Meta-analysis: Effect of Monotherapy and Combination Therapy with Inhibitors of the Renin–Angiotensin System on Proteinuria in Renal Disease

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Background: Reduction of proteinuria is associated with delayed progression of chronic kidney disease. Reports suggest that angiotensin-receptor blockers (ARBs) reduce proteinuria, but results are variable. The relative effect of ARBs and angiotensin-converting enzyme (ACE) inhibitors, and their combined administration, remains uncertain.

Purpose: To establish the effect of ARBs versus placebo and alternative treatments, and the effect of combined treatment with ARBs and ACE inhibitors, on proteinuria.

Data Sources: English-language studies in MEDLINE and the Cochrane Library Central Register of Controlled Trials (January 1990 to September 2006), reference lists, and expert contacts.

Study Selection: Randomized trials of ARBs versus placebo, ACE inhibitors, calcium-channel blockers, or the combination of ARBs and ACE inhibitors in patients with or without diabetes and with microalbuminuria or proteinuria for whom data were available on urinary protein excretion at baseline and at 1 to 12 months.

Data Extraction: Two investigators independently searched and abstracted studies.

Data Synthesis: Forty-nine studies involving 6181 participants reported results of 72 comparisons with 1 to 4 months of follow-up and 38 comparisons with 5 to 12 months of follow-up. The ARBs reduced proteinuria compared with placebo or calcium-channel blockers over 1 to 4 months (ratio of means, 0.57 [95% CI, 0.47 to 0.68] and 0.69 [CI, 0.62 to 0.77], respectively) and 5 to 12 months (ratio of means, 0.66 [CI, 0.63 to 0.69] and 0.62 [CI, 0.55 to 0.70], respectively). The ARBs and ACE inhibitors reduced proteinuria to a similar degree. The combination of ARBs and ACE inhibitors further reduced proteinuria more than either agent alone: The ratio of means for combination therapy versus ARBs was 0.76 (CI, 0.68 to 0.85) over 1 to 4 months and 0.75 (CI, 0.61 to 0.92) over 5 to 12 months; for combination therapy versus ACE inhibitors, the ratio of means was 0.78 (CI, 0.72 to 0.84) over 1 to 4 months and 0.82 (CI, 0.67 to 1.01) over 5 to 12 months. The antiproteinuric effect was consistent across subgroups.

Limitations: Most studies were small, varied in quality, and did not provide reliable data on adverse drug reactions. Proteinuria reduction is only a surrogate for important progression of renal failure.

Conclusion: The ARBs reduce proteinuria, independent of the degree of proteinuria and of underlying disease. The magnitude of effect is similar regardless of whether the comparator is placebo or calcium-channel blocker. Reduction in proteinuria from ARBs and ACE inhibitors is similar, but their combination is more effective than either drug alone. Uncertainty concerning adverse effects and outcomes that are important to patients limits applicability of findings to clinical practice.

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Proteinuria increases the risk for progression of chronic kidney disease and development of end-stage renal failure (1, 2). Experiments in animal models suggest that urinary protein excretion not only reflects the severity of the underlying renal disorder but also contributes to progressive renal scarring and therefore to progression of renal disease (1, 2). In an interventional study of diabetic nephropathy, the therapy-induced change of urinary protein excretion during the first few weeks was linearly related to renal outcome after several years (3).

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Inhibition of the renin–angiotensin system (for example, with angiotensin-receptor blockers [ARBs]) causes a reduction in urinary protein excretion that is in part independent of the reduction in blood pressure but depends on the activity of the renin–angiotensin system (1, 2). Clinical trials investigating the antiproteinuric action of ARBs have reported variable effect sizes. It is uncertain whether ARBs are equally effective antiproteinuric agents as ACE inhibitors, or whether the combination of ACE inhibitors with ARBs is preferable to either agent alone (4). We therefore conducted a systematic review and meta-analysis of the effects of ARBs on urinary protein excretion in patients with nephropathy compared with placebo and other antihypertensive agents and their combinations. Because improved renal outcomes probably require sustained reduction in proteinuria, we addressed the effects of ARB therapy over several months and up to 1 year.

Methods

Data Sources and Searches

We searched MEDLINE and the Cochrane Library Central Register of Controlled Trials (Issue 3, 2006) for relevant articles published between January 1990 and Sep-

tember 2006 by using the following Medical Subject Heading terms and keywords: *angiotensin-receptor-blockers**, the generic names of currently available ARBs (*losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, olmesartan*), *proteinuria, albuminuria, microalbuminuria*, and *diabetic nephropathies*. We screened the reference lists of included studies and related publications and approached experts for additional studies. We restricted the search to randomized, controlled trials (RCTs) published in English.

