the risk	
Antihypertensive drugs and risk of incident gout	CCBs and losartan associated with a lower risk of incident gout	[60]
Nested case-control study, UK General Practice database, 2000–2007	Diuretics, β-blockers, ACEIs, and non-losartan ARBs associated with increased risk of gout	
All incident cases of gout (n = 24,768) studied along with random sample of 50,000 matched controls		

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* basal metabolic index, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CV* cardiovascular, *CVD* cardiovascular disease, *ED* emergency department, *eGFR* estimated glomerular filtration rate, *HCTZ* hydrochlorothiazide, *HT* hypertension, *NSAID* nonsteroidal anti-inflammatory drug, *RCT* randomized controlled trial, *SCr* serum creatinine, *T2DM* diabetes mellitus

are not listed as first-line agents in the new guidelines [5–7]. The role of aldosterone blockade through spironolactone, a mineralocorticoid antagonist, has potential benefit in some cases of resistant hypertension; the main adverse effect of spironolactone use is hyperkalemia [70].

Overall, little difference exists between the classes of ACEIs and ARBs in lowering BP and outcomes, with the exception of ADEs [71]; therefore, factors other than hypertension, such as ADEs, tolerability, and economic factors influence the choice of class. A Cochrane Hypertension Group Specialized Database in conjunction with other sources demonstrated little difference between ACEIs and ARBs regarding mortality and cardiovascular events; but good evidence suggested a lower incidence of withdrawal-related adverse effects for ARBs than for ACEIs. Cough attributable to ACEIs was the main adverse effect, but not enough to substitute an ARB since there was little evidence between the two classes to favor outcomes [72].

In an interesting study on tolerability, ARBs had cough risk, angioedema risk, and discontinuation rates similar to placebo, but fewer cough events versus ACEIs [73]. The authors recommend that ACEI re-challenge should be discouraged in those with a history of prior intolerance. The hypothesis is that the mechanism of cough with ACEIs is secondary to accumulation of bradykinin, substance P, and prostaglandins; genetic pleomorphism and patterns may modify the risk of ACEI-induced cough [74]. One gene region (XPNPEP2) was associated with angioedema (but not cough) in some studies [75]. The incidence of ACEI cough and withdrawal may be influenced by ethnicity [76]; the cough is more common in females and African Americans [77].

While ACEI-induced cough occurs in 5–35 % of those receiving ACEIs, angioedema affects less than 1 % of patients; the odds of ARBs, when used as an alternative, causing angioedema and cross-reactivity is <10 % of those who developed angioedema while receiving ACEIs [77, 78]. Switching to an alternate ACEI is certainly not recommended, as the adverse reactions are class effects; the fatality rate is low, but deaths have occurred. The comparative risk for angioedema noted in a large study of drugs that target the RAAS is highest with ACEIs and aliskiren and lowest with ARBs compared with β-blockers [79]. ACEI-related angioedema typically affects the lips and tongue, but can also involve the mucosa elsewhere, such as eyelids, intestinal mucosa, or genitalia; abdominal pain, diarrhea, and vomiting can occur [78]. ARBs are an alternative for those who experience angioedema from an ACEI, as long as the use is relevant and there are clear indications for angiotensin blockade; management must include education and observation for signs of angioedema, including emergency management [80]. In one report, half the patients with ARB-induced angioedema had prior angioedema with

Table 3 Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and renin Inhibitors: data on adverse effects [72, 73, 76, 79, 85, 90, 91, 95, 96]

Study characteristics	Key results	References
ACEIs vs ARBs for hypertension. Outcomes on control, CV events, and mortality, and withdrawal due to AEs	No differences between ACEIs and ARBs for total mortality, total CV events or CV mortality	[72]
Cochrane, MEDLINE, EMBASE, WHO International Clinical Trial Registry Platform, ISI Web of Science database; 9 studies, 11,107 subjects	BP-lowering effect of ARBs similar to ACEIs as a class	
	High level of evidence indicated a slightly lower incidence of WDAE for ARBs vs. ACEIs, mainly attributable to higher incidence of cough with ACEIs	
	Substitution of ARBs for ACEIs while supported by evidence for tolerability, must be factored along with weaker benefits for mortality and morbidity outcomes for ARBs over ACEIs	
Tolerability of ARBs in those intolerant to ACEIs	ARBs were associated with fewer cough events vs. ACEIs	[73]
Databases: PubMed, MEDLINE/EMBASE, CENTRAL, ISI Web of Knowledge	ARBs had similar drug discontinuation rates, cough risk, angioedema risk to PL	
RCTs evaluated ARBs in those intolerant to ACEIs	Renal dysfunction and hyperkalemia occurred more often with ARBs vs. placebo	
	ACEI re-challenge should be discouraged in those with prior intolerance to ACEIs	
AHRQ's comparativeness of ACEIs, ARBs and DRIs	No overall differences noted in BP control, mortality rates, and CV events	[95]
Comparative effectiveness review of 3 classes of drugs; identify benefits and risks	ACEIs were consistently associated with higher rates of cough; WDAE more frequent in those on ACEIs (consistent with rates of cough)	
	No differences in differential effects on lipids, renal outcomes, carbohydrate metabolism, diabetes, and left ventricular mass, but evidence was not strong	
Rates, predictors of ACEI discontinuation following elevated SCr	SCr increased <30 % on average within 3 months of ACEI initiation	[85]
Retrospective cohort study; 3039 patients, SCr measures before start of study and after 3 months	Elevation in SCr not associated with ACEI discontinuation	
	Males and those with HF less likely to discontinue ACEI after SCr elevation post-ACEI initiation; females and absence of HF associated with discontinuation	
	Those on NSAIDs, diuretics, and β-blockers were more likely to discontinue ACEIs	
Incidence of discontinuing ACEIs due to cough in a primary healthcare center	129 (30.4 %) discontinued ACEIs due to cough; 90 (21.2 %) switched to ARBs	[76]
424 patients, in a Polyclinic, newly prescribed ACEIs	Incidence of discontinuation higher than other studies: possible role for ethnicity?	
ACE-associated cough: information from the PDR	Pooled weighted incidence of cough for enalapril was 11.48 %, ninefold higher than reported in the PDR; withdrawal rate was 2.57 %, 31-fold higher than reported in PDR	[96]
125 studies enrolled 198,130 patients	Incidence of cough and withdrawal is significantly higher in the literature than reported in the PDR	

