Current Guidelines for Using Angiotensin-Converting Enzyme Inhibitors and Angiotensin II–Receptor Antagonists in Chronic Kidney Disease: Is the Evidence Base Relevant to Older Adults?

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Angiotensin-converting enzyme inhibitors and angiotensin II–receptor antagonists are recommended for patients with chronic kidney disease because these drugs can slow disease progression. Older adults account for a large and growing number of patients with chronic kidney disease. The authors evaluated the relevance to adults older than 70 years of the evidence base for major U.S. practice guidelines for the use of these agents in chronic kidney disease. The authors first examined the representation of older adults in randomized trials that underpin these guidelines, then compared the characteristics of participants in these trials with those of a representative sample of older adults with chronic kidney disease in the general population. The authors found that current guidelines for the use of angiotensin-converting enzyme inhibitors and angiotensin II–receptor antagonists in chronic kidney disease are based on evidence with limited relevance to most persons older than 70 years with this condition.

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II–receptor blockers (ARBs) are widely recommended in clinical practice guidelines for patients with chronic kidney disease. Such recommendations are based on the results of randomized, controlled trials (RCTs) demonstrating that these agents slow progression of kidney disease. The unique renoprotective properties of ACE inhibitors and ARBs are generally attributed to their ability to reduce proteinuria (1, 2). Proteinuria is a major risk factor for end-stage renal disease (3, 4) and may play a direct pathogenic role in progression of chronic kidney disease (2).

In RCTs, both ACE inhibitors and ARBs are more likely to slow progression of kidney disease in participants with greater degrees of proteinuria (5–7). In patients without diabetes excreting less than 500 mg/d of protein, ACE inhibitors may be no more renoprotective than other antihypertensive agents (7). Use of these agents in patients with chronic kidney disease mandates close monitoring for acute renal failure and hyperkalemia, may require dietary modification or long-term administration of an ion-exchange resin, and may limit the use of other medications that also increase serum potassium level (8).

More than one third of adults in the general population age 70 years or older have chronic kidney disease (9). Whether evidence supporting current guidelines for the use of ACE inhibitors and ARBs in chronic kidney disease can be extrapolated to this large group is unknown. To address this question, we first examined the representation of older adults in RCTs used to formulate contemporary guidelines from the Kidney Disease Outcomes Quality Initiative (KDOQI); the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7); and the American Diabetes Association (**Table 1**) (8, 10–12). We also examined the representation of older adults in relevant major trials whose results were published after guideline preparation. Second, we compared the characteristics of participants in guideline trials with those of a representative sample of older adults with chronic kidney disease from the general population enrolled in the National Health and Nutrition Examination Survey (NHANES) 1999–2006.

Were Older Adults Well Represented in Trials Underpinning Major U.S. Practice Guidelines for the Use of ACE Inhibitors and ARBs in Chronic Kidney Disease?

Two coauthors screened all articles referenced in the aforementioned guidelines (**Table 1**). When the primary article cited in the relevant guideline did not provide all prespecified data elements, we performed directed searches to identify additional publications from that study that might include this information. We restricted these searches to English-language articles published before or during the evidence review period for the most recent guideline in which the primary study was cited (**Table 1**). We performed these directed searches by using MEDLINE and by hand-searching the reference lists of primary arti-

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Key Summary Points

Almost one half of adults in the general population who meet criteria for chronic kidney disease are older than 70 years.

Persons older than 70 years are underrepresented in most trials underpinning major U.S. practice guidelines for the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II–receptor blockers (ARBs) in chronic kidney disease.

More than 85% of persons older than 70 years who meet criteria for chronic kidney disease do not have proteinuria. The relevance of guideline trials to this group may be limited because most favored inclusion of participants with proteinuria.

Differences between guidelines in criteria for the use of ACE inhibitors and ARBs in chronic kidney disease lead to considerable variation across guidelines in the proportion of older adults targeted.

Practice guidelines specifically recommend the use of ACE inhibitors and ARBs in patients with chronic kidney disease because these agents are renoprotective. However, slowing progression of kidney disease may not be the most patient-centric goal of therapy in many older adults with this condition.

cles. When we could not identify all data elements from published sources, we requested needed information from corresponding authors.

For inclusion in our review, the study was required to be an RCT in which at least 1 group was treated with an ACE inhibitor or ARB and was compared with a control group not receiving either agent. Because the rationale for all of the guidelines reviewed here is that ACE inhibitors and ARBs slow progression of kidney disease, we also required that at least 1 of the following renal outcomes was reported in the article cited in the relevant guideline: change in urinary protein or albumin excretion, change in serum creatinine level, creatinine clearance, measured or estimated glomerular filtration rate (GFR or eGFR, respectively), requirement for dialysis, or onset of end-stage renal disease. Two coauthors separately abstracted relevant prespecified trial characteristics, participant characteristics, and entry criteria.

The guidelines referenced 37 articles describing 32 RCTs (6, 13–48). We excluded 2 trials because the referenced article did not include a renal outcome measure (45, 46) and 3 trials because they lacked a comparison with a control group not receiving an ACE inhibitor or ARB (44, 47, 48) (**Table 1**). We included the remaining 27 trials (total participants, 15 794) (**Appendix Table 1**, available at www.annals.org).

