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Aging and antihypertensive medication-related complications in the chronic kidney disease patient

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Abstract

Purpose of review—We have reviewed the recent literature to describe the potential medication errors and adverse drug events (ADEs) associated with antihypertensives among older adults with chronic kidney disease (CKD).

Recent findings—Overall, few studies have been published describing ADEs in older adults with CKD. Several examined hyperkalemia associated with angiotensin-converting enzyme (ACE)-inhibitor/angiotensin II receptor blocker (ARB), diuretic (potassium-sparing), and β-blocker use. Additional studies described acute kidney injury (AKI) most commonly with ACE-inhibitor/ARB therapy. Finally, orthostatic hypotension was evaluated in those taking ACE-inhibitor/ARB, β-blocker, or calcium-channel blocker therapy. In the absence of robust literature examining these events in this understudied population, one must consider age-related antihypertensive pharmacokinetic/pharmacodynamic profiles concomitantly with the patient's comorbidities and other medications in order to minimize the risk for potential medication errors, drug–drug interactions, and ADEs.

Summary—Some of the most common ADEs associated with antihypertensive use in older adults with CKD include hyperkalemia, AKI, and orthostatic hypotension. Diligent monitoring of laboratory data, vital signs, and potential drug–drug interactions may mitigate serious ADEs caused by antihypertensives in this high-risk patient population.

Keywords

adverse drug events; aging; antihypertensives; chronic kidney disease; older adults

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Conflicts of interest

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Introduction

It is widely known that aging is associated with renal changes (structural and functional) as well as altered drug pharmacokinetics and pharmacodynamics [1]. Moreover, older adults often have multiple chronic conditions that may worsen chronic kidney disease (CKD), including diabetes mellitus, hypertension (HTN), and heart failure, and take multiple medications to manage these conditions. Thus, it is challenging to distinguish age-related renal changes from those due to cumulative comorbidity and/or external exposures with other medications. For those older adults who develop CKD, specific age-related changes may occur that could affect blood pressure (BP) management. For example, it has been shown that aging can lead to impaired baroreceptor sensitivity, increased sympathetic nervous system activity, and increased vascular stiffness (in part through decreased vascular compliance) [2]. These physiologic changes may lead to increased BP variability and/or postural and postprandial hypotension [3], increased peripheral vascular resistance, and increased systolic BP and pulse pressure, respectively [2]. As a result, antihypertensive use in older adults with CKD may cause drug-related problems, necessitating more frequent monitoring for therapeutic response as well as adverse drug events (ADEs).

Unfortunately, specific safety data is limited given that older adults are rarely enrolled in clinical trials for antihypertensive use in CKD. The paucity of clinical trial data in older adults with HTN is highlighted in Table 1 [4-11], showing that there have only been eight large randomized controlled trials studying the efficacy of six different antihypertensive classes in older adults with HTN in the past 25 years. In this article, we will review previous as well as more recent literature on antihypertensive medication-related complications (i.e. medication errors and ADEs) in older adults with CKD.

Chronic kidney disease and antihypertensive treatment in older adults

There are multiple indications for antihypertensive use in patients with CKD. However, the overall goals of antihypertensive therapy are the same regardless of the indication – to lower BP, reduce the risk of cardiovascular disease (CVD), and slow the progression of CKD [12]. Specific classes of antihypertensives have been shown to be particularly effective at slowing down the progression of CKD. For example, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are specified as initial therapy options in adults by the National Kidney Foundation (NKF) and the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in those with CKD [12,13].

Because of the strong interplay between CKD, CVD, heart failure, and HTN in addition to older adults' other possible comorbid conditions, each patient's antihypertensive regimen must be individualized. Moreover, the NKF guidelines advise that 'monitoring for side-effects of antihypertensive agents should be more frequent than in the general population' [12]. Thus, it is important to recognize the potential risks associated with the different antihypertensive classes among older adults with CKD.