Table 3 continued

Study characteristics	Key results	References
Risk of angioedema due to drugs that target the RAAS	Over 10 years (2001–2010), 4511 angioedema events (ACEIs 3301; ARBs 288; aliskiren 7; β-blockers 915)	[79]
Retrospective observational cohort study from 17 health plans on the following: ACEI (n = 1,845,138), ARB (n = 467,313), aliskiren (n = 4867), or β-blocker (n = 1,592,278)	ACEIs or aliskiren had a 3-fold higher risk for angioedema vs. β-blockers; the risk was lower with ARBs vs. ACEIs and aliskiren	
Hyperkalemia in patients taking spironolactone and ACEIs or ARBs	Prevalence of hyperkalemia was 11.2 % in study	[90]
Retrospective, 534 outpatients, 1 year (2009); hyperkalemia defined as >5.0 mmol/L	Risk factors included CKD, initial K^+ >4.0 mmol/L, spironolactone dose over 25 mg/day	
Excluded patients with CKD receiving dialysis, and those with prior hyperkalemia		
Risk factors for hyperkalemia following hypertension control with aldosterone blockade	Mean increase in serum K^+ was 0.4 mEq/L over baseline	[91]
	17.3 % manifested hyperkalemia (>5.5 mEq/L)	
46 patients with resistant HT and stages 2 or 3 CKD; mean age 64.9 ± 10.7 years; all obese; 86 % had T2DM; 82 % were African American	Predictors: eGFR ≤45 mL/min in whom potassium was over 4.5 mEq/L and a SBP reduction of >15 mmHg associated with eGFR fall of >30 %	

ACE angiotensin-converting enzyme, *ACEI* angiotensin-converting enzyme inhibitor, *AE* adverse effect, *AHRQ* Agency for Healthcare Research and Quality, *ARB* angiotensin receptor blocker, *BP* blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *DRI* direct renin inhibitor, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *HT* hypertension, *NSAID* nonsteroidal anti-inflammatory drug, *PDR* Physicians' Desk Reference, *PL* placebo, *RAAS* renin-angiotensin-aldosterone system, *SBP* systolic blood pressure, *SCr* serum creatinine, *T2DM* type 2 diabetes mellitus, *WDAE* withdrawal-related adverse effects, *WHO* World Health Organization

ACEI therapy [81]. Antihistamines and corticosteroids are ineffective for angioedema, as the mechanism involves bradykinin; hence, bradykinin receptor antagonists may be beneficial [78]. ACEI-induced angioedema can have a delayed presentation, occurring years after initiating the drug; predisposition may include age over 65 years, atopy, and use of NSAIDs [82].

It is not uncommon to observe physician reluctance to use ACEIs in patients with CKD for fear of worsening renal function or development of hyperkalemia. In the presence of CKD, it is generally prudent to exercise caution regarding hazardous co-prescriptions and dietary habits that predispose to drug–drug and drug–nutrient interactions [23, 83]. Preexisting renal function and parenchymal kidney disease influence subsequent renal status following ACEI initiation [84]. Yet, data are lacking on predictors of rise in serum creatinine (SCr) and the course following ACEI use. A report suggests that the mean rise in SCr following ACEI initiation was 26 %, and relates to baseline function; factors other than SCr elevation were associated with discontinuing ACEIs: female sex, the absence of HF and use of NSAIDs, diuretics, and β-blockers [85]. Males and those with HF were likely to continue receiving ACEIs. A study demonstrated that if the SCr was >2 mg/dL at baseline, despite an increase in SCr after drug initiation, the continued ACEI use was actually associated with a decline in SCr in most patients [85].

In a South Indian teaching hospital study of 692 patients, 7.36 % developed ADEs, the majority in those aged >61 years; the ADEs included hypotension, acute renal failure, cough, and hyperkalemia [86]. Fortunately, 93.3 % were reversible. A common reason to either withdraw or not offer ACEI or ARB therapy in patients likely to benefit from these drugs is the development of hyperkalemia while receiving therapy, or the presence of pre-existing hyperkalemia. The incidence varies, with 10 % of those receiving therapy experiencing at least mild hyperkalemia [87]. Means to help predict a predisposition include estimating the GFR, baseline serum potassium check, and obtaining information on the intake of dietary potassium, supplements, and drugs that raise potassium [87]. Serum potassium needs to be measured after the first week and first and second months following the initiation of therapy; should hyperkalemia develop, prompt recognition of cardiac dysrhythmias is necessary to manage and optimize outcomes [87, 88]. Hyperkalemia may be totally asymptomatic. In particular, concomitant drugs that raise potassium are the basis. Examples include heparin, NSAIDs, potassium-sparing diuretics (especially spironolactone), and trimethoprim [89, 90]. Presence of prior CKD is a predisposition [91]. In summary, it is prudent to follow SCr and potassium levels in the weeks following initiation of ACEI or ARB therapy.

ACEI use has been infrequently linked to taste and smell disturbances. The evidence is not clear, as confounding factors (such as smoking) may be contributory [92]. Hypogeusia from high-dose captopril therapy may relate to interaction with zinc metabolism. A rare adverse effect is the development of intestinal inflammation and enteropathy manifesting as diarrhea following olmesartan therapy; the enteropathy can be severe but is reversible upon drug cessation [93]. ACEI-induced cough in a nursing home resident prompted replacement with another ACEI, only to then encounter dysgeusia and much weight loss, forcing drug withdrawal, which led to total recovery; the scenario suggests that different ACEIs in the same class could cause differing ADEs. [94].