The mean age of trial participants ranged from 29 to 71 years. The maximum age of participants could not be ascertained in 2 trials. Among the remaining trials, 19 (76%) either excluded or did not include participants older than 70 years. No trial provided information on the number and characteristics of participants older than 70 years. Although most trials did not enroll older participants, the 5662 participants in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) (30) with an eGFR less than 60 mL/min per 1.73 m^2 had a mean age of 71 years, indicating that this trial enrolled a

Table 1. **Summary of Guidelines***

Source Document (Reference)	Year of Publication	Guideline Number	Search Dates for Evidence	Target Population	Trials Cited, *n*	Trials Reviewed, *n*
2004 KDOQI Clinical Practice Guidelines on Hypertension and Hypertensive Agents in Chronic Kidney Disease (8)	2004	8.2	1966 to July 2002†	Diabetes with an eGFR <60 mL/min per 1.73 m^2 or ACR ≥30 mg/g; hypertension not required	19	18
		9.2	1966 to July 2002†	No diabetes with a protein–creatinine ratio ≥200 mg/g; hypertension not required	11	8
2007 KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease (10)	2007	3.1	January 1990 to August 2005	Diabetes and an eGFR <60 mL/min per 1.73 m^2 or "kidney damage"; blood pressure ≥130/80 mm Hg	18	16
JNC 7 (12)	2003		January 1997 to April 2003	eGFR <60 mL/min per 1.73 m^2 or ACR ≥200 mg/g; blood pressure ≥130/80 mm Hg	5	5
American Diabetes Association, Standards of Medical Care in Diabetes (11)	2008		1988 to October 2007	ACR ≥30 mg/g; hypertension not required	3	3
All sources					32	27

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; KDOQI = Kidney Disease Outcomes Quality Initiative.
* Some studies were cited in more than 1 guideline.
† Select studies identified by experts were added after this date.

substantial number of persons older than 70 years. With the notable exception of ALLHAT, older adults were poorly represented in most guideline trials.

What Were the Other Characteristics of Participants in Guideline Trials?

Most trials (70%) enrolled only participants with diabetes. Six trials were limited to those with type 1 diabetes ($n = 775$), 12 trials were limited to those with type 2 diabetes ($n = 6840$), and 1 trial included participants with either type 1 or type 2 diabetes ($n = 103$). Two trials included participants both with and without diabetes ($n = 6245$). The remaining 6 trials were conducted among participants without diabetes ($n = 1831$). Hypertension was an entry requirement for most trials. Female participants ranged from 23% to 70% across trials. Urinary protein excretion of at least 30 mg/d or equivalent was an entry criterion for 79% of trials in persons with diabetes. Only 1 trial that included participants without diabetes explicitly required a minimum level of proteinuria. Nevertheless, mean urinary protein excretion at baseline exceeded 500 mg/d in most trials of nondiabetic chronic kidney disease. The only trial not to ascertain urinary protein level was ALLHAT, which included participants both with and without diabetes. In summary, most guideline trials were conducted among participants with diabetes and most favored inclusion of participants with proteinuria.

Are Older Adults Well Represented in Recent Trials Comparing the Effect of ACE Inhibitors or ARBs With That of Other Agents on Progression of Chronic Kidney Disease?

We conducted a MEDLINE search from 1 July 2002 through 31 December 2008 to identify the results of major trials published after the most recent review dates for the 2004 KDOQI guideline (for studies of nondiabetic kidney disease) and the 2007 KDOQI guideline (for studies of diabetic kidney disease). We limited our search to English-language publications, human studies, and RCTs. One coauthor reviewed all titles, and abstracts and manuscripts as needed, to identify eligible studies. We included only RCTs that compared the effect of ACE inhibitors or ARBs with a control group not receiving either agent, enrolled more than 200 participants, and included at least 1 renal outcome measure. We excluded trials in specialized populations (for example, patients receiving dialysis, kidney transplant recipients, and patients with heart failure). Two coauthors separately abstracted prespecified baseline participant characteristics and exclusion criteria for eligible trials.

We identified 380 MEDLINE citations, obtained 68 articles for further review, and identified 6 eligible trials (**Appendix Table 2**, available at www.annals.org) (49–54). Only 1 trial did not enroll participants older than 70 years. Mean participant age ranged from 45 to 63 years across trials. All but 1 trial included participants without diabetes. Only 2 trials (49, 54) included a substantial number of participants without microalbuminuria or macroalbuminuria. Dagenais and colleagues (49) randomly assigned 5269 adults age 30 years or older with glucose intolerance and without clinical proteinuria to receive ramipril or placebo. The composite renal outcome (increase in proteinuria, decrease in eGFR ≥30%, or dialysis or transplantation) did not differ between groups over a 3-year follow-up. Vogt and colleagues (54) randomly assigned 614 adults to receive telmisartan, hydrochlorothiazide, or placebo. Most participants did not have diabetes, and only 25% had microalbuminuria or macroalbuminuria. Over a 6-week follow-up, urinary albumin excretion decreased to the greatest extent in the group receiving telmisartan. Change in creatinine clearance did not differ across groups. Our search also identified an age-stratified analysis of data from a trial that was referenced in several guidelines (the RENAAL [Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan] trial [55]). A total of 421 participants in this trial were older than 65 years at the time of enrollment (55). The mean albumin–creatinine ratio for these older participants was 1541 mg/g. The protective effect of losartan on risk for end-stage renal disease was similar to the effect in younger participants. In summary, most recent trials included participants older than 70 years but did not provide strong evidence that ACE inhibitors and ARBs slow progression in nonproteinuric chronic kidney disease.