Study Selection

We included full-text publications that investigated patients with microalbuminuria and proteinuria of diabetic and other causes and reported changes in urinary protein excretion during treatment with ARBs compared with placebo, ACE inhibitors, or other antihypertensive drugs. We also assessed combination therapy with an ARB plus an ACE inhibitor versus monotherapy with either drug alone. We included studies in which the investigators measured albuminuria or proteinuria by using timed quantitative measurement or spot urine specimens and calculated the albumin–creatinine or protein–creatinine ratio. We included RCTs lasting at least 4 weeks with parallel-group or crossover designs. We excluded studies with patients who had renal transplantation or normal urinary protein excretion, those with fewer than 10 participants per treatment group, those that examined other combination therapies, and those that only compared various doses of the same drug.

Data Extraction and Quality Assessment

We extracted the following information: participants' age, sex, underlying renal disease, and baseline and follow-up urinary albumin and protein excretion rates; type and dosage of ARB and control intervention; co-interventions (concomitant use of diuretics and sodium restriction) and duration of therapy; and mean arterial blood pressure at the end of the study. When studies compared 2 or more doses of the same drug against a control drug, we used data from the group with the highest dose. We assessed the methodological quality on the basis of crossover or parallel-group design, concealment of randomization, blinding (patients and caregivers), withdrawals and dropouts, and intention-to-treat or per-protocol analysis. In crossover studies, we noted the duration of the washout period and the presence of any carryover effects. We contacted the authors of the large registration studies (5–8) for additional data on proteinuria.

We collected information on the assessment methods for adverse drug reactions, the frequency of severe adverse drugs reactions leading to discontinuation of the study, and the frequency of moderate and mild adverse drug reactions. We investigated factors that might lead to underestimation of adverse drug reactions—study design, previous exposure to an ARB or ACE inhibitor, baseline potassium level, and baseline renal impairment as assessed by the National Kidney Foundation classification (9)—to judge reliability and generalizability of the reported adverse drug reactions. We compared overall discontinuation rates because we lacked information to distinguish among discontinuation due to severe adverse drug reactions, discontinuation with an indirect link to drug exposure (noncompliance, withdrawal of consent), and discontinuation unrelated to drug exposure (protocol violations, ineligibility). We calculated differences between treatment groups from parallel-design trials to account for the unclear denominator in crossover studies in the presence of discontinuation.

Two of the investigators independently screened titles and abstracts and retrieved all articles that either reviewer regarded as potentially relevant. Three of the investigators extracted data on population, intervention, outcomes, and methods. Disagreement was resolved by consensus or discussion with a fourth investigator.

Data Synthesis and Analysis

We prespecified the following explanations for heterogeneity: severity of baseline protein excretion (microalbuminuria, defined as 30 to 300 mg/d or 20 to 200 mg/g creatinine) versus proteinuria (>300 mg albumin/d or >500 mg protein/d or per gram of urinary creatinine); cause of renal disease (diabetic vs. nondiabetic); and design features, including crossover versus parallel-group design, concealment (reported vs. not reported), blinding (blinding vs. nonblinding), and type of analysis (intention-to-treat vs. per-protocol). For each comparison, we separately pooled studies with 1 to 4 months of follow-up and 5 to 12 months of follow-up to account for the short-term crossover design. To increase the power for subgroup anal-

Context

Although evidence suggests that both angiotensin-receptor blockers (ARBs) and angiotensin-converting enzyme (ACE) inhibitors reduce proteinuria, the relative effects of ARBs compared with ACE inhibitors and whether the effect of these agents is greater when they are used in combination are unclear.

Contribution

This meta-analysis of 49 randomized trials showed that ARBs delay progression of proteinuria over the short (1 to 4 months) and longer (5 to 12 months) terms and that ARBs reduce proteinuria to a similar degree as ACE inhibitors. Although data were limited, the combination of the 2 drugs seems to reduce proteinuria more than either drug alone.

Caution

Data on adverse effects and long-term outcomes are limited.

—The Editors

Table 1. **Angiotensin-Receptor Blockers versus Placebo: Included Studies and Outcomes***

