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. Although there are limited data explaining potential physiological mechanisms that contribute to muscle quality, sarcopenia is frequently associated with fat accumulation, and the percentage of body fat increases with age even if weight does not. However, the relationship between fat and muscle function may not be linear, suggesting that there may be an optimal ratio of lean to fat mass for 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 angiotensin-converting enzyme inhibitors (ACEIs). ACE is an important component of the renin-angiotensin system, the central hormonal regulator of blood pressure. Recent evidence suggests that ACEIs may improve physical function by means of direct effects on body composition in older persons, rather than through its blood-pressure-lowering effects. Clinical and genetic studies in humans and experimental evidence in animals suggest that modulation of the renin-angiotensin system is associated with metabolic and biochemical changes in skeletal muscle and fat, changes that are associated with declining physical function. ACEIs may modulate this process through a variety of molecular mechanisms including their influence on oxidative stress and on metabolic and inflammation pathways. This review describes potential biological mechanisms of ACE inhibition and its contribution to declining physical performance and changing body composition. Promising pharmacoepidemiological studies and experimental evidence in animals suggest that there are appropriate models in which to study this effect.

Rodents placed on a calorie-restricted diet across the life span show improved survival and a sparing of function in various motor performance tests including increased locomotor activity (6,7). Furthermore, caloric restriction delays age-related changes in physiological and molecular measures of muscle function and visceral adipose tissue accumulation that are observed in ad libitum-fed animals (8,9).

There are many examples of studies showing that exercise and strength training in elderly persons may prevent physical decline and increase muscle mass and strength (10–18). However, 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 angiotensin-converting enzyme inhibitors (ACEIs). This class of drugs has been demonstrated in a variety of studies to prevent morbidity, mortality, and decline in physical function and exercise capacity in patients with congestive heart failure (CHF), although the exact mechanism is only partially understood.

ACE is an important component of the renin-angiotensin system (RAS), the central hormonal regulator of blood pressure. ACE has two well recognized roles in this system.
called angiotensinogen, converting it into angiotensin I (ANGI). ANGI is then converted to angiotensin II (ANGII) by ACE. Thus ACEIs act to lower blood pressure by reducing ANGII, a potent vasoconstrictor, and increasing BK, a potent vasodilator (Figure 2).

Recent evidence suggests that ACEIs may improve physical function by means of direct effects on body composition in older persons (20–22), rather than through its blood-pressure-lowering effects. 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, changes that are associated with declining physical function (see “Potential Biological Mechanisms” below). ACEIs may modulate this process through a variety of molecular mechanisms including their influence on oxidative stress and on metabolic and inflammation pathways.

ACE INHIBITION AND PHYSICAL FUNCTION

Clinical Studies
Numerous randomized controlled trials of ACEI use in CHF patients have demonstrated a reduction in overall mortality and deaths due to progressive heart failure in elderly persons (23). 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 1492 Medicaid/Medicare certified nursing homes (24). Of 351,244 residents, 19,492 were identified as having a diagnosis of CHF, were over the age of 65 (mean age approximately 85 years), not comatose, and 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 14,890 patients taking digoxin and 4911 patients taking an ACEI. Physical function was measured using a 5-item 6-level activities of daily living scale. The overall mortality rate was 10% lower for ACEI 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 ACEIs used in a population of patients with a history of stroke or transient ischemic attack (25). Participants were 6105 individuals, mean age 64 years, chosen from 172 hospital outpatient clinics in 10 countries. Exclusion criteria included major disability at baseline or contraindication for use of ACEIs. Participants were randomly assigned to 4 mg/day of perindopril ($n = 1281$), a combination of perindopril and indapamide ($n = 1770$) if indicated, or a single ($n = 1280$) or double dose of placebo ($n = 1774$) to mimic the combination treatment. Outcome measures included disability and dependence as measured by the Barthel Index of Activities of Daily Living and a simple question “In the last two weeks has the patient required regular help with everyday activities?” respectively. Median follow-up after baseline assessment was 4 years. Participants receiving perindopril or combination treatments had a 24% and 30% reduced risk of long-term disability, respectively.

SAGE and PROGRESS do not dissociate ACEI pressor effects from other possible effects. A major focus of our research program has been to assess the effects of ACE status on physical performance. Initially we assessed the association of ACEI 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) (20). Participants were chosen from 1002 women, 65 years old or older, who were living in the Baltimore community and were disabled. After selecting 641 hypertensive women free of CHF (mean age 79 years), four antihypertensive drug regimens were compared: 1) continued ACEI use ($n = 61$),
2) intermittent ACEI use \((n = 133)\), 3) use of other antihypertensive drugs \((n = 301)\), and 4) never use of antihypertensive drugs \((n = 146)\). After 3 years of follow-up, and adjusting for several potential confounders, continued ACEI users had significantly higher muscle strength and walking speed compared with the other groups (Figure 3). These results were virtually unchanged after accounting for intercurrent diagnosis of stroke, CHF, or myocardial infarction, suggesting that effects of ACEIs were not due to the prevention of cardiovascular health events.