Are Older Adults With Chronic Kidney Disease in the General Population Similar to Trial Participants?

Serum creatinine, urine albumin, and urine creatinine measurements were available for 17 433 of the 20 311 participants age 20 years or older in NHANES 1999–2006 (**Table 2**). We used the reexpressed Modification of Diet in Renal Disease equation to estimate GFR for this group (56, 57). We excluded participants who were pregnant or menstruating at the time of the examination ($n = 1100$) and those whose eGFR was less than 15 mL/min per 1.73 m^2 or who reported receiving dialysis within the past year ($n = 42$). Among the remaining 16 291 participants, 1985 participants met the JNC 7 interpretation of the KDOQI definition of chronic kidney disease (eGFR <60 mL/min per 1.73 m^2 or albumin–creatinine ratio ≥200 mg/g) (12, 58). We also identified 3259 participants who met a broader interpretation of the KDOQI definition of chronic kidney disease (eGFR <60 mL/min per 1.73 m^2 or albumin–creatinine ratio ≥30 mg/g) for secondary analysis.

All analyses were conducted by using sample weights and statistical techniques to accommodate the complex survey design of NHANES (Stata, version 10, StataCorp, College Station, Texas). We estimated the prevalence of chronic kidney disease by age group, defined as an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creati-

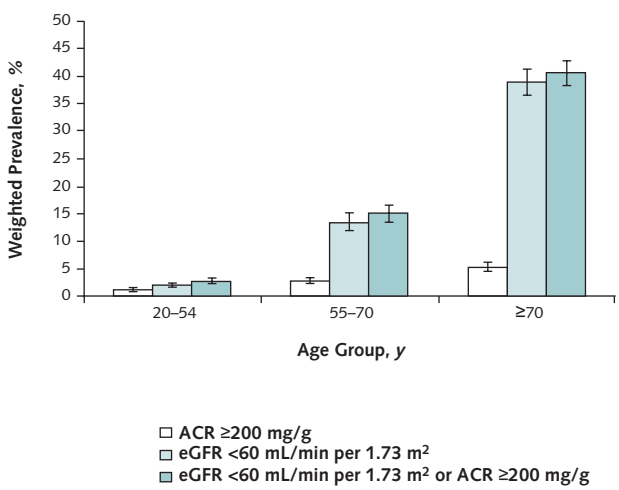
Table 2. **Derivation of Study Cohorts**

Cohort	NHANES 1999–2006 Participants, by Age Group, *n*			
	≥20 y	20–54 y	55–70 y	>70 y
All participants	20 311	12 090	4366	3855
Excluded because of missing creatinine or ACR measurements	2878	1423	545	910
Excluded for eGFR <15 mL/min per 1.73 m^2, dialysis, or pregnant or menstruating	1142	1109	21	12
Denominator of eligible participants with an eGFR ≥15 mL/min per 1.73 m^2	16 291	9558	3800	2933
Analytic sample with an eGFR <60 mL/min per 1.73 m^2 or ACR ≥200 mg/g	1985	253	542	1190
Analytic sample with an eGFR <60 mL/min per 1.73 m^2 or ACR ≥30 mg/g	3259	813	926	1520

ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey.

nine ratio of 200 mg/g or greater. Among the 1985 NHANES participants who met this definition of chronic kidney disease, we estimated the proportion age 20 to 54 years, 55 to 70 years, and older than 70 years, respectively. For each age group, we described the demographic characteristics, prevalence of diabetes (based on self-report, a fasting blood glucose level ≥6.99 mmol/L [≥126 mg/dL], or a nonfasting blood glucose level ≥11.1 mmol/L [≥200 mg/dL]), prevalence of hypertension (defined as an average measured blood pressure ≥130/80 mm Hg or self-report of treatment with antihypertensive medications), prevalence of self-reported ACE inhibitor or ARB use at the time of the NHANES examination, proportion with an eGFR less than 60 mL/min per 1.73 m^2, and proportion with an albumin–creatinine ratio of 200 mg/g or greater. We used logistic regression analysis adjusted for the aforementioned characteristics to estimate the association between age group and albumin–creatinine ratio of 200 mg/g or greater among adults with an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio of 200 mg/g or greater. Participants age 20 to 54 years were the referent category for this analysis. We conducted a secondary analysis among the 3259 NHANES participants who met the broader definition of chronic kidney disease (eGFR <60 mL/min per 1.73 m^2 or albumin–creatinine ratio ≥30 mg/g). For each age group, we estimated the proportion with an albumin–creatinine ratio of 30 mg/gor greater. We also measured the adjusted association ofage with albumin–creatinine ratio of 30 mg/g or greater.