Adverse drug events by antihypertensive medication class in older adults with chronic kidney disease

Older adults with CKD oftentimes are prescribed multiple medications, including more than one antihypertensive, leading to complex medication regimens. This complexity combined with age-related pharmaco-kinetic/pharmacodynamic changes as well as potential drug–drug interactions can lead to ADEs. For example, phase I hepatic metabolism of certain drugs (e.g. α-blockers: doxazosin, prazosin, and terazosin; β-blockers: metoprolol, propranolol,

and timolol; calcium-channel blockers (CCBs): diltiazem and verapamil) has been shown to decrease with aging because of reduced liver mass, hepatic blood flow, and albumin synthesis [14,15]. Antihypertensives that are highly protein bound and have high hepatic extraction ratios (e.g. propranolol and verapamil) are more likely to be affected by such changes, leading to higher concentrations of these drugs [14,15]. Furthermore, reduced glomerular filtration rate (GFR) and tubular function can occur with aging regardless of the presence of CKD [14,15]. Thus, antihypertensives that are renally excreted (e.g. ACE inhibitors, certain β-blockers, diuretics) can accumulate in older adults with CKD and potentially lead to ADEs. Moreover, those antihypertensives that undergo cytochrome P450-mediated metabolism (e.g. verapamil and diltiazem) are more likely to cause drug–drug interactions [16].

Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers

In general, ACE inhibitors are primarily renally eliminated, thus potentially leading to accumulation in renal impairment. Conversely, ARBs are more hepatically eliminated. Common ADEs that can develop from all renin–angiotensin–aldosterone system (RAAS) blockers include hyperkalemia (because of the inhibition of renal potassium excretion) [17], acute kidney injury (AKI), and/or orthostatic hypotension.

Hyperkalemia—Few studies have been published recently describing hyperkalemia in different populations of patients with CKD. The African American Study of Kidney Disease and Hypertension (AASK) was a randomized clinical trial of nondiabetic patients with hypertensive CKD (n = 1094; mean age: 54.6 years) who were randomized to initial treatment with one of three different classes of antihypertensives: an ACE inhibitor (ramipril, 2.5–10 mg/day); a β-blocker (metoprolol succinate extended release, 50–200 mg/day); or a CCB (amlodipine, 5–10 mg/day) [18]. Although the primary goal of the trial was to assess the efficacy of these antihypertensives on renal disease progression, the investigators also conducted post hoc analysis using the AASK database to describe factors associated with development of hyperkalemia (i.e. potassium >5.5 mEq/l or a clinical center initiated hyperkalemia stop point). Overall, 80 hyperkalemic events out of a total of 6497 potassium measurements (1.2%) were detected. Several independent risk factors were found to be associated with the occurrence of hyperkalemia, including the use of an ACE inhibitor (compared with a β-blocker or CCB), higher baseline protein excretion, decreased baseline and follow-up GFR, higher baseline potassium levels, and older age. This study advanced the literature by highlighting key clinical variables associated with hyperkalemia that can be used to make treatment decisions when initiating therapy in patients with hypertensive CKD. However, it was limited by the inclusion of only African Americans, the use of only one antihypertensive from each class, and by the clinical trial setting which may offer more aggressive monitoring than conventional care.

A retrospective cohort study was conducted to describe the incidence and predictors of hyperkalemia in adults with CKD who receive a RAAS blocker. Johnson *et al.* [19••] created a prognostic risk score using known predictors to predict the risk of hyperkalemia in adult patients with possible CKD (n = 5171; mean age 71.1 years) who were started on an ACE inhibitor (lisinopril) between 1998 and 2006. Overall, 145 patients experienced hyperkalemia (90-day risk of 2.8%). Significant predictors found in this study included age, lower eGFR, presence of diabetes mellitus or heart failure, use of potassium supplements or potassium-sparing diuretics, and a high dose for the ACE inhibitor. Importantly, the risk score was able to distinguish high-risk patients from low-risk patients, suggesting a potential tool for use in clinical practice to determine those patients who may need more frequent laboratory monitoring. In sum, based on available literature, hyperkalemia from RAAS blockade monotherapy occurs relatively infrequently in older adults with CKD and is

predictable or preventable in many cases. However, combination RAAS therapy with both an ACE inhibitor and an ARB has been shown to significantly increase the risk of hyperkalemia in older adults compared to monotherapy [20••].

