Renin-Angiotensin-Aldosterone System Blockade Effects on the Kidney in the Elderly: Benefits and Limitations

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The proportion of the population that is elderly (age ≥65 years) is growing across the world. The increasing longevity of humans results in a higher number of elderly patients presenting with multiple chronic diseases such as hypertension, diabetes, and chronic kidney disease (CKD). These problems increase morbidity and mortality in the elderly. Overactivity of the renin-angiotensin-aldosterone system (RAAS) is associated with the development of hypertension, cardiovascular events, and CKD, so targeting the RAAS is a logical therapeutic approach. Elderly patients present special concerns regarding the benefits versus risks of using RAAS blockers. Plasma renin activity declines with age, which has been attributed to the effect of age-associated nephrosclerosis. Plasma aldosterone is also reduced with age, resulting in a greater risk for hyperkalemia in older individuals, especially when coupled with the age-associated decline in GFR. Moreover, the elderly have a higher frequency of concurrent conditions and are on many medications, which may further increase the risk for adverse effects of RAAS blocking agents. Unfortunately, there is a paucity of literature that is specifically aimed at studying elderly using the RAAS blockers. We present in our in-depth review data regarding benefits and limitations of the use of the RAAS blockades on the various sites along the RAAS pathway for elderly patients. Specific attention was given to the role of combination RAAS blockade therapy and higher monotherapy dosing in the treatment of hypertension in the elderly.

Components and Effects of the RAAS

The RAAS is a widely known enzymatic cascade in which angiotensinogen is cleaved by renin to form angiotensin I (AngI), which, in turn, is converted to angiotensin II (AngII) by angiotensin-converting enzyme (ACE; Figure 1) (16). AngII has direct effects on renal tubular sodium resorption and also acts via receptors in the adrenal glands to stimulate the secretion of aldosterone, which stimulates salt and water resorption by the kidneys (17–19). Through its regulation of body fluids and electrolyte homeostasis, the RAAS acts as a major regulator of BP.

Concerns with RAAS Blocking in the Elderly

Elderly individuals have unique characteristics that make them more liable to experience renal adverse effects with the use of agents that block the RAAS. There is a greater potential risk for further deterioration of renal function in the elderly, especially in patients with advanced CKD (Table 1). In fact, a recent study by Ahmed et al. (20) that evaluated the impact of discontinuing RAAS blockers in elderly patients (mean age 73.3 years) with stages 4 and 5 CKD demonstrated an improvement of estimated GFR from 16.38 to 26.60 ml/min by 12 months after stopping these agents, suggesting that RAAS blockers contribute to further decline in GFR in elderly patients with advanced CKD. Although this study was limited in the number...
of patients studied (n = 52), it adds another reason to be concerned when using RAAS blockers in the elderly with CKD. The adverse effects that are most concerning with RAAS-blocking agents in the elderly are acute kidney injury (AKI), hyperkalemia, and hypotension.

Acute Kidney Injury

Elderly individuals are at more risk for developing AKI. Multiple causes contribute to the AKI noted in the elderly: Reduced renal perfusion by dehydration, hypotension, etc.; renal parenchymal diseases; frequent vascular diseases that affect renal arteries; and drug-related (e.g., use of diuretics and nonsteroidal anti-inflammatory drugs [NSAIDs]) (21). The use of drugs was estimated in one study to account for 36% of the elderly hospitalized with AKI (22). Furthermore, elderly patients have a high probability to require various therapeutic and diagnostic interventions that may also increase the risk for AKI. Unfortunately, the true incidence of AKI in the elderly is difficult to assess accurately by reviewing the literature because of the different criteria used by different studies to define AKI. Hopefully, with the new definitions of AKI (e.g., RIFLE and AKIN criteria), it will be easier to have a uniform definition of AKI.

Hyperkalemia

Plasma renin activity declines with age; this has been attributed to the effect of age-associated nephrosclerosis (23). Plasma aldosterone is also reduced with age, resulting in a greater risk for hyperkalemia in older individuals, especially when coupled with the age-associated decline in GFR (24). This decrease in plasma renin activity and low plasma aldosterone levels in the elderly make the elderly more susceptible to the hyperkalemia noted on using RAAS blockers in this population. The frequent use of NSAIDs in this population further contributes to the risk for hyperkalemia. Different studies used different parameters to define hyperkalemia: Whereas several studies used serum potassium levels of >5 mmol/L to define hyperkalemia, other studies used levels >6 mmol/L. A need for a standard definition of hyperkalemia is required.

