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Role of the renin–angiotensin system in age-related sarcopenia and diastolic dysfunction

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Abstract

The purpose of this review is to describe how recent pharmacological and genetic studies have contributed to our understanding of the role of the renin–angiotensin system (RAS) in age-related sarcopenia and diastolic dysfunction. Treatment strategies are limited in the context of both of these conditions, although interventions, which include blockade of the RAS (using angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) are successful and lead to improvements in functional outcomes that are not necessarily mediated by hemodynamic effects of the drugs. Studies in animal models of sarcopenia and diastolic dysfunction point to ubiquitous effects of RAS blockade on multiple biological mechanisms, including inflammation, oxidative damage and metabolic dysregulation. Therefore, a re-evaluation of the use of these drugs in other conditions should be considered for maintaining functional independence in older individuals.

Keywords

ACE inhibitors; ACE polymorphisms; aging; angiotensin-receptor blockers; diastolic dysfunction; disability; exercise capacity; renin–angiotensin system; sarcopenia

The renin–angiotensin system (RAS) is a ubiquitous hormonal pathway that modulates a variety of physiological functions, including sodium balance, body fluid volumes, cardiac output and arterial blood pressure. This homeostasis is primarily mediated through the production and modulation of the peptide angiotensin II (ANG II). ANG II is produced through a cascade that begins with the cleavage of angiotensinogen, an inactive peptide produced by the liver, into angiotensin I (ANG I) by renin. ANG I is then convertedto ANG II by the aptly named angiotensin-converting enzyme (ACE) in the vascular endothelium, particularly in the lungs, although many other tissues in the body (heart, brain and skeletal muscle) can also form ANG II. It has been clearly established that dysregulation of the RAS with age results in a variety of well-defined age-related pathologies, including hypertension, end-organ kidney disease, diabetes and chronic heart failure (CHF) [1,2]. The etiology of all of these conditions stems, in part, from regulation of the central peptide in this cascade, ANG II. In addition, recent

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novel findings from clinical and genetic studies in humans, and experimental evidence in animals, suggest that age-related changes in RAS function are associated with metabolic and biochemical changes in muscle and fat (see section titled Alternative Mechanisms of RAS Modulation), all of which are associated with declining functional status. Indeed, it has been widely recognized that age-related changes in body composition, including increased adiposity and decreased muscle mass and quality (sarcopenia), are associated with declining physical function, as assessed by standardized physical performance measures in both humans and rodent models of aging [3–7]. ACE inhibitors (ACE-Is) and ANG II-receptor blockers (ARBs), which both impede ANG II function, may modulate this process through a variety of molecular mechanisms, including their influence on oxidative stress and on metabolic and inflammation pathways, independent of their pressor effects. Furthermore, several disease conditions may indirectly contribute to the age-related decline in functional status, by accelerating the rate of muscle loss. For example, diastolic dysfunction, a common feature of cardiac aging in nearly all mammalian species has been associated with a reduced cardiac output response to exercise and marked elevation of left ventricular filling pressures in humans [11]. Inadequate hemodynamic response to exercise, in turn, is accompanied by exertional fatigue and/or dyspnea, subsequently leading to reduced physical activity, muscle deconditioning and, likely, causal atrophy.

In this review we will describe how recent pharmacological and genetic studies have contributed to our understanding of the role that the RAS plays in age-related sarcopenia and diastolic dysfunction. In addition, we will provide an overview of the current literature regarding potential biological mechanisms, other than changes in vascular hemodynamics, that are involved.

The renin–angiotensin system: effects on muscle mass, strength & physical function

The disablement process is often accompanied by sarcopenia or muscle loss, which is associated with virtually all identified disability risk factors. Clinically, the association between body composition and physical performance has been documented by several studies. However, loss of strength is greater than loss of muscle mass with age, implying that the quality of remaining muscle may be reduced [8]. Although there are limited data explaining potential physiological mechanisms that contribute to muscle quality, sarcopenia is frequently associated with fat accumulation. There are no definitive pharmacological interventions proven to prevent decline in physical function either by modulating body composition or by other means. One exception may be drugs that block the production or action of ANG II, such as ACE-Is. Indeed, ACE is an important component of the RAS, the central hormonal regulator of blood pressure. Recent evidence suggests that ACE-Is may improve physical function by means of a direct effect on body composition in older persons, rather than through its blood pressure lowering effects [9,10]. Clinical and genetic studies in humans and experimental evidence in animals suggest that modulation of the RAS is associated with metabolic and biochemical changes in skeletal muscle and fat, that may further contribute to age-related declines in physical function. ACE-Is, and potentially ARBs, may modulate this process through a variety of molecular mechanisms, including their influence on oxidative stress and on metabolic and inflammation pathways.