We have also evaluated whether older persons using ACEI have a larger lower extremity muscle mass (LEMM) than do users of other antihypertensive drugs (21). The cohort was a cross-sectional sample of 2431 community-based, well functioning individuals of the Health, Aging and Body Composition (Health ABC) study, aged 70–79, who were free of CHF and were selected according to use of antihypertensive medications: ACEIs \((n = 197)\), beta-blockers \((n = 169)\), thiazides \((n = 216)\), calcium-channel blockers \((n = 340)\), or none \((n = 1509)\). Outcomes included LEMM, as assessed using dual-energy x-ray absorptiometry, compared by index drug in analysis of variance models unadjusted and adjusted for potential confounders. LEMM significantly differed across the study groups, being larger in users of ACEIs than in users of other drugs (unadjusted and adjusted models). LEMM was comparable in users of ACEIs and no drug users. A trend toward larger LEMM was 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 ACEIs is associated cross-sectionally with larger LEMM. This finding suggests a possible explanation of the benefits of ACEIs 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. This suggestion is consistent with those of several studies describing the relationship between age-related changes in body composition and declining physical performance. A cross-sectional analysis of a cohort of men and women aged 70–79 years participating in the Health ABC study showed that lower strength was accounted for mostly by lower muscle mass, but that age and body fat also had a significant association with strength and muscle quality (26). Cross-sectional and prospective analyses in men and women aged 55–92 years found that both increased fat mass and decreased lean mass were associated with greater functional disability (2). A cross-sectional study in older men and women aged 55 years and older showed that physical performance and self-reported functional limitation were inversely associated with higher fat mass and higher fat-to-lean ratio (3). Finally, an analysis of the baseline data from The Cardiovascular Health Study showed a positive association between fat mass and disability but no relationship with lean mass. Of those not reporting disability at baseline, a higher fat mass (but not low lean mass) was predictive of disability 3 years later (4). These studies show that both lean and fat mass and, more specifically, fat-to-lean ratio are important predictors of disability.

**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 (27). Individuals homozygous for the I allele have lower ACE activity, increased blood flow, and better oxygen utilization as compared to individuals homozygous for the D allele (27). 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 (28–31).

For example, researchers have compared the ACE I/D alleles and genotype in 64 Australian rowers to those in 118 normal controls (29). The 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 (30) 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. The II genotype and the I allele were significantly more frequent among mountaineers than in controls.

In a prospective study, Montgomery and colleagues (32) demonstrated that enhanced responsiveness to exercise, perhaps mediated by an increase in muscle strength, is associated with the I rather than the D allele (32) in army recruits undergoing a 10-week boot camp training program. Participants with the II 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 (33) showed no effect of ACE allele status on enhanced responsiveness to endurance training. They compared male endurance athletes versus sedentary 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 (34). The results suggest that 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. The evidence for a role of ACE inhibition and the contradictory nature of the genetic evidence stress the importance of developing experimental animal models for testing hypotheses regarding the role of ACE status and intervention in modulating body composition and perhaps physical performance in elderly persons.

**ANIMAL STUDIES**

**Pharmacological**

We have demonstrated that performance measures, conceptually similar to those used in humans, can be assessed longitudinally in aged rats (35). Two of these procedures, the inclined plane and the swim test, provide a simple assessment of upper body muscle strength and endurance, respectively, without the necessity of invasive procedures. We have collected data to assess within-subject performance across a 6-month time period (24–30 months of age) for both measures. Performance declined progressively and significantly with increasing age (35). A similar pattern of decline in physical performance measures has been demonstrated in human studies (26,36,37).

In this same study (35) we found that lower physical performance scores, measured at baseline by means of the inclined plane and swim test, independently and significantly predict longevity over 8 months of follow-up. These results demonstrate that physical performance measures in older rats have similar predictive ability for longevity to those shown in human studies.