Hypotension

Elderly patients with stages 3 and 4 CKD had a higher percentage of systolic and diastolic hypotensive episodes (25). Elderly patients who receive RAAS blockers are at further risk for hypotensive episodes that contribute to patients’ experiencing worse outcomes such as falls and fall-related injuries.

RAAS Blockers in the Elderly

ACE Inhibitors and Angiotensin Receptor Blockers

Rationale. ACE inhibitors (ACEIs) reduce the production of AngII and also prevent the degradation of vasoactive peptide bradykinin. Angiotensin receptor blockers (ARBs) inhibit the RAAS by preferentially binding to the AT-1 receptors on cell membranes (26). Randomized clinical trials have extensively demonstrated that blockade of the RAAS with ACEIs or ARBs not only reduces BP but also reduces proteinuria, ultimately retarding or preventing renal disease progression in diabetic kidney disease (11–15,27–29). Although the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines rec-

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Table 1. Potential risk for further deterioration of renal function that may affect the use of RAAS blockers in the elderly

<table>
<thead>
<tr>
<th>Physiologic changes</th>
<th>Reduction in renal blood flow</th>
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<tbody>
<tr>
<td></td>
<td>Impaired renal autoregulation</td>
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<td></td>
<td>Decrease in renal tubular function</td>
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<td></td>
<td>Diminished repair response</td>
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<td>Hormonal changes</td>
<td>Decrease in RAAS activity</td>
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<td></td>
<td>Decrease in antidiuretic hormone responsiveness</td>
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<tr>
<td>Vascular changes</td>
<td>Reduction in nitric oxide production</td>
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<td></td>
<td>Renal artery stenosis</td>
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<td>Thickening of the intrarenal vascular intima</td>
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<td></td>
<td>Glomerular sclerosis and interstitial fibrosis</td>
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<tr>
<td></td>
<td>Volume depletion</td>
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<tr>
<td></td>
<td>Use of nephrotoxic drugs</td>
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<td>Use of contrast media</td>
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ommend ACEIs or ARBs to delay progression of CKD (30), it is important to note that many of the key studies that showed supporting evidence of beneficial actions of RAAS blockade did not include participants who were older than 70 (11,12,14).

**Studies of the Elderly.** A number of studies evaluated the effect of ACEIs and ARBs on cardiovascular outcomes and as a therapy for hypertension in the elderly. In the Second Australian National Blood Pressure Study (ANBP2), ACEIs led to better cardiovascular outcomes than diuretics (31). No adverse event was reported in this study. Lacourcière (32) reported that irbesartan and enalapril are effective and well-tolerated antihypertensive agents in elderly patients with mild to moderate hypertension. In that study, discontinuation of these drugs as a result of adverse events during active treatment occurred in only three patients of 70 in each group. There were no significant mean changes from baseline or between-group differences in renal function tests; however, this was a short-term study with a relatively small sample size to evaluate the long-term effects of those agents particularly on renal outcomes. The Hypertension in the Very Elderly Trial (HYVET) was designed as a randomized, double-blind, placebo-controlled trial that enrolled 3845 patients who were aged ≥80 years and had hypertension (33). That study was not designed primarily to evaluate the effect of ACEIs on renal outcomes; however, 73.4% of the patients were receiving perindopril in the treatment group at 2 years. The study showed significant benefit in reducing heart failure events in the treatment arm. There were no significant differences in serum creatinine levels as well as in serum potassium among the patients who were followed for at least 2 years. The number of serious events was lower in the actively treated group (348 versus 448; \(P = 0.001\)). These studies confirm the superiority of ACEIs in achieving beneficial cardiac outcomes, even in the elderly. Similarly, many different types of ARBs were investigated in the elderly. The Study on Cognition and Prognosis in the Elderly (SCOPE) was a randomized study that included 4964 elderly patients who had hypertension and were receiving multiple drugs (34). Patients were randomly assigned to receive the ARB (candesartan) or placebo. Reductions in risk for cardiovascular events of 11% were seen for those who were treated with candesartan versus placebo. Adverse effects were similar in both groups. Although this was not primarily designed to evaluate the renal outcomes, the increase in serum creatinine was minimal in both groups with no statistical significant differences noted between the two groups. Kereiakes et al. (35) showed that olmesartan-based treatment effectively lowered BP in the elderly without compromising tolerability. These results were confirmed by Heagerty and Mallion (36), who undertook a study to evaluate olmesartan efficacy and safety in elderly patients and showed that olmesartan reduces BP effectively and was well tolerated even in the very elderly patients (≥75 years). Furthermore, in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial, candesartan, besides being well tolerated, reduced sudden death and death from worsening heart failure in patients with symptomatic heart failure (mean age >65 years) (37). Thus, these studies that evaluated ACEIs and/or ARBs in elderly patients demonstrated some advantages of using these agents in treating hypertension as well as improving cardiovascular outcomes with limited adverse effects.