Table 3 provides data on renin inhibitors and ADEs [72, 73, 76, 79, 85, 90, 91, 95, 96].

4.3 β-Blockers

The ESH/ESC guidelines include β-blockers among the options for first-line therapy, while the JNC 8 and ASH/ISH recommendations do not [5–7]. Like diuretics, β-blockers have been used to treat hypertension for years; presently, they are ideally used in combination with other agents in settings to treat hypertension with the additional presence of CAD, HF, or arrhythmias [97]. BP-lowering mechanisms of β-blockers are multifactorial, including a decrease in cardiac output, renin release, sympathetic system activity, and more. Data have not confirmed the benefits of β-blockers in lowering outcomes compared with other antihypertensive classes; the development of new-onset DM and adverse effects noted in the presence of vascular disease are perceived adverse effects. Non-vasodilating β-blockers may reduce muscle blood flow and impair insulin sensitivity, in contrast with vasodilating β-blockers, which do not, offering an advantage to the latter [98]. Rarer settings in hypertensive patients, such as the presence of tremor or migraine may prompt their use.

The properties of β-blockers are diverse; drug kinetics and dynamics are influenced by lipid or water solubility, cardio-selectivity (higher affinity for the β-1 receptor), presence of intrinsic sympathomimetic activity, vasodilatory properties (through α-adrenergic blockade or release of nitric oxide), and route of elimination (renal or hepatic) [98–100]. Lipophilic properties allow entry into the central nervous system, with related ADEs; they are metabolized and eliminated by the liver, a process affected in heart failure; examples include metoprolol and propranolol [100]. Hydrophilic β-blockers such as atenolol and nadolol are excreted via urine, resulting in prolongation of half-life with impaired renal function [100]. Selectivity is a feature of second-generation β-blockers, e.g., atenolol and metoprolol, while vasodilatation is a property of third-generation drugs, e.g., carvedilol and nebivolol.

The newer β-blockers with vasodilatory properties have better outcome profiles and tolerability. The tolerability of nebivolol, a third-generation β-1-selective long-acting β-blocker that causes vasodilation through local nitric oxide stimulation, appears to differ; it is the most β-1-selective blocker [101] and is unlike carvedilol and labetalol, which also cause vasodilation through blocking α1 receptors [101]. Nebivolol monotherapy is efficacious and tolerated in older adults, as also combination therapy with valsartan, an ARB [102]. In a cohort of >130,000 individuals, different classes of drugs were compared for discontinuation rates [103]. As expected, rates of discontinuation differed within each class, with the greatest heterogeneity among β-blockers and CCBs; among the β-blockers, nebivolol had the lowest discontinuation rate [103].

Combining β-blockers with diltiazem or verapamil predisposes to bradycardia and heart blocks, while combination with diuretics might accentuate the negative metabolic effects involving glucose and lipid metabolism [104]. Combinations with dihydropyridines may improve heart rate and BP control [104].

An extensive review of studies and meta-analysis of β-blockers in hypertension (from 1973 to 2012) suggests that the class of drugs is effective in the reduction of cardiovascular morbidity and mortality in younger patients but less so in older adults; data comparing the different β-blockers with varying properties are insufficient. It is tempting to mention that the vasodilating agents may be associated with different outcomes, although this is yet to be proven in randomized controlled trials (RCTs) [100].

Adverse effects of this class of drugs include depression, insomnia, nightmares, hallucinations, fatigue, and lethargy; erectile dysfunction is discussed elsewhere in this review. The effects are significantly influenced by the pharmacological properties of the β-blocker [99]. Sinus bradycardia and nodal blocks occur, accentuated by drug interactions with digoxin, verapamil, diltiazem and cholinesterase inhibitors. Glucose intolerance can worsen. Manifestations of hypoglycemia may be masked by β-blockers. Worsening of symptoms attributed to peripheral arterial disease (claudication) and worsening of bronchospasm can occur in the predisposed individual. Severe hyperkalemia can occur with propranolol. Abrupt discontinuation can lead to rebound hypertension and a withdrawal syndrome. These ADEs may affect quality of life (QOL), rendering the class of drugs not particularly suitable for the old [97]. Even so, β-blockers as a class appear beneficial in hypertensive patients with certain comorbidities, such as acute and chronic cardiac ischemia or HF, and for the treatment of hypertension in those aged below 60 years [99].

4.4 Calcium Channel Blockers

CCBs are included among the options for initial therapy for hypertension in recent guidelines [5–7]. CCBs block influx of calcium ions into vascular smooth muscle and consist of three subclasses: phenylalkylamines (verapamil), dihydropyridines (nifedipine, amlodipine), and benzothiazepines (diltiazem), with significant differences [97]. The class of medications is useful in the setting of stiff arteries and particularly beneficial in isolated systolic hypertension. CCBs are effective regardless of age, sex, race, or ethnicity [105].

The nondihydropyridine CCBs are more negatively chronotropic and inotropic than the dihydropyridine subclass, warranting caution when combined with β-blockers [105]. Diltiazem and verapamil interactions with digoxin or β-blockers may result in conduction disturbances and bradycardia. Adverse effects are dose dependent and predictable: conduction disturbances and bradycardia are more apparent with verapamil and diltiazem; headache, flushing, ankle edema, and tachycardia occur more often with amlodipine and nifedipine [106]. Edema from use of dihydropyridine CCBs usually does not respond to diuretic therapy, necessitating dose reduction or withdrawal of the drug [107]. Constipation is most commonly encountered with verapamil. CCBs do not incur adverse effects involving glucose or lipid metabolism, nor with uric acid levels [106, 108]. Short-acting nifedipine is no longer used following awareness of its association with the risk of myocardial infarction and death when used in the setting of hypertension and CAD [108].