We have conducted long-term ACEI intervention studies in the rodent model of declining function to assess the effects on body composition and physical performance in aged rats (38). Male Brown Norway × Fisher 344 rats (n = 92) were randomly assigned to receive daily subcutaneous injections of enalapril (40 or 80 mg/kg) or saline control and were followed for 6 months. We found that ACE inhibition moderately attenuated declining physical performance. Relative to both treatment groups, animals receiving saline showed a greater 6-month decline in performance as measured by both grip strength and inclined plane tasks (Figure 4). There was an effect of ACE inhibition on total body weight that was mostly attributable to lower fat mass (Figure 5). Both the 40 and 80 mg/kg groups had a significantly lower total fat mass between 27 and 30 months of age relative to the saline group. This finding represented a change from baseline to 30 months of age of −12.3% and −22.4%, respectively, in the 40 and 80 mg/kg groups and an increase of 4.8% in the saline group. There were equivalent losses of lean mass in all groups that occurred between 24 and 27 months of age that remained stable thereafter (Figure 5). This loss represented a 5.7%, 5.4%, and 6.3% reduction in lean mass in the 40 mg/kg, 80 mg/kg, and saline groups, respectively.
A recent study examined the effect of ACE inhibition on endurance and skeletal muscle metabolism. Adult sedentary Wistar rats were randomly assigned to receive 2 mg/kg perindopril or vehicle daily for 10–12 weeks. Endurance capacity was assessed by placing animals on a treadmill at 20 m/min at a 5% grade until the animal could no longer maintain the speed. Oxidative capacity and regulation of mitochondrial respiration were evaluated in skinned fibers of soleus and gastrocnemius muscles. Endurance capacity did not differ between groups, and there were only slight differences in mitochondrial respiration (39). The authors concluded that ACE activity has no implication in endurance capacity in sedentary animals. However, it is still undetermined whether aged animals may benefit from such intervention given the vulnerability of this population to shifting fat-to-lean ratio and declining performance. In fact, these results in rodents reiterate the importance of the contribution of body composition to declining performance, and support epidemiological studies in humans, demonstrating that increasing fat mass and decreasing lean mass is an important predictor of physical decline.

Genetic
Polymorphisms in the rat ACE gene have been identified that result in differential levels of plasma ACE (40). Determination of plasma ACE levels across various inbred strains of normotensive rats demonstrated that within strain, ACE levels are homogenous but exhibit a wide range across strains suggesting the existence of different alleles. For example, ACE levels show a twofold difference between Brown Norway and Lou strains in animals as old as 9 months (approximately 100 vs 50 nmol/ml/min, respectively) (40). Subsequently, in the same study, Challah and colleagues cross-bred Brown Norway and Lou strains to determine the contribution of genetic variation in the ACE allele (B: Brown Norway allele; L: Lou allele) to circulating levels of ACE and vascular response to environmental insult.

Genotyping was accomplished using polymerase chain reaction (PCR) to amplify the microsatellite located at the 5’ end of intron 13 inside the rat ACE gene. All F1 progeny were heterozygous in the ACE allele (BL), whereas the distribution of ACE genotype in the F2 generation (BB, BL, LL) followed Mendelian segregation. F2 progeny homozygous for the BB allele had significantly higher levels of ACE (average 144.5 nM/ml/min) relative to progeny homozygous for the LL allele (average 58.7 nM/ml/min). Heterozygotes had ACE levels between the two homozygous genotypes (average 106.1 nM/ml/min). All F2 rats were normotensive regardless of genotype, and there were no differences in body weight. Further characterization of F2 progeny (Brown Norway × Lou) demonstrated that the ACE gene is responsible for 94% of the genetic variance of constitutively expressed plasma ACE. Thus, as in humans, rodents differentially express ACE. These differences could be studied to assess for differences in body composition and, potentially, physical function.

The relative contribution of circulating versus tissue levels of ACE to changing body composition has also been explored in genetic animal models of ACE deficiency. For example, in mice with decreased expression of the ACE gene (41), ANGII concentration in kidney, heart, and lung did not differ from wild-type mice, whereas ANGII concentrations in plasma were decreased. This effect was attributed to local non-ACE-mediated systems in tissue (e.g., chymase, in the case of cardiac tissue). A precautionary tone should be taken with these studies given the fact that these animals have a completely different developmental history from their wild-type controls and may have therefore developed compensatory mechanisms which could account for these changes. However, these studies emphasize the importance of evaluating tissue levels, in addition to plasma levels, of these components. In fact, very little is known regarding ACE inhibition and modulation of these local systems in skeletal muscle. Recently, Xiao and colleagues (42) have
developed a methodology to induce tissue-specific ACE gene expression through homologous recombination. Using such animal models could help to resolve the contradictory results noted in both rats and humans regarding the complex interaction between genetic and environmental determinants of physical function and body composition.