In the Evaluation of Losartan in the Elderly (ELITE) trial, the effects losartan on renal function were compared with those of captopril. There was no noted difference on renal dysfunction (10.5% in each group) between the drugs, yet hyperkalemia was noted more in the captopril group (22.7 versus 18.8%) (38). In a subgroup analysis among participants who were older than 65 years and enrolled in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, a trial among patients who had type 2 diabetes with macroalbuminuria, losartan was similarly renoprotective in these older participants as it was in the overall study population, as compared with placebo, suggesting that this agent is equally efficacious in elderly patients with albuminuria (39); however, the oldest patient in this study was 74 years old, so it might not be justified to extrapolate the findings from this study to patients who are older than 74 years. Furthermore, the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with Cardiovascular Disease (TRANSCEND) included patients with a mean age of >65 years. The researchers examined adults who had known cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure and could not tolerate ACEIs. Patients were given either an ARB (Telmisartan) or a placebo in addition to standard treatment, and composite renal outcomes (dialysis, doubling of serum creatinine, changes in estimated GFR, or in albuminuria) were followed. Albuminuria increased less with telmisartan than with placebo (32 versus 63%; \(P < 0.001\)), with no significant difference in the composite renal outcome when using telmisartan as compared with placebo (1.96 versus 1.55%) (40). Selected clinical studies that have evaluated the effects of ACEIs and ARBs in the elderly are summarized in Table 2.

**Limitations and Conclusions.** Although both drug classes (ACEIs and ARBs) have been found to be effective, limited data are available regarding renal outcomes in the elderly, and there are considerable safety limitations. Most trials excluded patients with stage 3 CKD and above; therefore, the question of whether the renal adverse effects and/or hyperkalemia that is associated with the use of RAAS blockers should restrict their use remains to be answered. Bakris and Weir (41) reviewed 12 clinical trials of 1102 patients; the average duration of follow-up for all studies was 3 years. The aim of the review was to answer whether the limited initial reduction in GFR or rise in serum creatinine noted with ACEIs or ARBs results in long-term protection against decline in renal function in patients with renal insufficiency. They suggested that an acute rise in serum creatinine of up to 30% that stabilizes within the first 2 months of RAAS-blocker therapy is strongly associated with a good prognosis and long-term preservation of renal function. They further suggested that hyperkalemia (serum potassium >5.6 mmol/L) occurs in <2% of patients who have moderate to severe renal impairment and receive RAAS blockers. On the basis of these data, the authors’ recommendation was that the use of RAAS blockers is appropriate for patients with renal insufficiency as long as serum creatinine rise does not exceed
Table 2. Selected clinical studies that evaluated the effects of RAAS-blocking drugs in the elderly