Acute kidney injury—In addition to hyperkalemia, RAAS blockers have been shown to cause AKI in patients with preexisting renal impairment. Given the fact that older adults have less physiologic reserve and are more susceptible to hemodynamic changes compared to younger adults, RAAS-induced AKI is of greater concern to older adults. Although an acute rise in serum creatinine with initiation or dose titration of RAAS blockers may occur, it is understood that levels of up to 30% above baseline do not represent clinical harm and should not lead to premature discontinuation of therapy [21]. However, ACE inhibitor/ARB therapy does increase the risk of AKI, especially because of prerenal azotemia or concurrent nonsteroidal anti-inflammatory drug (NSAID) use. In the setting of decreased renal perfusion, GFR becomes more angiotensin dependent. With RAAS blocker use, the kidney's ability to respond to this decreased perfusion is blunted, leading to an increased risk of AKI. This potential ADE was shown in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), which assessed whether combination therapy with an ACE inhibitor (rampipril) and an ARB (telmisartan) might be more effective than either treatment alone on renal effects [22]. The secondary renal outcome (dialysis or doubling of serum creatinine) occurred in 2.2% (189/8542) of the telmisartan group and 2.0% (174/8576) of the ramipril group, and 2.5% (212/8502) of the combination group (hazard ratio of combination vs. ramipril 1.24, 1.01–1.51. $P = 0.038$) [22]. This outcome was driven mainly by an increased risk for acute dialysis. Thus, caution should be exercised when using these agents in patients with decreased renal perfusion, and combination therapy warrants extra monitoring for negative renal outcomes. This is of concern in older adults who may experience decreased renal perfusion secondary to dehydration and/or concomitant pharmacotherapy (e.g. NSAIDs).

Orthostatic hypotension—Current guidelines for the treatment of HTN in patients with CKD recommend a BP goal of less than 130/80 mmHg [12]. This BP goal has been debated because of the lack of robust clinical trial data available to support it and the potential for harm from targeting a lower BP (e.g. orthostatic hypotension) [23]. Orthostatic hypotension is a common concern with older adults receiving antihypertensives and has been defined as a systolic BP decrease of 20 mmHg or more, or a diastolic BP decrease of 10 mmHg or more within 3 min of assuming an erect posture [24]. However, a review of orthostatic hypotension in the elderly suggests that RAAS blockers rarely cause orthostatic hypotension apart from their potential to cause first-dose hypotension [25]. Further research is needed to assess orthostatic hypotension as a potential ADE in other RAAS-blocking agents and in different populations of older adults with CKD. Caution should be exercised, however, by using a lower starting dose and slowly titrating to an effective dose.

Diuretics

Diuretics are frequently used in the treatment of older adults with CKD, including thiazide and thiazide-like (e.g. hydrochlorothiazide and metolazone), loop (e.g. furosemide), and potassium-sparing diuretics (e.g. eplerenone, spironolactone, and triamterene). Nonpotassium-sparing diuretics are frequently used in combination with other antihypertensives in CKD that may cause hyper-kalemia (e.g. ACE inhibitor and ARB), and they can negate these potential abnormalities in potassium levels. Furthermore, diuretics have been included in many of the clinical trials assessing antihypertensive efficacy in older adults, and some safety data can be drawn from these studies. For example, ALLHAT found that hypo-kalemia (serum potassium <3.5 mEq/l) occurred more frequently after 4 years of follow-up in patients receiving chlorthalidone compared with those receiving amlodipine or

lisinopril (8.5 vs. 1.9% and 0.8%, respectively) [10]. One possible reason for this is that compared to younger adults, older adults are more sensitive to small changes in regional and systemic perfusion. Consequently, the hemodynamic (and subsequent metabolic) effects of diuretics should be carefully monitored in older adults to prevent potential ADEs, including hypo/hyperkalemia [15].