Combining clarithromycin (vs. azithromycin) with a CCB may be associated with acute kidney injury, hypotension, and hospitalization, the risk being highest with dihydropyridines [109]. A study also reports the unusual association of CCBs with lower hemoglobin levels compared with nonusers of the drug in CKD patients not receiving renal replacement therapy or erythropoietin, iron, calcium, and folic acid [110]. A comparison of nicardipine and clonidine regarding cognitive function suggested that nicardipine did not impair central nervous system activity in older hypertensive patients with memory complaints, in contrast to the deleterious sedative effects of clonidine in psychometric tests and electroencephalogram analysis [111].

4.5 Miscellaneous Agents

Centrally acting antihypertensive agents (clonidine, methyldopa, and reserpine) are no longer recommended as first-choice antihypertensive agents in the elderly; although they do lower the BP, ADEs outweigh benefits. Clonidine, a central alpha agonist that stimulates alpha receptors in the brain, is associated with psychological adverse effects, including depression, hallucinations, and delirium [112, 113]. Hypertensive crisis may occur following abrupt drug withdrawal; hypertensive urgency has been reported following drug interaction with mirtazapine, an antidepressant [114].

α-Blockers are no longer first-line therapy for hypertension, although they help in the incidental control of hypertension when used primarily in the management of benign prostatic hyperplasia (BPH) [115]. α-blockers lost their place when ALLHAT demonstrated a higher risk of CVD and stroke with these drugs; the incidence of heart failure was also higher in the doxazosin arm than in the diuretic arm [116]. The BP-lowering effect of α-blockers is modest at best [117]. Adverse effects include dizziness, postural hypotension, syncope, and fatigue [115]. Some α-blockers may also be associated with ejaculatory dysfunction [118].

A less common consideration is the need for vigilance and early diagnosis of drug-induced lupus, particularly with hydralazine. Hydralazine-induced vasculitis mimics idiopathic anti-neutrophil cytoplasmic antibody-positive vasculitis, presenting as pulmonary or renal vasculitis and gangrene [119–121]. Toxic epidermal necrolysis has been reported, with recurrence following the reintroduction of hydralazine [122]. Hydralazine-induced lupus erythematosus appears related to dose and duration of drug use, and may present as a pericardial effusion, even with cardiac tamponade [123].

Minoxidil, a potent vasodilator, has been used in the past in difficult to control hypertension. Adverse effects, including salt and water retention, pericarditis, and pericardial effusion, and cardiac lesions in animal studies, have prompted a significant decline in use of the drug.

5 Hypertension Associated with Common Settings in Older Adults: Dementia, Depression, Sexual Dysfunction, Diabetes Mellitus, Falls, and Nocturia

5.1 Dementia

Cognitive impairment with varying degrees of dementia are common in the elderly. In such settings, the choice of antihypertensive agent regarding benefits versus harm, and ethical considerations, pose dilemmas. Studies are few, with little convincing evidence supporting benefit, harm, and safety for any agent, suggesting that providers must use the same judgment as in the non-demented [124]. Centrally acting ACEIs may be associated with a reduced rate of cognitive decline [125]. With both hypertension and dementia being common, there is uncertainty over whether

the benefit in prevention of cognitive impairment is secondary to a lowering of BP or is a specific drug class benefit [97]. An analysis of observational studies suggested the prevalence of hypertension in those with dementia was 45 %, with target BP achieved in 55 %; the majority were receiving medications, diuretics being most common. The findings suggest the need for more work to establish a risk–benefit ratio in the setting of dementia [126]. A systematic review of 18 longitudinal studies involving over 1.3 million subjects, average age 74 years, suggested that antihypertensive drugs, especially CCBs and renin-angiotensin system blockers may help in the prevention of cognitive decline and dementia. However, the authors wished to see a longer follow-up regarding cognition as a primary outcome [127]. In nursing home patients, use of antihypertensive agents generally lowered the likelihood of hospital admissions, while β-blockers were linked to an increased likelihood of falls [128].

5.2 Depression

While depression may be associated with hypertension, whether depression is a risk factor for hypertension is less clear; a meta-analysis suggests that depression is an independent risk factor [129]. Adherence to therapy seems to have an association with depression and anxiety disorders in men (but not in women), offering the opportunity for treatment of the disorders to improve outcomes [130]. Even mild anxiety and depression increase the risk of nonadherence [131]. Even the onset of depression increases the risk of nonadherence to antihypertensive drugs in hypertensive men [132]. The relationship of depression to hypertension is complex. Unawareness of hypertension is inversely associated with burden of depression, while controlled hypertension appeared positively associated with depression; β-blocker use is associated with severity of somatic symptoms (e.g., fatigue) [133]. In hypertensive Black men, nonadherence to medication regimen is understandably a contributor to poor control of BP, and greater depressive symptoms (in a community study) appears associated with nonadherence, as does alcohol misuse. These risks offer the opportunity to call for appropriate referrals [134].

5.3 Sexual Dysfunction

The effect of antihypertensive agents on quality of life (QOL) in the elderly is relevant since the deterioration in QOL may lead to reduced adherence. QOL in this regard includes several domains: wellbeing, emotions, physical, work–social, cognition, sexual function, and satisfaction with life. Antihypertensive treatments may have significant, little, or no negative impact on QOL, and may even improve it. A common denominator in hypertension is erectile dysfunction (ED). ED is complex in pathogenesis, with several factors that can modify the process; ED can exist prior to the onset of hypertension, appear in the course of the hypertensive disorder, or follow the use of an antihypertensive drug [135]. The literature is highly diverse regarding the matter. A study of over 5000 patients suggested that antihypertensive drug-induced sexual dysfunction received little attention from care providers [136]. A report describes high-dose β-blockers being prescribed to the young while ACEIs and CCBs were underutilized, although the ACEIs and CCBs were known to have a lesser impact on sexual function [136]. Sexual dysfunction is currently considered a serious QOL health issue [137] warranting treatment considerations to achieve a balance between BP control and least possible adverse sequelae involving sexual function [138]. Furthermore, dose-dependent and combination therapy-related adverse effects on sexual function are unresolved issues [139]. There appears to be a lack of understanding of the disorder; many care providers must be able to provide holistic care while prescribing medications [140]. On the other hand, BP control may help improve ED in older adults with high-risk hypertension, even in those treated with β-blockers [141].