Pharmacological studies

Numerous randomized controlled trials of ACE-I use in heart failure patients have demonstrated a reduction in overall mortality and deaths due to progressive heart failure in elderly persons [11]. These findings have been extended to older persons in a retrospective study using the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE)

database of Medicaid/Medicare certified nursing homes [12]. Included in this meta-analysis were individuals who had a diagnosis of CHF, were over 65 years of age, not comatose and who did not die within 30 days of admission to the facility. In this selected population, overall mortality, morbidity and physical function were compared at baseline and 1 year of follow-up in patients taking digoxin or an ACE-I. Physical function was measured using an activities of daily living (ADL) scale. The overall mortality rate was 10% lower for ACE-I users and the rate of functional decline was attenuated by 25%. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, double-blind, placebo-controlled trial of ACE-I used in a population of patients with a history of stroke or transient ischemic attack [13]. Participants were individuals, mean age 64 years, chosen from outpatient clinics in ten countries. Exclusion criteria included major disability at baseline or contraindication for use of ACE-Is. Participants were randomly assigned to 4 mg/day of perindopril, a combination of perindopril and indapamide if indicated, or a single or double dose of placebo to mimic the combination treatment. Outcome measures included disability and dependence as measured by the Barthel Index of ADL. Participants receiving perindopril or combination treatments had a 24% and 30% reduced risk of long-term disability, respectively, after approximately 4 years of follow-up.

However, SAGE and PROGRESS do not dissociate ACE-I pressor effects from other possible mechanisms. Our laboratory has assessed the association of ACE-I use, compared with the use of other antihypertensive medications, on muscle strength and physical performance in a cohort of women from the Women's Health and Aging Study (WHAS) [9]. After 3 years of follow-up, and adjusting for several potential confounders, ACE-I users had significantly higher muscle strength and walking speed compared with those individuals on other antihypertensive regimens. These results were virtually unchanged after accounting for intercurrent diagnosis of stroke, CHF or myocardial infarction, suggesting that effects of ACE-I were not due to the prevention of cardiovascular health events.

We have also evaluated whether older persons using ACE-Is have a larger lower extremity muscle mass (LEMM) than users of other antihypertensive drugs [10]. The cohort was a cross-sectional sample of community-based, well-functioning individuals of the Health, Aging and Body Composition (Health ABC) study, aged 70–79 years, who were free of CHF and were selected according to use of a variety of antihypertensive medications, including ACE-Is, β-blockers, thiazides and calcium-channel blockers. LEMM significantly differed across the study groups, being larger in users of ACE-Is than in users of other drugs. A trend towards larger LEMM was also observed in sex- and ethnicity-stratified analyses and in the subgroup of hypertensive participants without coronary heart disease. This study demonstrated that, in older persons, use of ACE-I is associated cross-sectionally with larger LEMM and suggests a possible explanation of the benefits of ACE-Is in wasting syndromes. If confirmed in longitudinal studies, this pharmacological action might have important implications for the prevention of physical disability in older patients with hypertension. Together, these data suggest that ACE inhibition may prevent declining strength and physical performance via effects on body composition.

Genetic studies

Several genetic studies suggest that the RAS may modulate the function of skeletal muscle tissue and may be a determinant of visceral adiposity. A human ACE gene polymorphism has been identified in which the presence (insertion or I allele) versus the absence (deletion or D allele) of a 287-bp segment in intron 16 is associated with differential ACE activity in peripheral tissues [14]. Individuals homozygous for the I allele have lower ACE activity, increased blood flow and better oxygen utilization as compared with individuals homozygous for the D allele [14]. Observational studies have demonstrated a higher prevalence of the *ACE I/I* genotype