Hyperkalemia—Khosla *et al.* [26] described the risk factors for hyperkalemia in patients with resistant HTN and CKD (stages 2 or 3) ($n = 46$; mean age: 64.9 years) who had a potassium-sparing diuretic (i.e. aldosterone antagonists, eplerenone, or spironolactone) added to current therapy with at least maximally dosed ACE inhibitor/ARB and a diuretic. Overall, the mean increase in potassium was 0.4 mEq/l above baseline ($P = 0.001$), leading to the development of hyperkalemia in 17.3% of the sample. Patients who had a baseline GFR less than or equal to 45 ml/min and potassium greater than 4.5 mEq/l (on diuretics) had a significantly increased likelihood of developing hyperkalemia. Thus, it has been suggested that patients with CKD receiving a potassium-sparing diuretic should be closely monitored for hyperkalemia [27].

Part of the monitoring for hyperkalemia involves evaluating the medication regimen for drug-drug interactions (Table 2) [28-30,31•]. One of the most clinically significant interactions is between potassium-sparing diuretics and ACE inhibitors, which was shown to significantly increase the rate of hospitalization for hyperkalemia and the associated mortality in patients recently hospitalized for heart failure following the publication of the Randomized Aldactone Evaluation Study (RALES) [32]. Another common and clinically significant drug–drug interaction leading to hyperkalemia involves the concomitant use of potassium-sparing diuretics and NSAIDs [30]. Consequently, patients receiving multiple potassium-sparing drugs should be closely monitored for the development of hyperkalemia, and control of dietary intake of potassium should be exercised to minimize/prevent the risk of hyperkalemia in patients with CKD [27].

β-Blockers

β-Blockers are also commonly used by older adults with CKD for antihypertensive as well as cardioprotective effects. When assessing β-blockers for their potential to cause ADEs, it is important to recognize the heterogeneity among different agents in this class, including their route of metabolism and elimination (e.g. hepatic/metoprolol or renal/atenolol), whether they have intrinsic sympathomimetic activity (ISA) (e.g. pindolol and ace-butolol), whether they are β_1-selective blockers (e.g. atenolol, bisoprolol, and metoprolol), and whether they have α-blocking activity (e.g. carvedilol and labetolol) [15]. Each of these pharmacokinetics/pharmacodynamics characteristics could play an important role in assessing potential ADEs (e.g. hyperkalemia and orthostatic hypotension) in patients with CKD.

Hyperkalemia—β-Blockers are thought to cause hyperkalemia by blocking β_2 receptor-mediated cellular potassium uptake, leading to a redistribution of potassium from intracellular to extracellular compartments [18]. However, this is a relatively small risk as shown in the AASK trial, in which ACE inhibitor use was associated with the greatest risk of hyperkalemia (compared to β-blocker and CCB) [18]. Specifically, among the patients in the ramipril group ($n = 417$), 30 hyperkalemic events (7.2%) occurred; among the patients in the metoprolol group ($n = 428$), 17 hyperkalemic events (4.0%) occurred [18]. Thus, although hyperkalemia can occur with β-blocker therapy, it is less common compared with other antihypertensive classes such as RAAS blockers.

Orthostatic hypotension—Data on β-blocker-associated orthostatic hypotension in general populations of older adults is limited, but some evidence exists to suggest that β-blockers with ISA could have a positive effect on orthostatic hypotension, whereas those with α-blocking activity (e.g. carvedilol) may be associated with increased risk of orthostatic hypotension [25]. However, further research is needed on different β-blockers and their effects on orthostatic hypotension in older adults with CKD.

Calcium channel blockers

CCBs may be used in older adults with CKD because of their antihypertensive and vasodilatory effects. It has been shown that the clearance of most CCBs is generally decreased with aging, resulting in higher drug concentrations in older adults [33]. In addition, older adults with CKD (regardless of pharmacokinetic/pharmacodynamic changes) may experience even greater antihypertensive response to these agents. Among the CCBs, the dihydropyridines (e.g. amlodipine and nifedipine extended-release) are a good choice for older adults with bradycardia, as they do not prolong the atrioventricular conduction time. Furthermore, nondihydropyridines (e.g. diltiazem and verapamil) should be avoided in older adults with atrioventricular block as they do prolong the atrioventricular conduction time and could lead to atrioventricular block. Interestingly, it has been shown that older adults receiving diltiazem or verapamil actually have a similar or even smaller delay in atrioventricular conduction time compared to younger patients suggesting that these agents are relatively well tolerated if used in the appropriate patients [33]. However, CCBs have the potential to cause ADEs in older adults with CKD, including verapamil causing constipation and dihydropyridine (e.g. amlodipine) CCBs causing peripheral edema. In addition, both dihydropyridine and nondihydropyridine CCBs can cause diastolic hypotension, especially when used in combination with other antihypertensives.