Studies on sexual function include few RCTs; methodology flaws and inconsistencies are common. Furthermore, more male populations are included and data are highly variable. Older antihypertensive agents such as diuretics, β-blockers, and central agents have been associated with adversely impacting erectile function [142]. A national community sample demonstrated no association between sexual function and antihypertensive medication class in either men or women [143]. Another study confirmed the complex associations between hypertension and disorders such as DM, CAD, atrial fibrillation, and depression, and suggests that ED is related to end organ damage rather than treatment [144]. An extensive review of several studies discussed the clinical impact of antihypertensives on sexual dysfunction: a table attributes largely neutral to negative impact for β-blockers (except nebivolol), diuretics, and α-blockers; largely neutral or beneficial effects for ACEIs and ARBs; and neutral effects for CCBs [140]. The combination of a CCB (felodipine) with irbesartan appeared more beneficial to sexual desire in hypertensive males than the combination with metoprolol, perhaps attributed to the prevention of oxidative stress with irbesartan [145]. A Swedish study of 225 reports on antihypertensive drugs and ED suggested that all classes of drugs were implicated in ED, including ARBs, suggesting that ARBs had neither a positive nor any effect on ED [146]. Diuretics and non-selective lipophilic β-blockers have been associated with negative QOL, depression, and impaired memory function. CCBs, ARBs, and ACEIs have been associated with a

positive QOL in some studies [147]. A study of 60 hypertensive adults suggested that valsartan did not contribute to ED [148]. A national opinion study of 4017 participants aged 57–85 years found no consistent association between antihypertensive drug classes and sexual problems [149]. A pathophysiological role for the renin-angiotensin system in ED involving angiotensin has been raised [150].

5.4 Diabetes Mellitus

When DM co-exists with hypertension, questions may arise regarding the preferred antihypertensive agent; the risk of new-onset DM associated with the use of antihypertensive therapy may also be a consideration. In a study over 7 years involving 3084 subjects receiving carvedilol and 9252 receiving other β-blockers, with a mean age of 56 years, new-onset DM in hypertensives was similar [151]. The use of losartan was well tolerated and effective in diabetic patients with ED, and was also tolerated in combination with a drug for ED, tadalafil [152]. A treatment algorithm suggests the use of an ACEI or ARB for diabetic patients with hypertension, and the addition of a diuretic, β-blocker, or CCB based on compelling indications or comorbidity [153]. The 2014 JNC 8 guidelines recommend that, in diabetic patients, the choice of drug is determined based on race (Black or non-Black) with several options: in the presence of CKD with or without diabetes, an ACEI or ARB is recommended alone or in combination with other drugs [5]. The 2013 ESH/ESC guidelines allow for compelling choices in situations such as coexisting DM or HF [7].

A nested case-control study suggested that exposure to thiazides and β-blockers increased the risk for DM, while CCB and renin-angiotensin-system blocker (RASB) exposure did not. Further, a combination of thiazides with β-blockers resulted in an additive risk, while addition of a RASB lowered the risk, highlighting the importance of considering diabetogenic potential when using combination therapy [154]. An elaborate review highlighted similar conclusions, with different antihypertensive categories having different effects on glucose metabolism: ACEIs and ARBs were beneficial, CCBs were largely neutral, while diuretics and β-blockers had disadvantages regarding glucose metabolism; carvedilol and nebivolol seemed to differ from other β-blockers regarding effects on glucose metabolism [155]. A double-blind placebo-controlled crossover trial on glucose tolerance in hypertension suggested the following: nebivolol did not impair glucose tolerance, thiazides impaired glucose tolerance, and potassium-sparing diuretics did not [156]. Conversely, a Japanese study suggested that low-dose thiazides did not increase the risk for new-onset diabetes in an RCT with a median follow-up of 4.4 years [62]. It must be noted that potassium-sparing diuretics have no significant effect on glucose tolerance [157].

5.5 Falls

Falls and fall-related injuries are common in older adults, with intrinsic disease, environmental factors, and medications playing a role in pathogenesis. Data on antihypertensive drugs and falls are quite conflicting. Meta-analysis of studies to determine whether any of five antihypertensive classes (thiazides, ACEIs, ARBs, CCBs, and β-blockers) were a predisposition in those aged ≥60 years failed to confirm a clear statistically significant association, suggesting that any antihypertensive class may increase risk of fall injuries [158]. Conversely, a community study of 598 adults aged 70–97 years with hypertension concluded that, in the relatively healthy old, even high doses of antihypertensive agents are not associated with an increased risk for falls [159]. The findings contrast with other data. In a study of subjects aged 66 years and older, an increased risk of injurious falls occurred in the first 45 days after initiating antihypertensive therapy for most classes [160]. The same study also indicated an increased risk of hip fracture after initiating antihypertensive drugs [161], calling for fall-prevention strategies during this period. Higher doses of antihypertensive medications in older people aged 60–86 was independently associated with falls, particularly in those with a history of previous stroke [162]. In another study of 4961 community-dwelling adults aged 70 years and older, antihypertensive medications were associated with increased risk of serious fall injuries, especially in those with prior falls, calling for a harm versus benefit analysis in deciding antihypertensive medication treatment [163].