**Potential Biological Mechanisms**

These converging lines of evidence in aged humans and rodent models of aging 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 and rats may be due to the varied effects of ACE inhibition. ACEIs reduce ANGII while simultaneously raising BK levels, both resulting in well documented and profound hemodynamic effects. There is also evidence that ACE inhibition may regulate many aspects of metabolic functioning (43), decrease oxidative stress in tissues (44–48), and act ubiquitously to reduce age- and disease-related chronic inflammatory states (49–57). However, there is still some debate as to how each pathway produces these changes and their relationship to changing body composition.

**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 (58,59). One current hypothesis suggests that age-related insulin resistance contributes to the disregulation of metabolic functioning of both adipose and skeletal muscle tissue and may contribute to declining performance (60,61). There are many studies in humans showing that the onset of diabetes begins with the development of insulin resistance in adipocytes and ultimately results in skeletal muscle and whole-body insulin resistance (62).

There is ample evidence to show that BK is a modulator of insulin action in muscle and adipose tissue through its action at the B2 receptor (63–65). The proteolytic degradation of BK is blocked by ACE inhibition. BK potentiates the downstream signaling of insulin-dependent (and possibly independent) glucose transporter 4 (GLUT-4) translocation in skeletal muscle through a cascade involving nitric oxide. Studies in aged Wistar rats (20 months old) demonstrated that both acute ACEI and BK administration enhanced insulin sensitivity and adipose tissue accumulation. Furthermore, compared with losartan, ACE inhibition improved whole body and tissue-specific insulin sensitivity (adipose or skeletal muscle). These effects are reversed with the B2 receptor blocker NG-nitro-L-arginine methyl ester (L-NAME) and the nitric oxide synthase blocker Hoe-140. In a murine model of type II diabetes, the KK-Ay mouse, those animals treated with a low dose of the ACEI temocapril had a decrease in plasma glucose and insulin, and enhanced 2-deoxyglucose uptake in skeletal muscle but not in white adipose tissue, an effect that was attenuated with either Hoe-140 or L-NAME (69).

Adipocytes also express BK B2 receptors. BK boosts tyrosine phosphorylation of the insulin receptor in insulin-treated adipocytes, and potentiates signaling of downstream effects such as phosphorylation of IRS-1 and activation of phosphoinositol 3-kinase and membrane translocation of the GLUT4 receptor—all insulin-dependent processes (65). Long-term enalapril treatment (but not losartan treatment) of SHR rats corrects insulin resistance of the adipocytes and is blocked by Hoe 140. Taken together, increased BK activity on adipocytes and skeletal muscle may help to ward off muscle insulin resistance and, potentially, diabetes (60).

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 (70), SHR (71), and fructose-fed rats (72), as well as in humans with essential hypertension (73). Although some evidence suggests that ARBs do not influence local insulin action at the cellular level (74,75), other studies demonstrate effects in soleus muscle (75), a muscle group that is more responsive to insulin action.

In rodent models (76), upregulation of both angiotensinogen and ANGII levels locally in adipose tissue leads to further adipose tissue development associated with adipocyte hypertrophy and an increase in lipogenesis and triglyceride accumulation. These findings are consistent with studies showing that age-related white adipose tissue hypertrophy is also prevented with long-term losartan administration (77). In contrast, there are studies demonstrating that chronic infusion of ANGII results in weight loss and reduction of white adipose tissue mass (78–80).

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 ACEIs 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 (81,82). 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. For example, in a cross-sectional study, Cohen and colleagues (83) demonstrated an association between interleukin-6 (IL-6), age, self-rated health, various disease conditions, and functional
status. Stronger evidence from a prospective study by Harris and colleagues (84) of a subset of this population has demonstrated an association between elevated levels of IL-6 and C-reactive protein and mortality in a group of nondisabled persons from the Established Population for the Epidemiologic Study of the Elderly (EPESE). This evidence was confirmed in studies that show that IL-6 levels prospectively predict incidence of disability in aging populations (85,86).

In the rat, the proteolytic system that appears to be responsible for major catabolism of long-lasting myofibrillar protein in muscle is the ubiquitin–proteasome pathway. The first step in this pathway is the covalent attachment of polyubiquitin chains to the targeted protein. Polyubiquitinated proteins are then recognized and degraded by the 26S proteasome complex. This pathway is indirectly induced by elevated levels of tumor necrosis factor-α (TNF-α) in rat skeletal muscle (87,88). It is hypothesized that this effect may be a direct result of the ability of TNF-α to modulate levels of IL-6 (89). Treatment with the IL-6 receptor antibody reverses muscle atrophy, enzymatic activity, and messenger RNA levels of cathepsin and elevated levels of messenger RNA of both poly- and mono-ubiquitins in IL-6 transgenic mice (90). Furthermore, rats bearing the asite hepatoma Yoshida AH-130 tumor demonstrate rapid tissue degeneration, which in turn results in skeletal muscle, that is correlated with an increase in ubiquitin gene expression (91) and elevated levels of TNF-α (92).