Diastolic hypotension—Older adults with CKD are at increased risk for diastolic hypotension from antihypertensive medications. This potential harm was reported in a substudy of a clinical trial of HTN guideline implementation conducted in three Veterans Affairs primary care outpatient clinics of older Veterans (mean age 67.6 years) diagnosed with HTN ($n = 9985$) [34]. The main objective of the study was to examine the effects of CKD (eGFR <60 ml/min/1.73 m^2) on achievement of BP control and antihypertensive medication use. Of note, among those with CKD ($n = 2075$), greater use of antihypertensives (0 vs. 4) was associated with a wider pulse pressure (Δ 8.3 mmHg; $P < 0.001$), which was mostly attributed to lower diastolic pressures (Δ 4.8 mmHg; $P < 0.01$). Diastolic BP has been shown to have a J-shaped association with adverse outcomes, suggesting the potential for harm from targeting aggressive systolic BP control. Interestingly, this pattern of a wider pulse pressure was observed among CCBs users (Δ 15 vs. Δ 6 mmHg in nonusers) but no other antihypertensive classes. Thus, the authors suggest that older adults with CKD may be particularly susceptible to diastolic hypotension from CCBs because of increased pulse pressures.

Moreover, there are several unanswered questions with regard to diastolic HTN and its association with adverse outcomes. Specifically, the exact mechanism of adverse outcomes associated with diastolic hypotension is unclear – is it related to decreased coronary artery perfusion or is it a marker of vascular stiffness? Further, in older individuals isolated systolic HTN is common, but it is unknown if there is a breakpoint where benefit of further reduction in systolic HTN is balanced by increased risk from diastolic hypotension. Although treatment of systolic HTN has been shown to reduce the risk of cardiac events in randomized studies, the alternative of backing off on antihypertensives when there is diastolic hypotension has not been tested.

Other antihypertensives

Finally, older adults with resistant HTN (or contraindications) and CKD may receive antihypertensives from several other classes, including α_1 blockers (e.g. doxazosin, prazosin, and terazosin), central α agonists (e.g. clonidine and methyldopa), and/or direct vasodilators (e.g. hydralazine and minoxidil). These agents are not considered first line and are associated with potential ADEs, including hypotension, volume retention, and syncope [10]. Thus, if use of these antihypertensives is necessitated, careful monitoring of BP and ADEs is warranted.

What should clinicians do?

When treating an older adult with CKD, multiple factors need to be considered to prevent or minimize potential antihypertensive-related ADEs. In the absence of robust literature examining these events in this understudied population, one must consider the individual antihypertensive pharmacokinetic/pharmacodynamic profile concomitantly with the patient's comorbidities and other medications in order to minimize the risk for potential drug–drug interactions (Table 2).

For example, the RAAS blockers would be considered the drugs of choice for older adults with proteinuric CKD and HTN, diabetes mellitus, and/or heart failure [12]. When choosing a specific medication within this class for a patient with significant renal impairment, one could consider selecting an initial reduced dose of an agent that is hepatically eliminated. Another key consideration for this class is cost. ACE inhibitors have historically been more cost-effective because of the availability of generic forms. However, losartan is now available in generic form and more generic ARBs are likely to reach the market in the coming years. ARBs may also be considered in those patients who experience adverse effects (e.g. cough) from ACE-inhibitor therapy. Moreover, the use of combination ACE-inhibitor/ARB therapy deserves further study to assess its relative safety and efficacy when prescribed to the appropriate patients. In addition, the use of the direct renin inhibitors (e.g. aliskiren) in older adults with CKD remains unknown [35].