Figure. **Prevalence of chronic kidney disease, by age group.**



ACR = albumin–creatinine ratio; eGFR = estimated glomerular filtration rate.

With increasing age, the prevalence of an eGFR less than 60 mL/min per 1.73 m^2 increases dramatically, and the prevalence of an albumin–creatinine ratio of 200 mg/g or greater increases more modestly (**Figure**). An estimated 40.6% (95% CI, 38.3% to 43%) of persons older than 70 years have an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio of 200 mg/g or greater. Persons older than 70 years account for 48.5% (CI, 45.3% to 51.6%) of all noninstitutionalized adults in the general population who meet this definition of chronic kidney disease (**Table 3**).

Among persons older than 70 years with an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio of 200 mg/g or greater, 85.8% (CI, 82.4% to 88.7%) have hypertension, 22.2% (CI, 19.0% to 26.9%) have diabetes, and only 12.9% (CI, 10.9% to 15.4%) have an albumin–creatinine ratio of 200 mg/g or greater. Even among the subset with diabetes, only 24.2% (CI, 19.0% to 30.2%) have an albumin–creatinine ratio of 200 mg/g or greater. The proportion of older persons with chronic kidney disease who have an albumin–creatinine ratio of 200 mg/g or greater is considerably lower than for younger age groups (**Table 3**). Even after adjustment for other differences between age groups, a smaller proportion of adults age 55 to 70 years with chronic kidney disease (odds ratio, 0.31 [CI, 0.20 to 0.48]) and older than 70 years (odds ratio, 0.26 [CI, 0.17 to 0.38]) have an albumin–creatinine ratio of 200 mg/g or greater compared with the referent group (age 20 to 54 years).

In a secondary analysis using the 3259 participants with an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio of 30 mg/g or greater (**Table 4**),a smaller proportion of persons age 55 to 70 years (odds ratio, 0.25 [CI, 0.18 to 0.35]) and older than 70 years

Table 3. **Characteristics of NHANES Participants With an eGFR Less Than 60 mL/min per 1.73 m^2 or ACR of 200 mg/g or Greater, by Age Group***

Characteristic	Age Group		
	20–54 y (*n* = 253)	55–70 y (*n* = 542)	>70 y (*n* = 1190)
Weighted proportion	20.4 (17.8–23.4)	31.1 (28.5–33.8)	48.5 (45.3–51.6)
Women	55.3 (48.5–61.8)	60.7 (56.8–64.6)	62.6 (59.8–65.4)
White persons	66.9 (60.4–72.8)	80.2 (75.8–84.0)	88.2 (85.1–90.8)
Hypertension†	75.2 (67.5–81.5)	77.1 (73.0–80.8)	85.8 (82.4–88.7)
Diabetes	20.8 (15.3–27.6)	28.4 (23.3–34.2)	22.2 (19.0–26.9)
Current ACE inhibitor or ARB use	17.7 (13.4–23.1)	38.5 (33.4–43.8)	37.4 (34.5–40.3)
eGFR <60 mL/min per 1.73 m^2	68.6 (60.5–75.6)	90.6 (87.3–93.1)	95.9 (94.5–97.0)
ACR ≥200 mg/g			
All participants‡	38.1 (30.0–46.8)	18.1 (14.4–22.4)	12.9 (10.9–15.4)
Participants with diabetes§	64.1 (46.8–78.4)	39.9 (29.7–51.1)	24.2 (19.0–30.2)
Participants without diabetes‖	31.2 (23.6–40.0)	9.4 (6.3–13.9)	9.7 (7.6–12.4)

ACE = angiotensin-converting enzyme; ACR = albumin–creatinine ratio; ARB = angiotensin II–receptor blocker; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey.
* Values are percentages (95% CIs). All percentages represent weighted population estimates. Diabetes is defined by self-report, a fasting blood glucose level ≥6.99 mmol/L (≥126 mg/dL), or nonfasting blood glucose level ≥11.1 mmol/L (≥200 mg/dL). Hypertension is defined as an average measured blood pressure ≥130/80 mm Hg or self-reported use of antihypertensive medications.
† A total of 150 participants in this cohort did not have 1 or more blood pressure measurements and are not included in these calculations.
‡ 1985 participants had an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥200 mg/g.
§ 552 participants with an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥200 mg/g had diabetes.
‖ 1433 participants with an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥200 mg/g did not have diabetes.

(odds ratio, 0.23 [CI, 0.17 to 0.32]) are estimated to have an albumin–creatinine ratio of 30 mg/g or greater compared with the referent group (age 20 to 54 years), after adjustment for other participant characteristics. In summary, older persons with chronic kidney disease differ considerably from participants in guideline trials, particularly in the frequency of proteinuria.