5.6 Diuretics and Nocturia

Diuretics are often incriminated by patients as a cause for nocturia. In a study of patients with benign prostatic hyperplasia (BPH), treatment with furosemide and doxazosin was safe and effective; the combination increased daytime urine output and decreased nocturia-related urine output [164]. Likewise, addition of a low-dose thiazide to losartan did not influence nocturia in older hypertensive adults [165]. The issue of urinary incontinence is often raised by patients as relating to diuretic use. Thiazides seldom cause urinary incontinence, while furosemide, not primarily an antihypertensive agent, may tend to increase the sensation of urgency and predispose to urge incontinence.

Table 4 Nonadherence and concerns pertinent to hypertension management in older adults [130, 143–145, 149, 154, 156, 160, 166–171, 175, 176, 182]

Study characteristics	Key results	References
Anxiety sensitivity and medication nonadherence	Twice as many pts with high anxiety sensitivity were nonadherent to antihypertensive medications vs. low anxiety sensitivity group	[166]
Study of 88 pts with uncontrolled HT	High anxiety sensitivity subjects with uncontrolled HT can be taught to manage anxiety sensitivity and lower CV risk	
Antihypertensive medication adherence in Black men	No psychosocial stressor variables associated with nonadherence	[167]
196 Black men enrolled in clinical trial to improve HT control	Greater depressive symptoms noted to be an association	
	Although alcohol misuse was an association, it was not a mediator between depression and nonadherence	
Veterans study, propensity score-matched cohort of 18,822 pts	Assignment of the code prior to treatment was associated with higher all-cause mortality in incident hypertensives, but did not worsen adherence to drugs	[168]
9411 pts with and without a V15.81 code (ICD-9 code for medical treatment nonadherence		
Mean age 50 years, 91.4 % men, 33.2 % Black		
Antihypertensive medication adherence and mortality, based on ethnicity	Chinese and South Asians significantly less likely to adhere to medications vs. Caucasians	[169]
Province-wide antihypertensive drug data base (1997–2005), British Columbia	Unlike in Caucasians, optimal adherence in these two groups was not associated with reduced mortality	
16,471 Chinese (11.1 %), 6099 (4.1 %) South Asian, 126,081 (84.8 %) Caucasians		
Triple-drug therapy, adherence and outcomes	Therapy with 2 vs. 3 pills associated with more adherence	[170]
16,290 pts, matched for adherence, CV events, costs, for 12 months	Costs were lower for β-blocker group only	
Drugs included ACEI, ARB, β-blocker, HCTZ, amlodipine	Fixed-dose combinations improved pill burden and adherence in all cohorts	
Improving adherence using combination therapy	Fixed-dose combinations improved adherence but improvement in clinical risk factors was small	[171]
Open-label, RCT, 54 practices in NZ, 2010–2013	Acceptability was high, but discontinuation rate was also high	
513 adults at high risk of CVD, on antiplatelet, statin, and 2 or more antihypertensives		
Usual care vs. fixed-dose combination; self-reported adherence to drug therapy		
Risk factor reduction and tolerability of a full-dose vs. low-dose polypill	Full-dose polycap® reduced BP and LDL-C to a greater extent than low-dose polycap®	[175]
518 pts with vascular disease or DM, from 27 centers in India	Both doses had similar tolerability	
Randomly assigned to single-dose polycap® or 2 capsules polycap® plus potassium; 3 BP-lowering drugs (included HCTZ, atenolol, ramipril), statin, aspirin		
Assessed effects on BP, HR, serum lipids over 8 weeks		
Efficacy and tolerability of polypills	Polypills reduced BP and lipids vs. PL	[176]
Systematic review and meta-analysis; Cochrane Central Register, MEDLINE, PubMed	Tolerability was lower with polypills than PL, but differences were moderate	
Of 44 controlled trials, 6 trials with 2218 pts met inclusion criteria		
Initial antihypertensive prescription and switching	6163 (3.9 %) switched their medication within 180 days	[182]
5-year cohort study, 250,851 Chinese pts in Hong Kong, 159,813 eligible	Highest switch rate for thiazides, followed by ACEIs, CCBs, and β-blockers	
	AEs were likely basis, suggesting the need to observe for tolerability	

Table 4 continued

Study characteristics	Key results	References
Association between depressive and anxiety disorders and adherence Population-based health survey, Quebec, Canada 2811 community adults, ages 65 and older, final sample 926 subjects who took antihypertensive drugs for 2 years	Adherence strongly associated with depression and anxiety disorders in men	[130]
Sexual activity and function in hypertensive pts (National Social Health, Life and Aging Project) Nationally representative sample of 3005 community-dwelling adults 37–85 years, classified by HT status: treated, untreated, and no HT ACEI, ARB, diuretic, CCB, β-blocker, and α-blocker	No significant associations between antihypertensive medication class and sexual activity or problems in men and women Relationship between HT and sexual health did not differ between men and women	[143]
ED in high-risk HT pts receiving β-blockers ED assessed by the IIED 1007 pts, mean age 57.9 years	Prevalence of ED was 71 % (38.1 % mild, 16.8 % moderate, 16.1 % severe) Pts with ED received more medications; independent associations noted between ED and diabetes, depression, CAD, AF, and CCBs ED was highly prevalent in hypertensives treated with β-blockade, and related to end organ damage rather than treatment, with lower prevalence noted with nebivolol	[144]
Effect of combining a CCB with either an ARB or β-blocker on ED Prospective randomized study in 218 males, over 48 weeks Randomized to treatment with felodipine combined with metoprolol or irbesartan	No significant difference in prevalence of ED before or after treatment in either group Felodipine-irbesartan was more beneficial to the sexual desire of hypertensive males	[145]
Sexual activity and function in middle-aged and older men and women with HT National Opinion Research Center sample of 4017 l community-dwelling adults, 57–85 years, of whom 75.5 % completed the interview	No consistent associations between specific antihypertensive medication classes and sexual problems, suggesting the need for prospective studies	[149]
Risk of falls after initiation of antihypertensive drugs in the elderly Population-based self-controlled study of elderly aged 66 and older, Ontario, Canada Risk period first 45 days divided into 0–14 and 15–44 days 543,572 new users of antihypertensive drugs, community based	8893 had an injurious fall New users had a 69 % increased risk of falls in the first 14 days for all classes and within the first 45 days for all classes except ARBs Initiation of antihypertensive drugs deemed a risk factor for falls in the elderly	[160]
Antihypertensive drug class interactions and risk for incident diabetes Nested case-control study, 134,967 pts, 9095 diabetic pts, 90,495 controls Exposure to thiazides, β-blockers, CCBs, and RASB	Thiazides and β-blockers increased diabetes risk; CCBs and RASBs did not Combination of RASB with either thiazides or β-blockers showed negative interaction	[154]
Role of diuretics, β-blockers, and statins, and risk of diabetes (NAVIGATOR trial) Pts treated with β-blockers (5640), diuretics (6346), statins (6146), and CCBs (6294); CCBs used as metabolically neutral control; median 5-year follow-up	Diuretics and statins were associated with an increased risk of new-onset DM; CCBs and β-blockers were not	[156]