Diuretics are appropriate for use in older adults with CKD and HTN and/or heart failure. They are effective at potentiating the effects of other antihypertensive classes, such as RAAS blockers. The use of diuretics in patients with renal impairment can be challenging because of frequent changes in fluid status, and thus requires close monitoring. The selection of the diuretic depends partially on the patient's eGFR such that thiazide diuretics may not be as effective as loop diuretics at more severe levels of impairment. In general, the use of thiazide and potassium-sparing diuretics should be avoided in those patients with eGFR less than 30 ml/min. However, some patients with a low eGFR can still receive BP lowering and edema reduction with thiazides.

β-Blockers are commonly used in older adults with CKD and coronary artery disease (CAD), atrial fibrillation, and/or heart failure. Although it is unclear which specific β-blockers are the most beneficial for older adults, it is important for patients with the above conditions to receive some form of β-blocker therapy, if tolerable, because of their beneficial effects on cardiovascular morbidity and mortality [36]. Of note, some β-blockers require renally adjusted doses (e.g. atenolol). Similar to β-blockers, CCBs are frequently prescribed in older adults with CKD and CAD, and/or atrial fibrillation. However, unlike β-blockers, nondihydropyridine CCBs should be avoided in patients with heart failure because of their ability to cause a heart failure exacerbation. In addition, short-acting nifedipine should be avoided in those with a history of CAD as this agent has been shown to increase mortality in such patients [37]. Patients receiving CCBs should be closely monitored for

signs and symptoms of peripheral edema, which may be resolved by a slight dose increase in a diuretic (if prescribed) or a reduction in the CCB dose.

After an antihypertensive regimen has been selected, diligent monitoring is important to minimize the risk of an ADE developing. Although the frequency and interval of monitoring will vary for each patient, there are some general guidelines available for monitoring high-risk medications (including some antihypertensives) in the ambulatory setting [38]. In addition, the KDOQI guidelines offer specific recommendations for the frequency and type of monitoring for ACE inhibitors and ARBs [12]. Overall, the monitoring plan should include key vitals (e.g. orthostatics), laboratory data (e.g. basic metabolic panel), potential drug–drug interactions, and patient/care-giver-reported adverse effects from the current medication regimen. Utilizing a multidisciplinary team approach, including the physician, nurse, pharmacist, and patient/caregiver, could offer the most comprehensive monitoring plan to enhance the pharmacotherapy regimen.

Conclusion

Antihypertensives are frequently used in older adults with CKD and may lead to medication errors and ADEs. Some of the most common ADEs include hyperkalemia, AKI, and orthostatic or diastolic hypotension. Diligent monitoring of laboratory data, vital signs, and potential drug–drug interactions may mitigate serious ADEs caused by antihypertensives in this high-risk patient population. Future research should focus on improving the monitoring of the most prevalent ADEs that occur in older adults with CKD so that future interventions can be developed to predict and prevent patient harm.

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References and recommended reading

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Key points

- Antihypertensives are frequently used in older adults with chronic kidney disease and may lead to medication errors and adverse drug events (ADEs).
- Some of the most common ADEs include hyperkalemia, acute kidney injury, and orthostatic or diastolic hypotension.
- Diligent monitoring of laboratory data, vital signs, and potential drug–drug interactions may mitigate serious ADEs caused by antihypertensives in this high-risk patient population.

Table 1

Summary of clinical trials assessing antihypertensive efficacy in older adults with hypertension