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wing et al. (31)</td>
<td>MC, open-label,</td>
<td>Elderly patients (aged 65 to 84 years)</td>
<td>ACEI ($n = 3044$) or diuretic ($n = 3039$); followed for a median of 4.1 years</td>
<td>Better cardiovascular outcomes in ACEI group despite the similar BP decline</td>
<td>None reported</td>
</tr>
<tr>
<td></td>
<td>randomized</td>
<td>with hypertension</td>
<td></td>
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<tr>
<td>Lacourcière (32)</td>
<td>MC, DB, randomized</td>
<td>Elderly patients (aged ≥65 years) with mild to moderate hypertension</td>
<td>Irbesartan 150 mg/d ($n = 70$) or enalapril 10 mg/d ($n = 71$) for 8 weeks</td>
<td>Similar reductions at week 8 in both diastolic and systolic BPs</td>
<td>No significant changes from baseline or between-group differences in laboratory values for renal variables</td>
</tr>
<tr>
<td>Pitt et al. (38)</td>
<td>MC, DB, randomized</td>
<td>Elderly patients (aged ≥65 years) with NYHA classes II to IV heart failure</td>
<td>Losartan titrated to 50 mg/d ($n = 352$) or captopril ($n = 370$) titrated to 50 mg three times a day for 48 weeks</td>
<td>Frequency of persisting increases in serum creatinine was the same in both groups (10.5%)</td>
<td>Fewer patients who were on losartan discontinued therapy for adverse experiences</td>
</tr>
<tr>
<td>Lithell et al. (34)</td>
<td>MC, DB, randomized</td>
<td>Elderly patients (aged 70 to 89 years) with stage 2 hypertension</td>
<td>Candesartan 8 mg/d ($n = 2477$) or control ($n = 2460$) for a mean of 3.7 years</td>
<td>No difference was found between groups in major cardiovascular events</td>
<td>Similar in both groups</td>
</tr>
<tr>
<td>Winkelmayer et al. (39)</td>
<td>Post hoc analysis</td>
<td>Elderly patients (aged ≥65 years) with type 2 diabetes</td>
<td>Losartan 50 mg (titrated to 100 mg as needed; $n = 204$) or placebo ($n = 217$) for a mean of 3.4 years</td>
<td>Losartan significantly reduced the event rate of ESRD by 50% compared with placebo</td>
<td>Similar in both groups</td>
</tr>
</tbody>
</table>

DB, double-blind; MC, multicenter; NYHA, New York Heart Association.
30% above baseline within the first 2 months of initiating therapy with RAAS blockade, but the use of these agents should be limited if more rise of serum creatinine and/or hyperkalemia develops. More recently, Weir and Rolfe (42) reviewed 39 clinical trials that investigated the effects on serum potassium levels of RAAS blockers to treat patients who had hypertension, heart failure, or CKD. They demonstrated a minimal increase in serum potassium (0.1 to 0.3 mmol/L) in <2% of the patients who had hypertension and were treated with RAAS-blocker monotherapy, which increased to 5% of the patients when RAAS dual therapy was used. Patients with heart failure were at a greater risk for hyperkalemia (5 to 10%). They concluded that hyperkalemia (serum potassium >5.5 mmol/L) is minimal and probably clinically insignificant in patients who are treated with RAAS blockers and should not be a reason to deny patients the benefits that they are likely to achieve by using these agents. Although these studies were not directed toward elderly patients in particular, it seems reasonable that rather than deny these patients, who stand to benefit from RAAS inhibitors (patients with hypertension, heart failure, and CKD) from receiving these agents, the better approach is to give these agents while trying to minimize the risks that are associated with their intake. Monitoring renal function and electrolytes (especially potassium), avoiding NSAIDs, and consuming a low-potassium diet are strongly recommended when elderly patients are placed on RAAS blockers.

It has not been determined with certainty whether ACEIs and ARBs have similar or better renoprotective effects as compared with one another in various renal diseases. One study showed no such difference; telmisartan was not inferior to enalapril in providing long-term renoprotection in patients with type 2 diabetes (43). Furthermore, the comparative anti-hypertensive effectiveness of ACEIs versus ARBs and their relative advantages and disadvantages are uncertain in the elderly. In light of available evidence, we recommend use of ACEIs or ARBs either to control BP or to retard the progression of CKD in elderly patients, especially in patients with proteinuria, but with measures to minimize risks that are associated with their intake as already mentioned.

**Renin Inhibitors**

**Rationale.** Targeting renin has been considered a logical step because it is the first and rate-limiting step in the RAAS cascade. The first renin inhibitor available, aliskiren, is highly specific for renin and inhibits the catalytic activity of renin by binding to its active site (44). Studies of patients with hypertension have demonstrated that aliskiren is an effective and long-acting antihypertensive agent (45–47). Aliskiren has also been shown to be well tolerated and effective in the elderly (48–50).

**Studies of the Elderly.** The safety and tolerability of aliskiren was studied in elderly patients with systolic hypertension (49). Although aliskiren lowered BP effectively, five patients who received aliskiren exhibited serum potassium levels >5.5 mmol/L (only one patient who took aliskiren 75 mg had serum potassium levels ≥6.5 mmol/L), compared with none of the patients who received lisinopril. None of the patients had serum creatinine levels >50% above baseline. There was no evidence of dosage-related increases in the incidence of adverse events in this elderly population. Aliskiren treatment was also well tolerated in the subset of very old patients (≥75 years). The Aliskiren for Geriatric Lowering of Systolic Hypertension (AGELESS) study, which investigated safety and tolerability of aliskiren in elderly patients with systolic essential hypertension, was presented at the American Heart Association 2008 Scientific Sessions (51). That study compared an aliskiren-based regimen with a ramipril-based regimen. The incidence of adverse events was similar in the two groups with the exception of cough, which was noted more with ramipril (4 versus 13%). In another randomized, double-blind study, Schmieder et al. (50,52) studied the BP-lowering effect of aliskiren 300 mg versus hydrochlorothiazide 25 mg or placebo in 1124 patients with essential hypertension. A post hoc analysis showed that the aliskiren-based regimen provided significantly greater reductions in systolic BP and pulse pressure in 289 elderly (≥65 years) and very elderly (≥75 years) patients. Only two patients of whole study population of 1124 had a creatinine level of >2 mg/dl. Neither drug regimen was associated with adverse events, although the incidence of potassium levels of >5.5 mmol/L was higher with the aliskiren regimen than with the hydrochlorothiazide regimen. That study indicated that aliskiren is well tolerated in elderly and very elderly patients. Finally, the Aliskiren Observation of Heart Failure Treatment (ALOFT) investigators studied the effects of adding aliskiren to an ACEI (or an ARB) and a β blocker in patients with heart failure New York Heart Association classes II to III (48). Although that study was not designed primarily for elderly patients, the mean age was 67 years in the treatment group. Aliskiren was well tolerated, with only slightly (but not statistically significant) higher rates of hypotension and hyperkalemia. There was no notable increase in renal dysfunction in the patients in the study. Selected clinical studies that have evaluated the effects of aliskiren in the elderly are summarized in Table 3.

**Limitations and Conclusions.** The limited available data suggest that renin inhibition with aliskiren is not only effective in decreasing BP but also well tolerated in elderly patients with hypertension. The most important limitation in interpreting the data is the variability in defining adverse effects of renal dysfunction and/or hyperkalemia in these few early clinical trials. Moreover, there are no data on treating patients with a creatinine clearance of <30 ml/min per 1.73 m². Aliskiren has some theoretical advantages that could contribute to its end-organ protection; however, there is as yet no evidence to justify replacing an ACEI or an ARB with aliskiren for renal outcomes in elderly patients.

**Aldosterone Antagonists**

**Rationale.** Aldosterone is an important but often overlooked component of the RAAS. During RAAS blockade by either ACEI or ARB therapy, aldosterone production is initially suppressed but subsequently may return to pretreatment levels; this is known as the aldosterone escape phenomenon (53).
Table 3. Selected clinical studies that evaluated the effects of the direct renin inhibitor aliskiren in the elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verdecchia et al.</td>
<td>MC, DB, randomized</td>
<td>Hypertensive patients, aged ≥65 years</td>
<td>Aliskiren 75 mg (n = 91), or lisinopril 10 mg (n = 94)</td>
<td>All treatment groups lowered BP significantly compared with baseline</td>
<td>No evidence of dosage-related increases in the incidence of adverse events</td>
</tr>
<tr>
<td>Schmieder et al.</td>
<td>Post hoc analysis</td>
<td>Hypertensive patients, aged ≥65 years</td>
<td>Aliskiren 300 mg (n = 145), hydrochlorothiazide 25 mg (n = 144) for 52 weeks</td>
<td>Aliskiren-based regimen provided significantly greater reductions in systolic BP, lower BP was significantly compared with baseline</td>
<td>Incidence of adverse events was similar between the two groups</td>
</tr>
<tr>
<td>Duprez et al.</td>
<td>MC, DB, randomized</td>
<td>Hypertensive patients, aged ≥65 years</td>
<td>Aliskiren 150 mg/day (n = 457), or ramipril 5 mg/day (n = 444) once daily (dosages were titrated as needed for 36 weeks)</td>
<td>All treatment groups lowered BP</td>
<td>Incidence of adverse events was similar between the two groups</td>
</tr>
</tbody>
</table>

DB, double-blind; MC, multicenter.

This phenomenon is a rationale for adding aldosterone antagonists to other RAAS blockers.

Studies of the Elderly. Two different agents that act as aldosterone antagonists are available: Spironolactone and more recently eplerenone. Because of the selectivity of eplerenone for the aldosterone receptor, adverse effects such as gynecomastia and vaginal bleeding seem to be less likely in patients who take eplerenone than in those who take spironolactone (54). The beneficial effects of aldosterone antagonists on cardiovascular outcomes are well established (55,56); however, elderly patients with congestive heart failure seem to be particularly at risk in terms of adverse effects (57,58). Whereas a previous study showed adverse effects of aldosterone in elderly patients not to be common, other studies contradicted those findings. The Randomized Aldactone Evaluation Study (RALES) reported that spironolactone was efficacious in reducing sudden cardiac death and death from progressive heart failure in patients with severe heart failure with minimal serious adverse effects. Serious hyperkalemia was minimal (serum potassium ≥6.0 mmol/L in 2%), and renal insufficiency (creatinine >4.0 mg/dl) occurred in none (55). Subsequently, relatively smaller studies reported that spironolactone-induced hyperkalemia and renal insufficiency are more common in elderly patients than reported in the RALES (57,58). It is worth noting that those studies were not randomized, controlled trials and that different patient characteristics might explain the contradictions between those studies.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), patients who were a mean age of 64 years were randomly assigned to eplerenone (25 mg/d initially, titrated to a maximum of 50 mg/d) or placebo (56). The addition of eplerenone to optimal treatment resulted in additional reductions in overall mortality and the rate of death from cardiovascular causes. Whereas serious hyperkalemia (defined in this study as serum potassium ≥6.0 mmol/L) occurred in more patients in the eplerenone group than in the placebo group (5.5 versus 3.9%; P = 0.002), the incidence of greater elevation in serum potassium (>7 and >8 mmol/L) was similar in both groups. In the subset analysis of the EPHESUS, eplerenone had a similar adverse effect profile to placebo, with the exception of increased incidence of hyperkalemia (serum potassium ≥6.0 mmol/L; 1.7-fold) in hospitalized patient groups with a mean age of >65 years (59). Although not primarily designed as studies of elderly patients, several other studies that included patients who were a mean age of ≥65 years showed that use of spironolactone or eplerenone in this older population was tolerated and safe (55,60,61).

Limitations and Conclusions. Aldosterone antagonists may be generally well tolerated, but, in elderly patients, they can cause life-threatening hyperkalemia, especially when combined with other RAAS blockers. Closer laboratory monitoring and more judicious use of aldosterone antagonists may reduce the occurrence of this complication. Although eplerenone with a profile slightly different from that of spironolactone may have fewer adverse reactions (54), both aldosterone antagonists seem to be closely associated with an increased risk for renal adverse effects.
effects. Nevertheless, there no clinical studies have demonstrated superiority of one aldosterone antagonist over the other.

**Intense RAAS Blockade: Combination Therapy and Higher Monotherapy Dosages**

**Rationale.** Inhibition of the RAAS at various points along the cascade (Figure 1) with monotherapy does not always result in complete RAAS blockade (62). ACEIs, for instance, do not entirely block production of AngII, because ACE accounts for approximately 60% of the AngI-to-AngII conversion and the remainder is converted through the activity of alternative pathways (chymase, cathepsin G) (63). The combination of ACEIs and ARBs has been proposed to maximize RAAS blockade; however, combining RAAS blockers may lead to more frequent adverse events than monotherapy (64).

**Studies of the Elderly.** In the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), 25,620 participants who were a mean age of 66 years were randomly assigned to ramipril 10 mg/d, telmisartan 80 mg/d, or a combination of both drugs (65). The frequency of the composite primary renal outcome of dialysis, doubling of serum creatinine, and death was similar with telmisartan and ramipril (13.4% versus 13.5%, respectively) but increased with combination therapy (14.5%; \( P = 0.037 \)). The combination therapy did not show clear benefit even though proteinuria was reduced. It must be pointed out that most of the patients in that study had normal renal function without proteinuria. Although not primarily designed as studies of elderly patients, the patients who were included in the Valsartan in Acute Myocardial Infarction (VALIANT) (66) had a mean age of \( \geq 65 \) years. Dosage reductions and permanent discontinuations of study medication for renal causes were more frequent with the combination of valsartan and captopril in the VALIANT study (66).