among elite endurance athletes, such as rowers and elite runners, relative to the general population. Conversely, the *D/D* genotype is associated with higher ACE activity and with power sports [15–18]. For example, researchers have compared the *ACE I/D* alleles and genotype in 64 Australian rowers with those in 118 normal controls [16]. The I/I genotype was found in 30% of the rowers and 18% of the controls, whereas the *I* allele was found in 57% of rowers and 43% of controls. In another study, Woods and colleagues compared the *ACE I/D* genotype of 25 British mountaineers who had a history of ascending beyond 7000 meters without the use of supplemental oxygen [17]. The *I/I* genotype and the *I* allele were significantly more frequent among mountaineers than in controls. In a prospective study, Montgomery and colleagues demonstrated that enhanced responsiveness to exercise, perhaps mediated by an increase in muscle strength, is associated with the *I* rather than the *D* allele in army recruits undergoing a 10-week boot camp training program [19]. Participants with the *I/I* genotype showed a significant increase in both fat and lean mass relative to those with the *D* allele, in whom physical training resulted in mild losses in fat and muscle.

In contrast, Rankinen and colleagues showed no effect of *ACE* allele status on enhanced responsiveness to endurance training [20]. They compared male endurance athletes withsedentary controls and found that both the genotype and allele frequencies were similar in the athletes and the controls. This contrast has also been explored in an epidemiological analysis of a cohort of initially well functioning adults aged 70–79 years participating in the Health ABC study [21]. The results suggest that the *ACE* genotype interacts with exercise in the magnitude of the benefit for the preservation of function in older adults, possibly through lower adiposity. However, in this analysis it was the *D* allele that appeared protective. This stresses the necessity of conducting genetic studies in animals in order to more fully elucidate these mechanisms.

Alternative mechanisms of renin–angiotensin system modulation

These converging lines of evidence collectively raise the question as to the biological mechanism by which ACE inhibition may affect declining physical performance and subsequent disability. These effects in humans may be due to the varied effects of ACE inhibition. ACE-Is reduce ANG II while simultaneously raising bradykinin levels, both resulting in well documented and profound hemodynamic effects. There is also evidence that ACE inhibition may regulate many aspects of metabolic functioning [2,22,23], decrease oxidative stress in tissues [1,24–29] and act ubiquitously to reduce age- and disease-related chronic inflammatory states [30–38]. However, there is still some debate as to how each pathway produces these changes and their relationship to changing body composition. Experimental studies in animals are beginning to address this gap.

Metabolic functioning

Disruption of metabolic functioning has been linked to pathophysiology in both skeletal muscle and adipose tissue and is associated with loss of strength and function [22,23]. One current hypothesis suggests that age-related insulin resistance contributes to the dysregulation of metabolic functioning of both adipose and skeletal muscle tissue and may contribute to declining performance [39,40]. Studies in aged Wistar rats demonstrated that both acute and chronic ACE-I administration improved insulin sensitivity, whereas losartan, an ARB, had no effect. Within skeletal muscle, acute or chronic ACE inhibition improves insulin-dependent glucose transport in Zucker rats [41,42]. In the spontaneously hypertensive rat (SHR), chronic administration of the ACE-I trandolapril enhanced insulin sensitivity of muscle glycogen synthesis [43]. Furthermore, compared with losartan, ACE inhibition improved whole-body and tissue-specific insulin sensitivity. The effects of specific ARBs on insulin sensitivity are more ambiguous regarding tissue-specific analyses. Chronic oral administration of ARBs

induce an enhancement of whole-body insulin action in Zucker [44], SHR [45] and fructose-fed rats [46], as well as in humans with essential hypertension [47]. Although some evidence suggests that ARBs do not influence local insulin action at the cellular level [48,49], other studies demonstrate effects in soleus muscle [49], a muscle group that is more responsive to insulin action. A more detailed examination directly comparing the long-term effects of ARBs would lead to a better understanding of the mechanisms by which they modulate tissue-specific insulin sensitivity and adipose tissue accumulation. Furthermore, the link between ARB intervention in humans and function is not known. Long-term clinical trials directly comparing the effects of ACE-Is with ARBs, and their respective impact on body composition and physical performance are necessary to identify this link.