Discussion

Older adults have been underrepresented in most RCTs used to develop major contemporary U.S. practice guidelines and recommendations for the use of ACE inhibitors and ARBs in patients with chronic kidney disease. Whereas almost one half of U.S. adults who meet criteria for chronic kidney disease are older than 70 years, most trials on which these guidelines were based did not include participants from this older age group. The relevance of these trials to older adults may be further limited because most trials required that participants have proteinuria, whereas most elderly people who meet criteria for chronic kidney disease do not have proteinuria.

Table 4. **Characteristics of NHANES Participants With an eGFR Less Than 60 mL/min per 1.73 m^2 or ACR of 30 mg/g or Greater, by Age Group***

Characteristic	Age Group		
	20–54 y (*n* = 813)	55–70 y (*n* = 916)	>70 y (*n* = 1520)
Weighted proportion	35.8 (33.1–38.6)	28.4 (26.2–30.6)	35.8 (33.4–38.4)
Women	56.5 (53.2–59.8)	56.9 (53.5–60.3)	61.3 (58.4–64.1)
White persons	59.5 (54.8–64.1)	76.4 (72.1–80.2)	87.1 (83.7–89.8)
Hypertension†	63.3 (58.3–67.9)	78.0 (74.3–81.4)	86.1 (83.0–88.6)
Diabetes	19.6 (16.2–23.5)	31.4 (27.1–36.0)	22.0 (19.5–24.6)
Current ACE inhibitor or ARB use	14.0 (11.6–16.9)	35.1 (31.3–39.2)	35.4 (32.6–38.4)
eGFR <60 mL/min per 1.73 m^2	23.0 (19.0–27.4)	58.3 (54.0–62.6)	76.2 (73.4–78.8)
ACR ≥30 mg/g			
All participants‡	81.5 (77.1–85.3)	53.3 (49.0–57.6)	47.0 (44.0–50.1)
Participants with diabetes§	89.9 (82.7–94.3)	72.6 (65.4–78.8)	60.8 (54.8–66.4)
Participants without diabetes‖	79.5 (74.3–83.8)	44.5 (39.8–49.3)	43.1 (39.8–46.6)

ACE = angiotensin-converting enzyme; ACR = albumin–creatinine ratio; ARB = angiotensin II–receptor blocker; eGFR = estimated glomerular filtration rate; NHANES = National Health and Nutrition Examination Survey.
* Values are percentages (95% CIs). All percentages represent weighted population estimates. Diabetes is defined by self-report, a fasting blood glucose level ≥6.99 mmol/L (≥126 mg/dL), or nonfasting blood glucose level ≥11.1 mmol/L (≥200 mg/dL). Hypertension is defined as an average measured blood pressure ≥130/80 mm Hg or self-reported use of antihypertensive medications.
† A total of 239 participants in this cohort did not have 1 or more blood pressure measurements and are not included in these estimates.
‡ 3259 participants had an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥30 mg/g.
§ 914 participants with an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥30 mg/g had diabetes.
‖ 2345 participants with an eGFR <60 mL/min per 1.73 m^2 or an ACR ≥30 mg/g did not have diabetes.

The greater preponderance of nonproteinuric chronic kidney disease in older adults may be due to several factors. The accuracy of the Modification of Diet in Renal Disease equation for estimating true GFR in persons older than 70 years is unknown (59). The most common underlying causes of kidney disease probably also vary with age. However, longitudinal data suggest that even without known renal disease, hypertension, and other comorbid conditions, creatinine clearance tends to decrease with advancing age (60). Thus, in many older adults, moderate reductions in eGFR may be more indicative of renal senescence than of a true disease process (61). Glomerulosclerosis, interstitial fibrosis, tubular atrophy, reduction in nephron number, and alterations to the renal vasculature are all thought to occur as a result of aging and may not be associated with proteinuria (61).

It is possible that ACE inhibitors and ARBs slow progression of nonproteinuric, nondiabetic chronic kidney disease through their antifibrotic and antiinflammatory effects on the kidney (62, 63). However, most trials we reviewed were not designed to test this hypothesis, and trial evidence for ACE inhibitors does not support this (30, 49). The only guideline trial that enrolled participants without diabetes and did not select for proteinuria was ALLHAT (mean urinary protein excretion was at least 500 mg/d in all other guideline trials among participants without diabetes). With the possible exception of 1 small trial for which we could not ascertain maximum participant age, ALLHAT was also the only trial to enroll participants without diabetes who were older than 70 years. This large trial demonstrated that an ACE inhibitor, thiazide diuretic, and calcium-channel blocker all had similar effects on progression of renal disease. These negative results have been attributed partly to entry criteria that did not favor recruitment of participants with proteinuria or progressive kidney disease (64). At the same time, these entry criteria are precisely what make the results of ALLHAT so relevant to older persons with nonproteinuric chronic kidney disease.

The size and appropriateness of the elderly population targeted varies considerably across guidelines. For example, JNC 7 recommends ACE inhibitors or ARBs for the treatment of hypertension in everyone with an eGFR less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio of 200 mg/g or greater. Although this recommendation applies to more than one third of persons older than 70 years, use of these agents to slow progression in this large group is not supported by available evidence. It is also not clear that slowing progression of kidney disease represents the most patient-centric goal of therapy for many of these individuals. Progression of kidney disease is often slow in elderly persons, and the vast majority of older adults with chronic kidney disease will die before reaching end-stage renal disease (65–69). Other clinical outcomes, such as cardiovascular events and the development of cognitive impairment and disability, are far more common in this population and may in many instances represent more meaningful therapeutic targets (70–72).