ACEI angiotensin-converting enzyme inhibitor, *AE* adverse effect, *ARB* angiotensin receptor blocker, *BP* blood pressure, *CAD* coronary artery disease, *CCB* calcium channel blocker, *CV* cardiovascular, *DM* diabetes mellitus, *ED* erectile dysfunction, *HCTZ* hydrochlorothiazide, *HR* heart rate, *HT* hypertension, *ICD-9* International Classification of Diseases–Ninth Revision, *IIED* International Index of Erectile Dysfunction, *LDL-C* low-density lipoprotein cholesterol, *PL* placebo, *pt* patient, *RASB* renin-angiotensin blockers, *RCT* randomized controlled trial

Table 5 A summary of adverse effects by class of antihypertensive drug

Drug class/ agent	Prominent adverse effects
Diuretic	Hyponatremia; hypokalemia (thiazides, thiazide-like, loop); hyperkalemia (aldosterone antagonists); hypomagnesemia; hypercalcemia (thiazides); fatigue, lethargy, altered mentation (electrolyte abnormalities); glucose intolerance, decrease in insulin sensitivity; worsening of hyperlipidemia; hyperuricemia, predisposition to gout; sexual dysfunction; pancreatitis; interstitial nephritis; thrombocytopenia
ACEI	Cough (common 5–35 %); angioedema (<1 % of patients); taste and smell disturbances (linked to zinc deficiency?); worsening of renal function; hyperkalemia (in CKD and relating to drug or disease interactions)
ARB	Worsening of renal function; hyperkalemia (in CKD and with drug or disease interactions); angioedema (occurs in <10 % of those who developed it with ACEIs); diarrhea (inflammatory enteropathy, a rare association with olmesartan)
Renin inhibitor	Headache; nasopharyngitis; diarrhea; cough (rare); hyperkalemia
CCB	Ankle edema (more with felodipine and nicardipine); constipation (most with verapamil); headache and flushing (more with felodipine and nicardipine); tachycardia (with felodipine and nicardipine); bradycardia (with verapamil and diltiazem); aggravation of angina (by some short-acting CCBs)
β-Blocker	AEs vary in the class, based on properties; depression; insomnia, nightmares; fatigue, lethargy; glucose intolerance; sexual (erectile) dysfunction; worsening of claudication; bronchospasm; sinus bradycardia, heart block
Central agents	Depression; sedation; hallucinations; delirium; dry mouth; hypertensive crisis (following abrupt drug withdrawal)
Hydralazine	Tachycardia; hemolytic anemia; drug-induced lupus; vasculitis; toxic epidermal necrolysis
Minoxidil	Salt and water retention, including worsening of HF; hair growth; pericarditis and pericardial effusion; cardiac lesions, largely noted in animal studies
α-Blockers	Dizziness, fatigue; postural hypotension and syncope; sexual dysfunction; increased risk for cardiac and cerebrovascular disease

ACEI angiotensin-converting enzyme inhibitor, *AE* adverse event, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *CKD* chronic kidney disease, *HF* heart failure

6 Nonadherence to Medications

Several factors contribute to nonadherence to medications and resultant suboptimal control of hypertension; poor tolerability due to ADEs is only one contributory factor. Anxiety sensitivity is strongly associated with antihypertensive drug nonadherence, a situation that can be managed through the use of adaptive strategies for anxiety, with resultant better control of hypertension and lower cardiovascular risk [166]. In Black men, depression may play a role in adherence; alcohol misuse is a contributory factor, although it does not appear to mediate the association between depression and nonadherence [167]. A large veterans study concluded that assignment of a code (V15.81) for nonadherence to medical treatment before initiating antihypertensives was associated with higher all-cause mortality, although, interestingly, the association was not mediated by worse nonadherence to antihypertensive drugs [168]. A large study in a Canadian province suggested that nonadherence was more prevalent in Chinese and South Asian patients; however, optimal adherence had no association with mortality [169]. ACEIs and CCBs may be favorable choices in dementia, with adherence offsetting the costs and ultimately providing savings [97]. The costs of medications, insurance coverage for drugs and laboratory testing costs (especially with diuretics) may all be variably influential in eventual adherence or nonadherence to therapy.