Inflammation

A candidate physiological process that is common to various disease conditions associated with aging is inflammation [50,51]. Data from studies in humans and rats suggests that elevated levels of inflammatory cytokines during aging are responsible for muscle mass loss and are correlated with loss of function and disability [52–55]. In the rat, the proteolytic system that appears to be responsible for major catabolism of long-lasting myofibrillary protein in muscle is the ubiquitin–proteasome pathway. This pathway is indirectly induced by elevated levels of TNF in rat skeletal muscle [56,57]. It is hypothesized that this effect may be a direct result of the ability of TNF to modulate levels of IL-6 [58]. Treatment with the IL-6-receptor antibody reverses muscle atrophy, enzymatic activity and reduces messenger RNA levels of cathepsin, and elevates messenger RNA level of both poly- and monoubiquitins in IL-6 transgenic mice [59]. A possible mechanism by which these inflammatory cytokines are released, and subsequently activate the ubiquitin–proteasome pathway, is via activation of local RAS in skeletal muscle. In fact, there are documented links between the RAS and the inflammatory response in rat vascular smooth muscle cells mediated by ANG II. In a series of studies, Han and colleagues have shown that ANG II induces the activity of NF-κB in hepatocytes, which in turn translocates to the nucleus to bind and induce expression of cytokine, specifically IL-6, and acute-phase response genes [60]. Other laboratories have shown that, in both *in vitro* and *in vivo* preparations, there are local RAS in skeletal muscle [61]. Further characterization of these local systems in skeletal muscle and how they interact to modulate cytokine expression would allow for an assessment of ACE-I effects on improving age-related muscle loss.

Oxidative damage

The generation of oxygen-free radicals causes cumulative oxidative damage, degeneration and functional decline of almost all tissue systems, and many researchers accept that oxidative stress is the predominant cause of age-associated degenerative changes [62]. How such an oxidative insult plays a role in the age-related decrease of muscle performance and mass has yet to be defined. The data are controversial as to whether oxidative damage impacts aging skeletal muscle function [63]. In rodents, researchers have demonstrated that aging and sarcopenia are associated with increased mitochondrial and electron transport system abnormalities [64,65]. Functionally, Hepple and colleagues observed a decrease in oxidative capacity of aged rat skeletal muscle that was associated with a decline in maximal aerobic activity [66], whereas others have failed to find similar relationships in studies of aged humans [67]. This is perhaps partially explained by the fact that currently no standard measures for assessing oxidative damage are established. Standardization of these measures in validated models of sarcopenia and declining performance would enhance the field. The data regarding ACE inhibition and its effects on oxidative damage are limited but promising. Enalapril administered for 11 weeks to 4-month old female CF-1 mice increased CuZn-superoxide dismutase and selenium-dependent glutathione peroxidase and reductase activities, as well as overall glutathione content in many tissues, including kidney, brain and liver [25–27]. Both

enalapril and losartan also protect against age-related mitochondrial dysfunction and ultrastructure alterations in aged rats [68]. Finally, enalapril treatment reverses stress-induced tissue fibrosis in heart, liver and kidney using a rat model of streptozoticin-induced diabetes [28].

Diastolic dysfunction

A growing body of evidence indicates that diastolic heart failure (DHF), also termed heart failure with normal ejection fraction (HFNEF), may be almost as common, and perhaps as deadly, as 'classic' heart failure with reduced ejection fraction (reduced systolic function). Given that DHF is predominately a disease of old age, accounting for more than 50% of all heart failure patients over 70 years of age while its prevalence in heart failure patients between the ages of 50 and 70 years is less than 35%, there is a need for clinically useful information on effective treatment strategies that may halt the progression of diastolic dysfunction or even postpone cardiac aging.

Indeed, aging is associated with marked changes in cardiac structure, such as cardiomyocyte loss, hypertrophy of remaining cells and the development of fibrosis [69,70]. While these changes are presumed to be a major reason for the altered diastolic compliance of the senescent heart, age-related increases in arterial stiffness can further lead to vascular–ventricular uncoupling [71] that, when taken together, predispose to DHF. Indeed, lowering systolic pressure and peripheral vascular resistance, which are often increased in older people [72], might indirectly improve heart function. However, there is now evidence that cardiac aging *per se* is associated with local cardiac RAS activation, which has critical implications with respect to pathogenesis and treatment of diastolic dysfunction and, ultimately, DHF. Increases in gene expression of angiotensinogen, ACE and ANG I and II receptors have been identified in hearts from senescent rats – independent of circulating RAS [73,74]. Likewise, the mineralocorticoid, aldosterone, which was thought to have its sole production in the zona glomerulosa of the adrenal gland and its sole site of action in the kidney, is now known to be produced in cardiovascular tissues, and has been implicated in the development of left ventricular (LV) hypertrophy and cardiac fibrosis. Increases in cardiac ANG II and aldosterone levels in aged rats have been associated with LV remodeling [75]. Specifically, ANG II promotes myocyte hypertrophy, increases in collagen synthesis and is mitogenic to neonatal cardiac fibroblasts [76–78]. Locally produced ANG II also regulates *de novo* aldosterone production, which likewise contributes to interstitial fibrosis [79]. Taken together with the growing body of evidence suggesting that locally produced ANG II can elicit functional changes in the aged heart [80], and the unique role of the renin–angiotensin–aldosterone system (RAAS) in establishing fibrosis at a molecular level, RAAS blockade provides an opportunity to expand the therapeutic options for diastolic dysfunction.

To date, neither ACE-Is, ARBs or aldosterone antagonists have been studied for the treatment of preclinical diastolic dysfunction in a major trial. However, with respect to symptomatic diastolic dysfunction, specifically, diastolic heart failure, RAAS blockade has shown some promise. The Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-preserved) trial [81], the first, large prospective, outcome trial in 3023 patients (≥18 years; mean age 67 years) with HFNEF/DHF, indicated that treatment with the ARB candesartan reduces hospital admission for worsening heart failure but does not alter mortality. Findings from the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial of more than 4000 subjects (≥60 years) will likely provide conclusive data regarding the primary end point of death and the role of ARB blockade in the management of DHF [82]. Moreover, results from the recently completed Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) trial suggest an important role for ACE-Is in the management of DHF [83]. This was a randomized, double-blind trial, comparing placebo with the ACE-I

perindopril in patients who were 70 years or over. However, due to lower than anticipated enrollment and event rates and patient withdrawal, the study was insufficiently powered for its primary end point all-cause mortality. Nonetheless, the authors did observe a trend after 1 year in primary outcome in those patients treated with perindopril and hospitalization for heart failure. Interestingly, New York Heart Association functional classification and the 6-min walk distance were significantly improved in those assigned to perindopril, suggesting that RAAS blockade may improve exercise tolerance in patients with DHF. Given that excessive fibrosis may contribute to impaired relaxation and filling of the ventricles in patients with DHF, and that aldosterone is thought to have an important role in the extracellular changes associated with the disease process [84], we look forward to the NIH-funded Trial of Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT). Approximately 4500 DHF patients (>50 years of age) will be randomized to placebo or spironolactone (15–45 mg daily) with primary end points of composite cardiovascular mortality, aborted cardiac arrest or hospitalization for heart failure over a 4.5-year period. Secondary end points will address all-cause mortality, new-onset of diabetes, atrial fibrillation and quality of life. Indeed, pending the results of these trials, contemporary treatment of chronic DHF, unlike that for systolic heart failure, remains empiric. The current therapeutic guidelines for heart-failure patients with normal ejection fraction and diastolic dysfunction include lifestyle changes (e.g., weight reduction, salt and volume restriction and maintenance of physical activity), optimal control of systolic and diastolic blood pressure (using ACE-Is, ARBs or β-adrenergic blockade), control of ventricular rate in atrial fibrillation and careful use of diuretics to control pulmonary congestion and edema.

Executive summary

Introduction

- Recent findings suggest that age-related changes in regulation of the renin–angiotensin system (RAS) are associated with metabolic and biochemical abnormalities in muscle and fat, independent of hemodynamic mechanisms.
- Functional status is compromised in the elderly owing to a loss of muscle mass and diastolic dysfunction, both common features of aging in nearly all mammalian species and both of which may be ameliorated through blockade of the RAS.

The renin–angiotensin system: effects on muscle mass, strength & physical function

- There are no definitive pharmacological interventions proven to prevent decline in physical function either by modulating body composition or by other means. One exception may be drugs that block the production or action of angiotensin II (ANG II), such as angiotensin-converting enzyme inhibitors (ACE-Is).

Pharmacological studies

- Several observational and epidemiological studies demonstrate that ACE-Is have a profound impact on skeletal muscle mass and strength, independent of their hemodynamic effects.