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 ANGII. In a series of studies, Han and colleagues (93) have shown that ANGII induces the activity of nuclear factor-kB (NF-kB) in hepatocytes, which in turn translocates to the nucleus to bind and induce expression of cytokine, specifically IL-6, and acute-phase response genes. Other laboratories have shown that, in both in vitro and in vivo preparations, there are local RAS in skeletal muscle (94,95). Further characterization of these local systems in skeletal muscle and how they interact to modulate cytokine expression would allow for an assessment of ACEI 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 (96). 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 (97). In rodents, researchers have demonstrated that aging and sarcopenia are associated with increased mitochondrial and electron transport system abnormalities (98,99). Functionally, Hepple and colleagues (100) observed a decrease in oxidative capacity of aged rat skeletal muscle that was associated with a decline in maximal aerobic activity, whereas others have failed to find similar relationships in studies of aged humans (101). 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 (44,45,48). Both enalapril and losartan also protect against age-related mitochondrial dysfunction and ultrastructure alterations in aged rats (102). Finally, enalapril treatment reverses stress-induced tissue fibrosis in heart, liver, and kidney using a rat model of streptozoticin-induced diabetes (46).

**Conclusions**

Currently, the indications for use of ACEI include CHF, hypertension, and possibly diabetes. Results from studies investigating the effects of long-term ACEI use in both aged humans with these conditions and animal models of these conditions suggest an attenuation of the various associated pathologies and increases in mean life expectancy (24,47,103–109). It is not yet known by which mechanisms ACE inhibition may lead to these outcomes. ACEIs may counteract disorganization 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 physical performance. These mechanistic studies remained to be addressed.

However, the evidence is promising enough to warrant further investigation in long-term clinical trials of ACEI use in aged populations for the prevention of disability and declining physical function. For these future trials several considerations should be addressed. First, are all ACEIs equally effective? A recent retrospective cohort study has shown that not all ACEIs are associated with similar rates of mortality in a population of men and women 65 years old 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, and lisinopril (110). 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 which effect maximum efficacy. Future studies are needed to determine which is the most effective treatment in elderly persons for prevention of disability and declining physical function.

Second, are ARBs equally as effective as ACEIs in preventing physical decline? ARBs antagonize the ANGII receptor, (AT1) thereby selectively blocking the action of ANGII 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 (73). 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 ACEI treatment, significantly reduced the combined end point of mortality and morbidity (111,112). This question is especially relevant given that long-term use of ACEIs results in what is known as the ACE escape. ACE escape refers to the slow return of circulating ANGII to pretreatment levels after long- and short-term administration of ACEI (113). In fact, long-term use of ACEI results in changes to other components of the RAS including a rebound of initially reduced aldosterone levels, which has been experimentally linked to adverse outcomes in patients with CHF (114). However, the impact of ARBs (either alone or in combination with ACEI) on physical performance and body composition has not been evaluated.

Third, studies in patients with CHF suggest that ACE escape may be due to inadequate doses of ACEI. For example, Jorde and colleagues (115) have shown that doubling the maximally recommended doses of enalapril (from 40 to 80 mg/d for 1 week) completely blocks the pressor response to intravenously infused ANGII. In fact, many individuals experiencing heart failure are treated at doses well below those recommend by evidenced-based clinical trials (116,117). Recent evidence suggests that ACEIs are maximally effective when used at very high doses [see (118) for review]. However, although biological outcomes are improved, there is little evidence to suggest that high doses provide more of a benefit than do low doses in clinical outcomes.

This review raises many questions as to the exact mechanism of ACE inhibition and its contribution to declining physical performance and changing body composition. However, promising pharmacopeidemiological studies and experimental evidence in animals suggests that there are appropriate models in which to study this phenomenon.

ACKNOWLEDGMENTS

Drs. Carter, Kritchevsky, and Pahor were supported by the Claude Pepper Older Americans Independence Center grant P30 AG021332-01. Address correspondence to Christy Carter, PhD, University of Florida, Department of Aging and Geriatric Research, 1329 SW 16th St. PO Box 100143, Gainesville FL, 32610-0143. E-mail: ccarter@aging.ufl.edu

REFERENCES