Our study has several limitations. First, our analyses relied on single measurements of creatinine and urinary albumin–creatinine ratio, whereas the KDOQI definition of chronic kidney disease requires that kidney damage or abnormalities in eGFR be present for at least 3 months (58). Second, we address the question of whether the evidence cited in contemporary U.S. practice guidelines advocating the use of ACE inhibitors or ARBs in chronic kidney disease can be generalized to older adults with this condition. Because the effect of these agents on progression of chronic kidney disease provides the rationale for these guidelines, we do not address the effect of these agents on other clinical outcomes in older adults.

In conclusion, older adults were underrepresented in most trials used to formulate major contemporary U.S. practice guidelines and recommendations for the use of ACE inhibitors and ARBs in patients with chronic kidney disease. Most trials favored inclusion of participants with proteinuria and thus may not be relevant to the great majority of older adults with nonproteinuric chronic kidney disease.

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Appendix Table 1. Baseline Participant Characteristics and Entry Criteria of Guideline Trials*

Study, Year (Reference)†	Intervention	Total Participants, *n*	Follow-up, *y*	Sponsor	Women, %‡	Mean Age, *y*‡	Entry Criteria				
							Age (Range), *y*	Proteinuria (Mean or Median Value)	Hypertension	Diabetes Mellitus	Renal Function (Mean)
Mathiesen et al, 1991 (28)	Captopril and thiazide vs. control	44	4	Government, professional organization	50	29	<50	MICRO	DBP <95 mm Hg	Type 1	GFR >90 mL/min per 1.73 m^2 (GFR, 128 mL/min per 1.73 m^2)
Viberti et al, 1994 (41)	Captopril vs. placebo	92	2	Industry	45	32	18–55	MICRO	<160/95 mm Hg if ≥35 y and <145/90 mm Hg if <35 y	Type 1	SCr <1.7 mg/dL (GFR, 124 mL/min per 1.73 m^2)
Laffel et al, 1995 (24)	Captopril vs. placebo	143	2	Industry	69	33	14–57	MICRO	<140/90 mm Hg	Type 1	SCr within "normal" range (CrCl, 80 mL/min)
Lewis et al, 1993 (25)	Captopril vs. placebo	409	3	Industry, government	47	35	18–49	PER ≥0.5 g/d (mean PER, 2.8 g/d)	NS (75.5% >140/90 mm Hg)	Type 1	SCr <2.5 mg/dL (CrCl, 82 mL/min)
Tarnow et al, 2000 (37)	Lisinopril vs. nisoldipine	48	4	Industry	33	38	18–55	AER >300 mg/d (mean AER, 1.3 g/d)	DBP, 90–105 mm Hg	Type 1	NS (GFR, 85 mL/min per 1.73 m^2)
Sawicki, 1997 (34)	Ramipril vs. metoprolol vs. felodipine	39	2	Industry	41	39	NR	AER >300 mg/d (mean AER, 2.2 g/d)	>140/90 mm Hg	Type 1	GFR <100 mL/min per 1.73 m^2 (women) <110 mL/min per 1.73 m^2 (men) (GFR, 68 mL/min per 1.73 m^2)
Ravid et al, 1996 and 1993 (31, 32)	Enalapril vs. placebo	108	7	Private grant	52	44	<50	AER <30 mg/g	>140/90 mm Hg	Type 2	SCr ≤1.4 mg/dL (CrCl, 108 mL/min)
Ruggenenti et al, 1999 and 1997 (6, 13)	Ramipril vs. placebo	352	2.3–2.6	Industry	24	49	18–70	PER ≥1 g/d (mean PER, 3.4 g/d)	NS (86% ≥140/90 mm Hg)	Nondiabetic	GFR, 20–70 mL/min per 1.73 m^2 (GFR, 43 mL/min per 1.73 m^2)
van Essen et al, 1997 (39)	Enalapril vs. atenolol	89	3	Industry	36	50	18–65	NS (mean PER, 1.3 g/d)	NS (47% DBP ≥90 mm Hg)	Nondiabetic	CrCl, 30–90 mL/min (GFR, 53 mL/min)
Maschio et al, 1996 (27)	Benazepril vs. placebo	583	3	Industry	28	51	18–70	PER ≤10 g/d (mean PER, 1.8 g/d)	NS (82% DBP ≥90 mm Hg)	NS (4% diabetes)	CrCl, 30–60 mL/min (SCr, 2.1 mg/dL)
Hannedouche et al, 1994 (23)	Enalapril vs. β-blocker	100	3	Industry	47	51	18–70	NS (mean PER, 2.2 g/d)	DBP ≥90 mm Hg	Nondiabetic	SCr, 2.3–4.5 mg/dL (GFR, 20 mL/min per 1.73 m^2)
Suzuki et al, 2001 (36)	Benazepril and amlodopine vs. arotinolol and amlodopine	65	2	Institutional	43	53	NS (NR)	PER <3 g/d (mean PER, 1 g/d)	≥140/90 mm Hg	Nondiabetic	SCr >1.5 mg/dL (NR)
De Cesaris et al, 1996 (21)	Benazepril vs. nicardipine	103	0.5	Industry	46	53	NS (23–68)	MICRO	NS (45% DBP ≥95 mm Hg)	Type 1 or 2 (12% type 1)	NS (GFR, 141 mL/min)
Velussi et al, 1996 (40)	Cilazepril vs. amlodopine	44	3	Government	23	54	≤70	MICRO	>140/90–114 mm Hg	Type 2	Not specified (GFR, 113 mL/min per 1.73 m^2)
Agodoa et al, 2001 (15), and Wright et al, 2002 (42)	Metoprolol vs. ramipril and vs. amlodopine	1094	6.4	Government, industry	39	55	18–70	PER <2.5 g/d (mean PER, 0.5 g/d)	DBP ≥95 mm Hg	Nondiabetic	GFR, 20–65 mL/min per 1.73 m^2 (GFR, 43 mL/min per 1.73 m^2)
Trevisan and Tiengo, 1995 (38)	Ramipril vs. placebo	122	0.5	Industry	23	57	18–65	MICRO	<180/105 mm Hg	Type 2	SCr <1.5 mg/dL (SCr, 0.99 mg/dL)
Chan et al, 1992 and 2000 (18, 19)	Enalapril vs. nifedipine	102	1	Industry	60	58	>18 (32–76)	NS (geometric mean AER, 67 mg/d)	SBP, 150–220 mm Hg, or DBP >100 mm Hg	Type 2	SCr <2.3 mg/dL (CrCl, 81 mL/min)
Parving et al, 2001 (29)	Irbesartan, 150 mg vs. 300 mg, vs. placebo	590	2	Industry	32	59	30–70	MICRO	>135/85 mm Hg	Type 2	SCr <1.5 mg/dL (CrCl, 108 mL/min)
Agardh et al, 1996 (14)	Lisinopril vs. nifedipine	335	1	Industry	29	59	18–75	MICRO	DBP, 90–100 mm Hg	Type 2	CrCl ≥30 mL/min (CrCl, 100 mL/min)