Study abbreviation	Antihypertensives assessed	Randomized sample, *n* (mean [SD] age)	Patients with CKD in trial	Patients with diabetes mellitus in trial
EWP [4]	HCTZ/triamterene; methyldopa	840 patients (72 [8] years)	Unreported	Unreported (patients with diabetes mellitus requiring insulin excluded)
Coope and Warrender [5]	Atenolol; bendrofluazide; methyldopa	884 patients (68.7 [5.2] years in treatment group; 68.8 [5.1] years in control group)	Unreported (baseline mean SCr ~1 mg/dl)	Unreported (baseline mean fasting blood gluose ~85 mg/dl)
SHEP [6]	Chlorthalidone; atenolol; reserpine	4736 patients (71.6 [6.7] years)	Patients with established renal dysfunction excluded	10.1%
MRC-WP [7]	HCTZ/amiloride; atenolol; nifedipine	4396 patients (~70.3 years)	Patients with impaired renal function excluded	Unreported
SYS-EUR [8]	Nitrendipine; enalapril; HCTZ	4695 patients (70.3 [6.7] years in treatment group; 70.2 [6.7] years in control group)	Patients with SCr ≥2 mg/dl excluded	Unreported
STOP-HTN [9]	Atenolol; metoprolol; pindolol; HCTZ/amiloride; enalapril; lisinopril; felodipine; isradipine	6614 patients (76.0 years)	Unreported	10.9%
ALLHAT [10]	Chlorthalidone; amlodipine; lisinopril; atenolol; reserpine; clonidine; hydralazine	33357 patients (66.9 [7.7] years)	Unreported	36.2%
HYVET [11]	Indapamide (sustained-release); perindopril	3845 patients (83.6 [3.2] years in treatment group; 83.5 [3.1] years in control group)	Patients with SCr >1.7 mg/dl excluded	6.8%

ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CKD, chronic kidney disease; EWP, European Working Party on High Blood Pressure in the Elderly Trial; HCTZ, hydrochlorothiazide; HYVET, Hypertension in the Very Elderly Trial; MRC-WP, Medical Research Council Working Party; SCr, serum creatinine; SHEP, Systolic Hypertension in the Elderly Program; STOP-HTN, Swedish Trial in Old Patients with Hypertension; SYS-EUR, Systolic Hypertension in Europe.

Table 2

Clinically significant drug-drug interactions involving antihypertensives

Object drug or drug class	Precipitant drug or drug class	Effect of interaction	Mechanism of interaction
Atorvastatin; lovastatin; simvastatin	Diltiazem, verapamil	Increased concentrations of atorvastatin/lovastatin/simvastatin	Diltiazem/verapamil-mediated inhibition of CYP-3A4 metabolism of atorvastatin/ lovastatin/simvastatin
ACE inhibitors/ARB	Diuretics (potassium-sparing), NSAIDs, potassium supplements	Hyperkalemia; reduced renal function	Combined potassium-elevating effects; additive nephrotoxic effects
Antihypertensives CCB	Vasodilators (nitrates), levodopa Erythromycin, clarithromycin	Orthostatic hypotension Hypotension or shock	Combined hypotensive effects Erythromycin/clarithromycin-mediated inhibition of CYP-3A4 metabolism of CCB
Carbamazepine	Diltiazem, verapamil	Increased effect of carbamazepine	Reduced clearance of carbamazepine
Clonidine	TCA	Inhibition of antihypertensive response	Unknown
Clonidine	Mirtazapine	Inhibition of antihypertensive response	Mirtazapine inhibition of central α2-receptors
Colchicine	Diltiazem, verapamil	Increased effect of colchicine	Diltiazem/verapamil-mediated inhibition of CYP-3A4 metabolism of colchicine; diltiazem/verapamil-mediated inhibition of P-glycoprotein transport of colchicine
Digoxin	Diltiazem, verapamil	Increased effect of digoxin	Reduced clearance of digoxin
Digoxin	Diuretics (loop and thiazides)	Increased effect of digoxin	Diuretic-induced hypokalemia
Diuretics (potassium-sparing)	ACE inhibitors/ARB, NSAIDs, potassium supplements	Hyperkalemia, reduced renal function	Combined potassium-elevating effects; additive nephrotoxic effects
CCB (DHP)	Carbamazepine	Decreased CCB bioavailability	Enhanced CYP-3A4 mediated metabolism of CCB by carbamazepine (enzyme induction)
Lithium	ACE inhibitors/ARB, diuretics (thiazides)	Increased effect of lithium	Reduced clearance of lithium

Data from [28–30,31•]. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CCB, calcium-channel blockers; DHP, dihydropyridine; NSAID, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressants.