The efficacy and safety of renin angiotensin system (RAS) inhibition for lowering blood pressure in older populations has been demonstrated in a number of clinical trials. Whether a patient’s age influences the overall ability of these drugs to lower blood pressure and protect against progress of cardiovascular and kidney disease has been the focus of few clinical trials. Herein, we review the mechanism of action of the renin angiotensin cascade and then discuss the clinical evidence surrounding the use of RAS-blocking drugs in the older population.

**RENIN ANGIOTENSIN SYSTEM BLOCKADE**

RAS is an autocrine, paracrine, and enzymatic cascade that can regulate blood pressure, cell proliferation, and vascular remodeling.\(^1\) Renin is synthesized by the juxtaglomerular cells in the afferent glomerular arterioles in the kidney. The release of renin occurs in response to certain physiologic stimuli, such as renal hypoperfusion, that occur in the setting of volume depletion and hypotension.

Renin release leads to cleavage of angiotensin I from angiotensinogen, which is primarily produced in the liver. Angiotensin I is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE), which is found in the lung, in the vascular endothelial cell luminal membrane, and locally in the glomerulus.\(^2\) Over the past 40 years, it has been recognized that there are renal and other extrarenal RAS pathways leading to angiotensin II synthesis located in the brain, vascular endothelium, and adrenal gland. It is speculated that such systems are important in the regulation of vascular injury and repair responses.

Locally synthesized angiotensin II in the vascular endothelium and that generated by the kidneys may play a pivotal role in the development of hypertension by regulation of vascular tone, renal vasoconstriction, and sodium retention.
It has been recognized that plasma renin activity falls with increasing age. Therefore, it might be anticipated that the blood pressure response to RAS inhibition may be reduced in older persons. In contrast, Ajayi and colleagues demonstrated greater blood pressure control with enalapril and intravenous enalaprilat in the older population (age, 65–73 years) compared with that in the younger population (22–30 years). Physiologic aging is associated with increased angiotensin II production in arterial tissue. This may explain the age-related decrease in endothelial function in the healthy older population. The localized angiotensin II production may explain the beneficial effect of RAS inhibition even in older patients with low circulating angiotensin II levels or plasma renin activity. In recent years, the pathophysiological implications of the RAS pathway has been a major focus of attention, and inhibitors of the RAS such as ACE inhibitors, angiotensin II receptor blockers (ARBs), and direct renin inhibitors have become important clinical tools in the treatment of blood pressure and cardiovascular and renal diseases.

RENIN ANGIOTENSIN SYSTEM AND AGING

Older persons in better health have a longer life expectancy than that of persons in poorer health, yet they have similar cumulative health care expenditures until death. A person with no functional limitation at 70 years of age has a life expectancy of 14.3 years and expected cumulative health care expenditures of about $136,000 (in 1998 dollars). It makes important sense to focus on ways of diminishing the morbidity and mortality of cardiovascular disease, especially in the healthy, older population. Aging is strongly correlated with endothelial dysfunction in animals and humans. Mukai and colleagues have demonstrated that long-term inhibition of the RAS ameliorates the endothelial dysfunction associated with aging by inhibiting the synthesis of cyclooxygenase related vasoconstriction factors and superoxide anions. Will this effect prove helpful in reducing the risks of vascular disease? Will RAS inhibition in the older population have a different effect compared with that in younger persons on the different vascular pathologic processes that are more prevalent with aging? What age is the cutoff for dichotomizing the population into older versus younger, given that age and life expectancy are moving targets? Although there are numerous studies addressing different questions and multiple prevalent diseases, such as diabetes mellitus and cardiovascular and kidney diseases, few target the older population (Fig. 1). This is partly due to the ethical dimension that is placed to protect this more fragile population with multiple comorbidities, which could possibly confound clinical trials. Hence, most of the data used in this review were extracted from trials that had an average age of 65 years, with a lower age limit of 55 years and an upper age limit of 80 years.

RAS INHIBITION ADVANTAGES IN OLDER PATIENTS

Congestive Heart Failure

A meta-analysis of 32 randomized, controlled trials by Garg and Yusuf in 7105 patients, with advanced New York Heart Association functional class II or worse and ejection fraction less than 0.35 to 0.4 with or without limitation of exercise, concluded that ACE inhibitors reduced total mortality (odds ratio, 0.77; 95% confidence interval [CI], 0.67–0.88; P<.001) and the combined risk of mortality and hospitalization for congestive heart failure (CHF). When these patients were dichotomized based on age less than or greater than 60 years, there was no observable difference in the benefits of ACE inhibitor on all-cause mortality. In the Effect of Enalapril on Survival in Patients with reduced Left Ventricular Ejection Fraction (Studies of Left Ventricular Dysfunction) trial
The addition of enalapril significantly reduced morbidity and mortality in patients with CHF. The effect of enalapril on 12-year survival and life expectancy follow-up in patients with and without symptomatic left ventricular dysfunction demonstrated that, compared with placebo, enalapril equally improved long-term survival in persons younger and older than 61 years of age.

The Survival and Ventricular Enlargement (SAVE) Trial, which investigated the effect of captopril versus placebo on morbidity and mortality in patients with left ventricular dysfunction post myocardial infarction patients, demonstrated that all-cause mortality was significantly reduced and a greater benefit observed in patients aged 65 years and older.

In a retrospective study of an older population with CHF, where the mean age was 85 years, The Systematic Assessment of Geriatric Drug Use via Epidemiology study group demonstrated a 10% reduction in the mortality rate among the cohort that used ACE inhibitors in comparison with the group that used digoxin. However, the question of efficacy of ACE inhibitors among older patients with asymptomatic left ventricular dysfunction remains controversial.

The efficacy of ACE inhibitors and ARBs in reducing cardiovascular morbidity and mortality in older patients with heart failure has been established. The effect of ACE inhibition—angiotensin receptor blockade—or a combination regimen on events in older persons postmyocardial infarction complicated by left ventricular dysfunction has been investigated by Pfeffer and colleagues in a double blind, placebo-controlled (Valsartan in Acute Myocardial Infarction trial) trial, with a mean age of 64.8 ± 11.8 years. This trial compared the effect of valsartan, captopril, or both on cardiovascular outcomes and demonstrated that valsartan is as effective as captopril in improving survival and reducing cardiovascular morbidity among patients with high cardiovascular risk after myocardial infarction. However, combination therapy did not
show any advantage in reducing mortality or cardiovascular morbidity and mortality. The beneficial effect of both valsartan and captopril was similar in patients older as well as younger than 65 years of age.

Angiotensin II, which is a potent vasoconstrictor and growth-stimulating hormone contributes to progression of heart failure. The long-term effect of adding an ARB valsartan to patients with heart failure was evaluated by Cohn and colleagues\textsuperscript{13} in a randomized, placebo-controlled, double-blind, parallel-group trial, of patients with a mean age of 62 years. Valsartan reduced combined morbidity and mortality incidence by 13.2\% compared with placebo (relative risk, 0.87; 97.5\% CI, 0.77–0.97; $P = .009$) and improved clinical signs and symptoms of heart failure. The beneficial effect of valsartan was consistent among older as well as younger persons.

Whether ARB alone, or with ACE inhibitor, is effective in managing older patients with heart failure has been investigated by Pfeffer and colleagues\textsuperscript{14} by studying the effect of candesartan on mortality and morbidity in patients with chronic heart failure (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity overall program). This study was a randomized, double-blind, placebo-controlled trial in patients with a mean age of 65 years. Candesartan was well tolerated, and it reduced cardiovascular morbidity and mortality irrespective of baseline ejection fraction or type of treatment. Similarly, patients aged 75 years and older demonstrated as much benefit with candesartan as did younger patients. Thus, these data demonstrate that RAS blockade in persons with and without symptomatic heart failure provides comparable mortality and morbidity benefits across all age groups, including patients older than 75 years.

**Hypertension**

Hypertension is a major risk factor for coronary artery disease, stroke, and progression of diabetes-related kidney disease in older persons. As the number of older individuals increases among the general population, it is important to note that the risk of medication-related adverse outcomes also increases with age. Thus, more studies are needed to evaluate the risks and benefits of different antihypertensive therapies such as RAS inhibitors in older persons. Unfortunately, most of the studies are performed in younger populations.\textsuperscript{15} There is continued debate over which antihypertensive medication is most appropriate as a first-line therapy in the older population. In the past, thiazide diuretics have been recommended as the preferred agents (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). However, since older persons often have multiple medical comorbidities, other agents such as RAS inhibitors are an important consideration. Hypertension in older persons is characterized by increased peripheral resistance and decreased arterial compliance. RAS blockade leads to dilatation of small and large arteries, which helps correct these 2 age-related pathophysiological changes.\textsuperscript{16} Plasma renin activity is known to fall in older populations, yet some studies have demonstrated that ACE inhibitors lead to greater fall in blood pressure in older patients compared with that in younger patients. In a single-blind, placebo-controlled, randomized, crossover study in normotensive healthy young (22–30 years) and older (65–73 years) persons, both enalapril and intravenous enalaprilat were found to reduce blood pressure effectively. The decrease in blood pressure was numerically greater in the older group. However, this study was limited by the small number of subjects used, and baseline blood pressure was higher in the older population.\textsuperscript{15} However, not all studies showed the same results. Some feel that RAS inhibitors may be more effective in younger rather than in older populations.\textsuperscript{16}

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which included patients who were 55 years of age or older, chlorthalidone
and lisinopril were found to have similar efficacy for reducing the primary endpoint of all-cause, fatal, and nonfatal coronary heart disease (CHD) events (relative risk (RR), 0.99; 95% CI, 0.91–1.08) and the secondary outcomes of all-cause mortality, combined CHD, peripheral arterial disease, and end stage renal disease (ESRD). Nonetheless, the conclusion of the study was that thiazide-type diuretics (chlorthalidone) were superior in preventing one or more of the cardiovascular outcomes in comparison to the ACE inhibitor (lisinopril). This conclusion was likely based on the higher overall risk for stroke and combined cardiovascular events in the lisinopril group compared with that in the diuretic group, because patients on chlorthalidone had their blood pressure much more effectively controlled than did the patients on lisinopril.\textsuperscript{17} However, older patients will likely require two or more drugs to lower their blood pressure, and thiazides are quite effective in lowering blood pressure with RAS-blocking drugs such as ACE and ARB.

The Losartan Intervention for Endpoint Reduction (LIFE) study, which was a double-blind, randomized trial, compared losartan and atenolol plus other medications in older patients with isolated systolic hypertension (ISH) (mean age, 70 years). The mean sitting systolic blood pressure was reduced by 28 mm Hg in both losartan and atenolol regimens. However, patients who were on losartan had 25\% relative risk reduction (RRR) in cardiovascular death, stroke, and myocardial infarction. Thus, this trial showed that the RAS-blocking regimen is superior to a beta-blocking regimen in reducing cardiovascular events with ISH in older patients.\textsuperscript{18}

Although RAS-blocking drugs are well tolerated, in older populations, they will often need to be combined with other drugs such as thiazide diuretics or calcium channel blockers to help reduce systolic blood pressure. Since systolic blood pressure is the most important treatment variable in older populations, more trials are needed to establish which drugs are best to use with RAS inhibitors to both lower pressure and cardiovascular events. The recently published Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)\textsuperscript{19} study suggests that calcium channel blocker when combined with RAS-blocking therapy may have some advantages in older populations with cardiovascular risk factors.

**Cardiovascular Disease**

In The Heart Outcomes Prevention Evaluation Study, 9,297 high-risk subjects (age, 55 years or older) with high risk for cardiovascular events (without left ventricular dysfunction) were randomized to treatment with ramipril versus placebo in addition to their current cardiovascular-risk-reducing therapy. Ramipril treatment reduced the rates of death from cardiovascular disease (RR, 0.74; \(P<.001\)), myocardial infarction (RR, 0.8; \(P<.001\)), revascularization (RR, 0.85; \(P=.002\)), cardiac arrest (RR, 0.63; \(P=.03\)), and heart failure (RR, 0.77; \(P<.001\)) compared with placebo. However, there was also a 3/2 mm Hg blood pressure advantage in the ramipril treatment group.\textsuperscript{20} Thus, RAS inhibition does help in older populations. Similar results were observed in the The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial study when an ACE inhibitor-based or an ARB-based antihypertensive regimen was compared on cardiovascular events in an older population with risk factors for cardiovascular disease.\textsuperscript{21}

Hypertension is a well-documented risk factor for myocardial infarction, heart failure, and atherosclerosis. In a secondary analysis of the SAVE trial, the investigators evaluated the efficacy of captopril versus placebo in younger and older patients (age, more than 60 years) who survived a myocardial infarction. The overall incidence of combined cardiovascular events, such as heart failure, fatal and nonfatal recurrent myocardial infarction, and cardiovascular and all-cause death, was less in the
captopril group in comparison with that in the placebo group in both hypertensive and normotensive patients. Greater benefit was observed in patients who were older than 65 years (absolute risk reduction 8.2%).

Not all studies have demonstrated the benefit of RAS inhibition in the secondary prevention of CHD. These conflicting results may be explained by the age difference in the different trial populations. Trials that enrolled older persons demonstrated the beneficial effect of ACE-inhibitor therapy in secondary prevention of CHD, because older patients had greater cardiovascular risk and higher mean blood pressure. Thus, some of the most consistent data with RAS inhibition benefits on cardiovascular disease are observed in older populations.

Cerebrovascular Disease

Effective blood pressure control is beneficial in reducing the risk of stroke. However, there is limited evidence of benefit in treating patients 80 years of age and older. Most previous studies either excluded patients older than 80 years, or the number of subjects enrolled was small. In the Hypertension in the Very Elderly Trial, which included only hypertensive patients who were 80 years of age or older, patients were randomized to receive indapamide alone, or with perindopril, versus placebo. The goal blood pressure with treatment was 150/80 mm Hg. Those who were in the active treatment group demonstrated a 30% reduction in the rate of fatal and nonfatal cerebrovascular accidents (95% CI, -1 to 51; \( P = .06 \)) and a 39% reduction in the rate of death from stroke. More importantly, there was no significant change in baseline serum potassium level or creatinine between the two groups. The investigators concluded that even older patients, older than 80 years, derive benefit with antihypertensive therapy using thiazide diuretics with or without ACE inhibitors.

In the ALLHAT trial, the importance of blood pressure control on stroke prevention was evident. Patients who received lisinopril demonstrated a higher risk of stroke in comparison to the group on chlorthalidone (6.3% versus 5.6%; RR, 1.15; 95% CI, 1.02–1.30). This important difference was attributed to lower blood pressure attained in the chlorthalidone group compared with that in the lisinopril group (Fig. 2). In a randomized, double-blind, placebo-controlled trial (Perindopril Protection Against Recurrent Stroke Study [PROGRESS]) in patients with a prior history of cerebrovascular accident or transient ischemic attack, with a mean age 64 years, treatment with perindopril (4 mg/d) with or without the use of a diuretic (indapamide) was found to decrease the risk of stroke. The investigators concluded that combination therapy with RAS blockade and a diuretic reduces the risk of stroke recurrence among hypertensive patients.

In the LIFE trial, the ARB-based regimen demonstrated a reduction in nonfatal and fatal stroke, cardiovascular mortality, all-cause mortality, and new-onset diabetes compared with a beta-blocker-based antihypertensive regimen. The majority of patients had systolic hypertension and left ventricular hypertrophy, which is a major risk factor for stroke. This study provided more evidence that RAS blockade (with an ARB) provides an important opportunity to reduce the risk of stroke in older persons. In summary, blood pressure control with the use of RAS blockade and other drugs in older populations reduces the risk of stroke and its related disabilities.

Left Ventricular Hypertrophy

The prevalence of Left ventricular hypertrophy (LVH) increases with age. It is known that angiotensin II plays a role in development of LVH. LVH prevalence by echocardiography is common and is found in 33% of men and 49% of women by the time they are 70 years or older. LVH is recognized to be an independent predictor for CHD events,
heart failure, and cerebrovascular accidents. In a meta-analysis of double-blind, randomized, controlled trials, LVH regression occurred in 13% of patients receiving ARB, 11% with calcium channel blockers, 10% with ACE inhibitors, 8% with diuretics, and 6% with beta-receptor blockers.27

Secondary analyses of clinical trials demonstrate that regression of LVH is associated with reduced cardiovascular risk. The LIFE study (previously discussed) evaluated the long-term effect of the ARB losartan in comparison to the beta-blocker atenolol in older patients with LVH. The investigators noted that losartan was more effective than atenolol in reducing LVH. Despite similar changes in blood pressure, the losartan-based regimen was associated with 25% RRR in the cardiovascular mortality, fatal and nonfatal stroke, and total mortality.18 Thus, RAS blockade with similar blood pressure reduction in older persons results in LVH regression and a reduction as that seen with beta blockade of cardiovascular and stroke mortality.28

**Chronic Kidney Disease and Diabetic Nephropathy**

With aging, chronic diseases, including chronic kidney disease (CKD), are expected to increase with a resultant rise in disability and financial burden on the health care system.29 For example, in the National Health and Nutrition Examination Survey database, the prevalence of CKD increases with age, such that the prevalence for stage 3 to 4 CKD increases from 27.8% to 37.8% after the age of 70 years.30

The ALLHAT study did not demonstrate differences in the rate of CKD progression based on whether the patients were treated with diuretic, calcium channel blocker, or ACE inhibitor. However, the study did not enroll patients with kidney disease and...
lacked the power to evaluate the possible differences between therapies. The Ramipril Efficacy in Nephropathy study was a prospective evaluation of 322 patients with nondiabetic renal disease and proteinuria who were treated with the ACE inhibitor, ramipril, or placebo. Ramipril treatment slowed the progression of renal disease. The renoprotective and dialysis-saving effects were independent of the severity of kidney disease.\(^{29}\) However, most of the patients were younger than 65 years of age with a median age of 50 years. During the study period, those with proteinuria less than 2 g/24 h of protein or polycystic kidney disease did not benefit by treatment to an appreciable extent.\(^{31}\)

The Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study compared a losartan-based regimen and a placebo-based regimen in patients with type 2 diabetes with nephropathy. The average patient age was 60 years. The patients were followed for a mean period of 3.5 years. The study demonstrated that the ARB-based regimen (losartan) reduced the risk of serum creatinine doubling by 25% and (ESRD) by 28% independent of blood pressure reduction.\(^{32}\) This benefit was observed regardless of age. The Irbesartan Diabetic Nephropathy trial had a similar age distribution as that of the RENAAL study, with an average age just under 60 years. In this study, three different blood pressure lowering regimens, amlodipine-based, irbesartan-based, or placebo-based multiple drug regimens, were used in a randomized design in patients with type 2 diabetes and nephropathy. As in the RENAAL study, the irbesartan-based therapy slowed diabetic nephropathy progression by increasing the time to serum creatinine doubling, ESRD, and all-cause cardiovascular events compared with the other regimens.\(^{33}\) The results of these studies clearly demonstrate the utility of RAS blockade (either ACE inhibitor or ARB, depending on the study) to prevent progression of renal disease even in older populations. We suspect that this benefit is evident regardless of age, even though none of these studies purposely studied patients older than 75 years.

In a multinational, randomized, double-blind, placebo-controlled trial, the added benefit of RAS inhibition by using a direct renin inhibitor (aliskiren) and an ARB (losartan) was evaluated in both young and older individuals with type 2 diabetes complicated by nephropathy and hypertension (subjects ages ranged from 18–85 years with a mean of \(~60\) years). The trial demonstrated that RAS inhibition using both a renin inhibitor and ARB had a greater antiproteinuric effect than the ARB alone, independent of the blood pressure lowering effect.\(^{34}\) Thus, this type of dual RAS inhibition may be useful in older populations.

**Physical Performance**

It has been recognized that there is an age-related decline in physical function and exercise capacity. This decline eventually leads to disability in the older population. The functional decline is usually caused by underlying comorbidities, that is, stroke, CHF, and chronic degenerative joint disease, or sometimes may be related to cognitive functional decline. Onder and colleagues theorized that ACE inhibitors have direct metabolic and mechanical effects on skeletal muscle by affecting the myosin heavy chain. This stimulates the conversion of muscle fibers to a slow, aerobic, and fatigue-resistant isoform. Moreover, ACE inhibition augments muscle sensitivity to insulin and glycogen storage. An increase in kinins, as a result of ACE inhibition, is thought to enhance skeletal-muscle blood flow through its vasodilator effect.\(^{35}\)

It is also speculated that an inhibitory effect of ACE inhibitors on the inflammatory mediators, interleukin-6, and tumor necrosis factor-\(\alpha\), could improve muscle function and decrease disability.\(^{36}\) Graziano and colleagues evaluated the effects of ACE inhibition in an observational study on muscle strength in 755 hypertensive women with an
average age 78.9 years. They were selected from the Women’s Health and Aging Study population. They observed that treatment with an ACE inhibitor may decrease or stop the deterioration of muscle strength in older women with hypertension.35

Another smaller trial (n = 95), mean age 78.8 years, studied older patients with the ACE inhibitor perindopril or placebo. The trial demonstrated that perindopril significantly improved exercise capacity in functionally limited older subjects who had no CHF. As a result of this improvement, they were able to maintain health-related quality of life (Fig. 3).37 ACE inhibition is also known to reduce physical function decline in older persons with CHF.11,35

In summary, there is evidence of positive association between RAS blockade and muscle-function improvement in the older patients. This improvement may hinder health-related quality-of-life deterioration. ACE inhibitors have multiple functional beneficial effects on muscle function. Whether ARB has a comparable beneficial effect needs further evaluation.38 Future clinical trials with longer follow-up are needed to establish the durability of improvement and impact on survival.

Cognitive Impairment

With increasing life expectancy, the prevalence of vascular and Alzheimer’s dementia is expected to increase from 33 million in 2007 to 81.1 million by 2040. There is substantial evidence that antihypertensive drug therapy reduces the incidence of dementia and cognitive impairment.8 On the other hand, hypertension and stroke are associated with increased risk of vascular dementia in older persons.39 There is an interest in evaluating the effect of RAS blockade on the risk of dementia, as an ACE-gene insertion deletion polymorphism is implicated in Alzheimer’s dementia pathogenesis.40 ACE is overexpressed in the hippocampus, frontal cortex, and caudate nucleus of patients with Alzheimer’s disease.41 Thus, targeting the RAS may be of benefit in older persons at risk of dementia.

In a randomized, prospective trial 162 older, long-term facility residents with hypertension (BP >140/90 mm Hg), with mild-moderate Alzheimer’s dementia, and aged 65 years and older, patients were randomized to a brain-penetrating ACE inhibitor, a non–brain-penetrating ACE inhibitor, or a calcium channel blocker. The investigators

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**Fig. 3.** Change in 6-min walking distance in perindopril and placebo groups from baseline to 10 wk and 20 wk. (From Sumukadas D, Witham MD, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ 2007;177(8):867–74; with permission.)
demonstrated slower mean 1-year decline in the Mini Mental State Examination score in the brain-penetrating ACE inhibitor-regimen group (0.6 ± 0.1) in comparison with the non–brain-penetrating ACE inhibitor-regimen (4.6 ± 0.3) and calcium channel blocker-regimen (4.9 ± 0.3) groups. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a double-blind, placebo-controlled trial (n = 6105), with patients with a mean age of 64 years. Patients with previous stroke or transient ischemic attack were randomized to a perindopril, perindopril and indapamide, or matching placebo regimen. The study demonstrated that patients receiving the ACE inhibitor, perindopril, had a lower risk of dementia and progression of their cognitive decline associated with recurrent stroke. In the SCOPE trial, patients aged 70 to 89 years with systolic hypertension (160–179 mm Hg) were randomized to receive candesartan or placebo. During the study, the investigators noted that there was more blood pressure reduction with candesartan-based therapy, but there was no difference in cognitive decline or dementia development observed between the candesartan or placebo groups. Unfortunately, only 25% of the active treatment group were taking their originally assigned regimen, which likely limits the interpretability of the results. Thus, apart from high blood pressure control, RAS blockade may play a direct role in reducing the risk of Alzheimer’s dementia and cognitive decline in older patients. Whether one category of antihypertensive drug, and particularly the RAS blockers, is more effective in slowing cognitive decline and development of dementia compared with other drugs is unknown.

RAS INHIBITION LIMITATIONS IN OLDER PATIENTS

In the medical community, there is concern that RAS inhibition in older persons may aggravate the risk of hypotension, which could lead to increased risk of fall. Other concerns about RAS inhibition include reduction in kidney function, hyperkalemia, angioedema, and cough. The results of multiple studies do not support these concerns, as the risk of adverse events does not appear to be different in older persons compared with that in younger persons. In fact, the overall incidence of serious adverse events is often lower in patients on RAS inhibitors (4.6%/6.6%). Studies with RAS inhibitors in older hypertensive patients do not show an increased risk of side effects despite effective blood pressure reduction. Even combining diuretics with RAS inhibitors in older patients does not appear to increase the risk of changes in serum creatinine or potassium. In general, the data for clinical trials demonstrate no evidence that age plays a role in the risk of adverse events with RAS inhibitor drugs.

SUMMARY

RAS inhibitors are effective and well-tolerated antihypertensive drugs for older persons. The efficacy and safety of these drugs are also evident in older persons even in the presence of CHF, LVH, and left ventricular dysfunction. There is evidence that the RAS plays an important role in the pathobiology of vascular disease among the older population. These drugs should be considered routinely in older populations due to their tolerability and cardiovascular benefits. Individualized use of these drugs is necessary to properly adjust the dose and use them in conjunction with other drugs.

ACKNOWLEDGMENTS

We thank Tia A. Paul, University of Maryland School of Medicine, Baltimore, MD, for editing the manuscript.
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