Clinical studies have also evaluated the effects of dosages of ACEIs and ARBs that exceed those approved by the Food and Drug Administration for lowering BP (67,68). Hollenberg et al. (67) reported that higher dosages of valsartan reduced albuminuria more than the more commonly used 160-mg dosage. Forty percent of the patients were aged \( \geq 65 \) years in their study. Fourteen patients developed hyperkalemia (serum potassium \( >5.5 \) mEq/L) that was neither dosage related nor life threatening. No patient developed azotemia.

A subgroup analysis of a randomized, double-blind trial of patients with hypertension demonstrated that the effects of aliskiren, valsartan, and the combination of both were equally well tolerated in elderly patients and patients who were younger than 65 years (69). Again, McMurray et al. (48) reported that addition of aliskiren to an ACEI or anARB was effective in patients who were a mean age of \( \geq 65 \) years. Both the treatment and placebo groups had similar incidences of hyperkalemia and renal dysfunction.

It has been shown that the addition of aldosterone blocker to other RAAS blockers further reduces proteinuria in patients with CKD (70). Unfortunately, the available data are limited in that regard in the elderly. In an analysis of case series, it was observed that a combination of ACEIs and spironolactone caused significant increase in serum potassium levels in elderly patients with a mean serum creatinine level of 1.9 mg/dl (71).

**Limitations and Conclusions.** Elderly patients may need combination therapy to achieve optimal end-organ protection. The combination of an aldosterone antagonist and other RAAS blockers should be a useful strategy if patients are carefully selected and carefully monitored. Elderly patients require further close monitoring or termination of aldosterone antagonist administration. No outcome studies have demonstrated a benefit on survival or on delaying progression of kidney disease in elderly patients who have CKD and are treated with ACEIs or ARBs in combination with aldosterone antagonists. In addition, no clinical studies have demonstrated superiority of one combination therapy over another. With the limited available data, unless there is compelling indication, combination therapy should be avoided in the elderly with CKD.

**Conclusions and Recommendations**

It is well established that patients with CKD require aggressive cardiovascular risk reduction; however, not all elderly patients with CKD require an emphasis on therapy to delay progression of kidney disease, except for patients with diabetes or significant proteinuria. Physiologic and pathophysiologic changes that are associated with aging and comorbidities should be considered when choosing drugs for the elderly. Thus, in deciding whether to start RAAS-blocking agents in an older patient with CKD, the clinician should consider whether the patient has proteinuria, whether his or her CKD is clearly progressive, and whether he or she has other health concerns or priorities that might make another antihypertensive agent preferable. It has been shown that potassium monitoring decreases RAAS blocker--induced hyperkalemia, especially in patients who have both diabetes and CKD (72). Thus, RAAS blockade, particularly in patients with CKD, mandates careful monitoring for acute renal failure and hyperkalemia, often requiring extra laboratory testing and clinic visits after initiation of these agents and after any change in dosage. It is advisable to check renal function and serum potassium levels 1 to 2 weeks after starting RAAS blockers in these patients because they usually have some degree of renal impairment. Dietary guidance about potassium intake and avoidance of NSAIDs and other drugs that increase serum potassium may help to avoid hyperkalemia in this patient group. There is also a paucity of evidence on when these agents should be discontinued. A recent small study of patients who were a mean age of 73 years reported that discontinuation of RAAS blockade delayed the onset of renal replacement therapy for patients with advanced CKD (20). Conversely, Segura et al. (73) demonstrated that absence of ACEIs is a predictor of poor renal events in patients with hypertensive nephrosclerosis, emphasizing the benefits of using ACEIs as part of the therapy for patients with hypertensive nephrosclerosis.

Although most available data on the use of RAAS-blocking agents in the elderly have shown promising results, caution should be used in the interpretation of these trials. Despite the risks of treating the elderly with RAAS blockade, there are far greater precise risks of not using these agents, with many
studies showing superiority of therapy of RAAS blockers versus other agents in the treatment of hypertension as well as delaying progression of CKD. Clearly, long-term outcome studies are needed to define the therapeutic role and safety concerns that arise with the use of RAAS blockers in elderly patients with CKD, and these outcome studies need to address slowing progression to ESRD.

Disclosures

None.

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