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Appendix Table 1—Continued

Study, Year (Reference)†	Intervention	Total Participants, *n*	Follow-up, *y*	Sponsor	Women, %‡	Mean Age, *y*‡	Entry Criteria				
							Age (Range), *y*	Proteinuria (Mean or Median Value)	Hypertension	Diabetes Mellitus	Renal Function (Mean)
Lewis et al, 2001 (26)	Irbesartan vs. amlodopine vs. placebo	1715	2.6	Industry	34	59	30–70	PER ≥0.9 g/d (median PER, 2.9 g/d)	>135/85 mm Hg	Type 2	SCr 1–3 mg/dL (women), 1.2–3 mg/dL (men) (SCr, 1.7 mg/dL)
Estacio et al, 1998 (22), and Schrier et al, 2002 (43)	Enalapril vs. nisoldipine vs. placebo	950	5	Government, industry	37	60	40–74	NS (mean AER, 246 mg/d)	NS (50% ≥140/90 mm Hg)	Type 2	SCr ≤3 mg/dL (GFR, 84 mL/min per 1.73 m^2)
Brenner et al, 2001 (17)	Losartan vs. placebo	1513	3.4	Industry	37	60	31–70	AER >300 mg/d (mean AER, 1.3 g/d)	NS (96.5% hypertension)	Type 2	SCr, 1.3–3 mg/dL (SCr, 1.9 mg/dL)
Ruggenenti et al, 2004 (33)	Trandolopril and verapamil vs. each alone vs. placebo	1204	3	Industry	47	62	≥40 (39–85)	AER <30 mg/g	≥130/85 mm Hg	Type 2	SCr <1.5 mg/dL (SCr, 0.9 mg/dL)
Bakris et al, 1996 (16)	Lisinopril vs. verapamil or diltiazem vs. atenolol	52	6	Professional organization, foundation	50	63	≥45 (45–69)	PER >2 g/d (mean PER, 3.8 g/d)	Hypertension ≥8 y	Type 2	CrCl ≤70 mL/min (CrCl, 63.6 mL/min)
Schnack et al, 1996 (35)	Ramipril vs. atenolol	105	1	NR	70	67	40–80	MICRO	>160/95 mm Hg	Type 2	Severe renal failure excluded (SCr, 1 mg/dL)
Cinotti et al, 2001 (20)	Lisinopril vs. other	131	1.9	Industry	35	67	18–70	PER <1 g/d (mean PER, 0.5 g/d)	DBP ≥95 mm Hg	Nondiabetic	GFR, 20–50 mL/min per 1.73 m^2 (GFR, 36 mL/min per 1.73 m^2)
Rahman et al, 2005 (30)	Chlorthalidone vs. lisinopril and vs. amlodopine	5662	4.9	Government, industry	52	71	≥55 (55–103)	NA	Stage 1 or 2 hypertension	NS (34% diabetes)	SCr ≤2 mg/dL (subgroup all with GFR <60 mL/min per 1.73 m^2)

AER = albumin excretion rate; CrCl = creatinine clearance; DBP = diastolic blood pressure; GFR = glomerular filtration rate (estimated or measured); MICRO = microalbuminuria (or an albumin excretion rate of 30–300 mg/d or equivalent); NA = not ascertained; NR = not reported; NS = not specified; PER = protein excretion rate; SBP = systolic blood pressure; SCr = serum creatinine.