Combination therapy may lower pill burden and improve adherence and clinical outcomes in some cases, without an increase in costs [170]; acceptability to therapy may be high, but discontinuation of medications, nevertheless, still occurs [171]. Combination therapy may also help synergistic enhancement of drug effects and reduction in adverse effects, with positive influence on safety and tolerability [104, 172, 173]. Triple fixed-dose combination therapy with an ARB, a CCB, and a thiazide favorably impact BP control [174]. A comparison of low-dose versus full-dose polypills (consisting of atenolol, ramipril, and hydrochlorothiazide) demonstrated greater BP reduction with the full-dose pill (which also included potassium supplement), with similar tolerability [175]. Several combination therapies have been found effective in BP control [176–178], including in diabetic hypertensive patients [179], although tolerability was lower than placebo for some combinations. Thus, use of combination pills for hypertension may be one way to enhance control and tolerability (with fewer adverse effects) and perhaps reduce healthcare costs [180]. As several combination therapies seem effective, the strategy is an acceptable option in

hypertension guidelines. Finally, market availability may be associated with optimal adherence, rather than improved tolerability [181].

Table 4 addresses data pertinent to nonadherence and common concerns with management of elderly hypertensive patients [130, 143–145, 149, 154, 156, 160, 166–171, 175, 176, 182].

Table 5 provides a summary of ADEs attributable to antihypertensive medications.

7 Lifestyle Always, Along With Medications: Synergy Helps Tolerability

Guidelines on management of hypertension uniformly call for the use of lifestyle measures including a diet that is low in salt and rich in potassium (barring contraindications). Patients and providers must generally adopt the approach of combining dietary approaches with medications; the value of a diet-based strategy with lifestyle changes may even substitute for a drug-based approach [183]. The choice of diet may be a Mediterranean-like diet, modified to include plenty of vegetables, fruit, low carbohydrate, high-quality protein, and fats such as monounsaturated fats and omega-3 fatty acids [184]. Many natural compounds in the diet are touted to have antihypertensive properties [184]. Dietary approaches must be combined with physical activity for optimal benefit in management of hypertension. Leisure time physical activity is not associated with harm (unlike the scenario of adverse effects due to medications) and has beneficial effects for longevity; healthcare professionals must encourage inactive adults to engage in leisure time physical activity [185].

8 Choice of Antihypertensive Medication in Older Adults: Is There An Ideal Agent?

With the increasingly complex need to follow guidelines in the setting of treating older patients with much comorbidity, the choice of drug class is debatable [97]. Data from 147 randomized trials involving over 400,000 subjects suggest that all antihypertensive drug classes are effective and work [186]. A comparison of 55,569 older hypertensive subjects with a similar number of controls confirmed that similar BP reduction irrespective of the drug resulted in similar lowering of risk [187]. Furthermore, a meta-analysis comparing drug efficacy between the young and old (aged over 65 years) demonstrated similar class effects [187]. Combination antihypertensive therapy (with two or more agents) in the frail elderly with relatively low systolic BP (<130 mmHg) may result in higher risk of mortality [188]. Additionally, BP variability, white coat hypertension, postural and postprandial hypotension, and widened pulse pressure are presentations that deserve consideration in older adults [97]. As the activity of the renin-angiotensin system declines with age, the efficacy of drugs targeting the RAAS system may be lower [97]. In a sample of nearly 5000 community-dwelling older adults with multiple chronic conditions, antihypertensive treatment was associated with reduced mortality but not cardiovascular events (myocardial infarction, angina, stroke, and HF hospitalizations) [189].

The American Geriatrics Society Beers Criteria for potentially inappropriate medication use in older adults suggests the avoidance of α-blockers for hypertension because of risk for orthostatic hypotension; it discourages the use of clonidine as a first-line antihypertensive agent due to adverse central nervous system effects [190]. The STOPP (Screening Tool of Older People's Potentially Inappropriate Prescriptions) and START (Screening Tool to Alert doctors to the Right Treatment) address under-treatment as well as potential errors of omission and commission [191]. The criteria consider the following settings inappropriate: use of thiazides with a history of gout; CCBs in the presence of chronic constipation; and diltiazem with HF [191].

A suggestion is to use a condition–drug correlation [7] in the elderly. The JNC 8 guidelines recommend specific medication classes for racial, CKD, and diabetic subgroups [5]. The ESH/ESC statement offers suggestions for preferred drugs to manage hypertension associated with comorbid states such as stroke, CAD, aortic aneurysm, atrial fibrillation, CKD, peripheral artery disease, DM, and HF, amongst others [7]. Orthostatic hypotension is a prevalent disorder in older treated hypertensive subjects; standing BP must be verified before and during therapy [192]. Several classes of antihypertensives are available with unique pharmacologic properties and adverse effects; but not all agents in the same class have identical pharmacodynamics, calling for careful selection and individualization of therapy [193]. As most classes are effective for hypertension, selection is best individualized based on factors that go beyond BP control, such as comorbidity, patient and physician perception of ADEs, economic implications, and the need to avoid certain agents or prefer others [97]. Medication costs are often ignored by the provider; expensive medications may certainly contribute to nonadherence. Generics are adequate where applicable, while a better adverse event profile may more than offset higher costs. Providers must attempt to reduce barriers and enable patients to adhere to drug therapy and lifestyle modifications [194]. Finally, patient and physician preferences for antihypertensive medication(s) influence the final choice, assuming drug tolerability is adequate. The above considerations help decide the agent that would be closest to ideal for a given individual.

9 Conclusions

Hypertension is common in the elderly, increasing in prevalence with age. Hypertension is best addressed by primarily promoting a healthy lifestyle appropriate to the individual, with medications playing an additional role. Although guidelines provide direction, the ultimate choice of agent is best individualized based on age, race, and the presence or absence of coexisting disorders, such as DM, CAD, HF, and CKD. In the elderly, drug therapy may be further influenced by the presence of dementia, depression, and socio-economic considerations. ADEs differ significantly with antihypertensive drug classes and influence tolerability; changes between or within the classes may improve tolerability. Nonadherence to therapy may be a result of several factors, including drug tolerability. Although guidelines offer a pathway, the final choice of antihypertensive medication(s) must be tailored to each individual following provider–patient discussions on benefits and risks, least likelihood for ADEs, and highest potential for adherence. Utilizing correct principles, hypertension can be safely managed in most older adults.

Compliance with Ethical Standards

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