Genetic studies

- Studies of individuals with *ACE* gene polymorphisms demonstrate that varied expression of ACE results in differential response to exercise and remodeling of body composition.

Alternative mechanisms of renin–angiotensin system modulation

- Animal models indicate that pharmacological and genetic blockade of the RAS may impact underlying biological mechanisms, such as inflammation, oxidative

damage and metabolic dysregulation, which contribute to aging and age-related pathologies.

Diastolic dysfunction

- Growing evidence suggests that diastolic heart failure (DHF) may be almost as common, and perhaps as deadly, as 'classic' heart failure with reduced ejection fraction (reduced systolic function).
- Given that DHF is predominately a disease of old age, accounting for more than 50% of all heart failure patients over 70 years of age, there is a need for clinically useful information on effective treatment strategies that may halt the progression of this age-related disease process or even postpone cardiac aging.
- There is now evidence that aging is associated with local cardiac renin–angiotensin–aldosterone (RAAS) activation, which has critical implications with respect to pathogenesis and treatment of diastolic dysfunction.
- Past and current clinical trials suggest that ACE-Is, angiotensin-receptor blockers (ARBs) and aldosterone antagonists may have a role in reversing diastolic heart failure, although the mechanisms are only now being addressed using animal models of this condition.

Conclusion

- Collectively these data suggest that RAS blockade may be beneficial in older individuals with sarcopenia and declining functional status and in those with diastolic dysfunction.
- Promising pharmaco–epidemiological clinical and experimental evidence suggests that treatment with drugs such as ACE-Is and ARBs may serve to simultaneously ameliorate these conditions in both traditional (hypertensive, chronic heart failure and stroke) and nontraditional (obese, overweight and sarcopenic) at-risk populations.
- Further mechanistic studies and long-term clinical trials are necessary to more thoroughly address these hypotheses.

Conclusion

In this review we have described how recent advances in the literature are contributing to our understanding of the role of the RAAS in age-related sarcopenia and diastolic dysfunction. In addition, we provide an overview of our current understanding regarding the potential biological mechanism other than affects on hemodynamic function. In fact, this review raises many questions as to the exact role of the RAS in functional aging. Indeed, promising pharmacoepidemiological, clinical and experimental evidence suggests that treatment with drugs such as ACE-Is and ARBs may serve to simultaneously ameliorate these conditions in both traditional (hypertensive, CHF and stroke) and nontraditional (obese, overweight and sarcopenic) at-risk populations. Further mechanistic studies and long-term clinical trials are necessary to more thoroughly address these hypotheses.

Future perspective

Currently, the indications for use of ACE-Is include CHF, kidney disease, hypertension and diabetes [12,24,85–90]. In addition, ACE-Is and ARBs may counteract disregulation of a variety of physiological pathways that lead to age-related upregulation of chronic stress and

inflammation as well as abnormal metabolic functioning, which may lead to declining functional status. These mechanistic studies remained to be addressed.

However, the evidence is promising enough to warrant further investigation with long-term clinical trials of ACE-I and ARB use in aged populations for the prevention of disability, declining functional status and reversal of diastolic dysfunction. For these future trials, several considerations should be addressed. First, are all ACE-Is equally effective? A recent retrospective cohort study has shown that not all ACE-Is are associated with similar rates of mortality in a population of men and women aged 65 years and older who have had an acute myocardial infarction. Those individuals taking ramipril had increased survival benefit relative to those taking enalapril, fosinopril, captopril, quinapril or lisinopril [91]. These effects may be due to subtle differences in binding groups, half-life of the drug, route of elimination and lipophilicity, all characteristics of the drug that effect maximum efficacy. Second, are ARBs equally as effective as ACE-Is in preventing physical decline? ARBs antagonize the ANG II receptor type 1, thereby selectively blocking the action of ANG II without directly affecting other ACE pathways. There is considerable debate in the CHF literature as to which therapy is superior in preventing mortality and morbidity [47]. For example, in the Valsartan Heart Failure Trial (Val-HeFT), overall mortality was similar in the valsartan and placebo groups. Interestingly, valsartan, in addition to ACE-I treatment, significantly reduced the combined end point of mortality and morbidity [92,93]. However, the impact of ARBs (either alone or in combination with ACE-Is) on physical performance and body composition and diastolic dysfunction has not been evaluated. We eagerly await results from such trials.

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