* When studies reported serum creatinine in μmol/L, we converted the units to mg/dL by dividing by 88.4. When more than 1 measure of renal function was provided (either at baseline or as an entry criteria), we abstracted the following in order of preference: measured GFR > estimated GFR > creatinine clearance > serum creatinine. The value of a protein or albumin–creatinine ratio was considered equivalent to daily protein or albumin excretion in grams. Because albumin does not account for all urinary protein, we specify whether studies referred to albumin or to protein excretion. When both were reported, we abstracted only protein excretion.

† All trials were referenced in either (or both) the 2004 or 2007 KDOQI guidelines. JNC 7 referenced Lewis et al, 1993 (25); Lewis et al, 2001 (26); Brenner et al, 2001 (17); Wright et al, 2002 (42); and Ruggenenti et al, 1997 (13). The American Diabetes Association Standards of Medical Care in Diabetes 2008 referenced Lewis et al, 1993 (25); Laffel et al, 1995 (24); and Ruggenenti et al, 2004 (33).

‡ Values rounded to the closest integer.

Appendix Table 2. Baseline Participant Characteristics and Entry Criteria of Trials Published After Guideline Preparation*

Study, Year (Reference)	Intervention	Total Participants, *n*	Follow-up Duration	Sponsor	Women, %†	Mean Age, *y*†	Entry Criteria				
							Age (Range), *y*	Proteinuria (Mean or Median Value)	Hypertension	Diabetes Mellitus	Renal Function (Mean)
Hou et al, 2006 (51)	Benazepril vs. placebo	224	3.4 y	Industry, government	51	45	18–70	PER >300 mg/d (mean PER, 1.7 g/d)	NS (91.5% hypertension)	Nondiabetic	SCr, 3.1–5 mg/dL (GFR, 26 mL/min per 1.73 m^2)
Asselbergs et al, 2004 (52)	Fosinopril vs. placebo	864	3.8 y	Industry, foundation	35	51	28–75	MICRO	160/100 mm Hg	NS (2.6% diabetes)	CrCl >60% normal value for age (SCr, 1 mg/dL)
Dagenais et al, 2008 (49)	Ramipril vs. placebo	5269	3 y	Industry, government	59	55	≥30‡	AER <300 mg/d§ (19% MICRO)	NS (43.4% hypertension)	Nondiabetic with glucose intolerance	SCr, 0.6–2.3 mg/dL (SCr, 0.9 mg/dL)
Esnault et al, 2008 (50)	Amlodopine vs. enalapril	263	2.9 y	Industry	41	58	18–80	PER <3 g/d (mean PER, 1.3 g/d)	DBP, 90–119 mm Hg	Nondiabetic	CrCl, 20–60 mL/min (GFR, 46 mL/min per 1.73 m^2)
Makino et al, 2007 (53)	Telmisartan vs. placebo	514	1.3 y	Industry	27	62	30–74	MICRO	180/100 mm Hg	Type 2	SCr <1.5 mg/dL (men), <1.3 mg/dL (women) (SCr, 0.8 mg/dL)
Vogt et al, 2005 (54)	Telmisartan vs. hydrochlorothiazide vs. placebo	614	6 wk	Industry	55	63	35–84	Detectable albuminuria (25% MICRO or MACRO)‖	SBP, 150–179 and DBP <90 mm Hg	NS (10.4% diabetes)	SCr ≤1.8 mg/dL (CrCl, 103 mL/min)

AER = albumin excretion rate; CrCl = creatinine clearance; DBP = diastolic blood pressure; GFR = glomerular filtration rate (estimated or measured); MACRO = macroalbuminuria (or an AER greater than 300 mg/d or equivalent); MICRO = microalbuminuria (or an AER of 30–300 mg/d or equivalent); NS = not specified; PER = protein excretion rate; SBP = systolic blood pressure; SCr = serum creatinine.

* When studies reported serum creatinine in μmol/L, we converted the units to mg/dL by dividing by 88.4. When more than 1 measure of renal function was provided (either at baseline or as an entry criteria), we abstracted the following in order of preference: measured GFR > estimated GFR > creatinine clearance > serum creatinine. The value of a protein or albumin–creatinine ratio was considered equivalent to daily protein or albumin excretion in grams. Because albumin does not account for all urinary protein, we specify whether studies referred to albumin or to protein excretion. When both were reported, we abstracted only protein excretion.

† Values rounded to the closest integer.

‡ Maximum age >80 y but exact age range not available.

§ AER was estimated from the reported albumin–creatinine ratio in mg/mmol.

‖ Defined as AER ≥2.2 mg/L.