Study, Year (Reference)	Population					Intervention			
	Patients, *n*	Mean Age, *y*	Renal Disease	Stage of Chronic Renal Disease†	Baseline Proteinuria‡	Comparator, *mg*	Use of Diuretics/ Sodium Restriction	Mean Arterial Pressure at End of Treatment, *mm Hg*	Mean Follow-up, *mo*§
Andersen et al., 2000 (39)¶	16	42	Type 1 DM	1	1.2 g/d**	Losartan, 100	Yes/No	96	3
	–	–	–	–	–	Placebo	–	104	–
Lewis et al., 2001 (7);	579	59	Type 2 DM	2	2.9 g/d††	Irbesartan, 300	Yes/No	98	12
Atkins et al., 2005 (29)	569	58	–	–	–	Placebo	–	102	–
de Zeeuw et al., 2004 (3);	751	60	Type 2 DM	2	1.2 g/g creatinine††	Losartan, 50–100	Yes/No	101	12
Brenner et al., 2001 (8)	762	–	–	–	1.3 mg/g creatinine††	Placebo	–	103	–
Haneda et al., 2004 (40)	34	64	Type 2 DM	2	2.6 g/g creatinine	Candesartan, 8	No/No	93	3
	32	63	–	–	–	Placebo	–	95	–
Ishimitsu et al., 2005 (22)¶	22	56	Other	3–4	1.1 g/g creatinine	Valsartan, 40–80	Yes/Yes	101	12
	–	–	–	–	0.9 g/g creatinine	Placebo	–	101	–
Jacobsen et al., 2003 (41)¶	18	43	Type 1 DM	NR	0.4 g/d††	Valsartan, 80	Yes/No	92	2
	–	–	–	–	–	Placebo	–	101	–
Li et al., 2006 (42)	54	40	Other	2	1.8 g/d	Valsartan, 80–160	Yes/No	93	3 and 12
	55	41	–	–	2.4 g/d	Placebo	–	101	–
Muirhead et al., 1999 (43)	31	58	Type 2 DM	2	58.1 μg/min**	Valsartan, 160	Yes/No	99	12
	–	56	–	–	63.3 μg/min**	Placebo	–	101	–
Parving et al., 2001 (6)	194	57	Type 2 DM	1	53.4 μg/min**	Irbesartan, 300	Yes/No	101	12
	201	58	–	–	54.8 μg/min**	Placebo	–	102	–
Rossing et al., 2003 (44)¶	24	59	Type 2 DM	NR	NR	Candesartan, 16	Yes/No	92	2
	–	–	–	–	–	Placebo	–	101	–
Sasso et al., 2002 (45) (hypertensive)¶	32	49	Type 2 DM	NR	120 μg/min	Irbesartan, 150	No/No	109	2
	–	–	–	–	123 μg/min	Placebo	–	116	–
Sasso et al., 2002 (45) (normotensive)¶	30	49	Type 2 DM	NR	101 μg/min	Irbesartan, 150	No/No	94	2
	–	48	–	–	112 μg/min	Placebo	–	95	–
Zandbergen et al., 2003 (46)	74	57	Type 2 DM	1	78.6 μg/min	Losartan, 50–100	No/No	94	2.5
	73	59	–	–	89.4 μg/min	Placebo	–	99	–

* DM = diabetes mellitus; NR = not reported.
† Renal impairment according to the classification of the National Kidney Foundation (9): 1 = glomerular filtration rate >90 mL/min (or serum creatinine level ≤106 μmol/L [≤1.2 mg/dL]); 2 = glomerular filtration rate of 90–60 mL/min (or serum creatinine level ≤176 μmol/L [≤2 mg/dL]); 3 = glomerular filtration rate <60 mL/min (or serum creatinine level >176 μmol/L [>2 mg/dL]).
‡ Data are expressed as means, unless indicated otherwise.
§ For crossover studies: number of months per treatment period.
‖ Parallel-design studies only, accounting for the unclear denominator in crossover studies in the presence of discontinuation.
¶ Crossover trial.
** Geometric mean.
†† Median.

yses, we pooled comparisons with similar treatment effects and similar mechanisms of action (for instance, combination therapy versus monotherapy with an ARB or an ACE inhibitor). We plotted standard error against treatment effect ("funnel plot") for the comparisons at 4 months to detect publication bias. The small number of studies precluded funnel plot explorations of outcomes at 5 to 12 months. To assess the blood pressure–independent effect of ARBs on proteinuria, we examined the antiproteinuric effect in studies comparing ARBs with calcium-channel blockers—antihypertensive drugs without intrinsic antiproteinuric action—in which both treatment arms had similar blood pressure (for instance, difference in mean arterial blood pressure ≤3 mm Hg) at the end of the study.

Studies reported the main outcome, albuminuria or proteinuria, in different units that cannot easily be converted (for example, mg/d and mg/mmol creatinine). Identical measurement units are necessary to statistically analyze the results by using the weighted mean difference as the measure of treatment effect. An alternative approach to pool measures of different units uses the standardized mean difference (the absolute treatment effect in pooled SD units). This approach, however, leaves clinicians with the challenge of translating the effect measure into a clinically meaningful effect. Moreover, the distribution of urinary protein excretion values is highly skewed, suggesting a logarithmic transformation of the data before the analysis. For these reasons, we chose to summarize the treatment effects on urinary protein excretion by the ratio of the average treatment effect in the intervention group relative to the control group (10). This relative effect summary is roughly comparable across different measurement units and can be directly applied in a clinical context. In accordance with the meta-analysis by Friedrich and colleagues (10), we term this relative treatment effect the "ratio of means." We aggregated the log-transformed treatment effect ratios across studies with a random effects model. The pooled log-transformed treatment effect was then reverse transformed to

Table 1—**Continued**

Outcome			
Change in Proteinuria Ratio of Means (95% CI)		Discontinuation of Medication for Any Reason, % *(n/n)*	Risk Difference in Discontinuation Rates (Angiotensin-Receptor Blocker vs. Placebo), %‖
Short-Term Follow-up	Extended Follow-up		
0.56 (0.25–1.26)	–	0	–
–	–	0	–
–	0.7 (0.63–0.78)	23.7	NR
–	–	–	–
–	0.69 (0.63–0.76)	46.5 (over 3.4 y)	−7.0
–	–	53.5 (over 3.4 y)	–
0.74 (0.56–0.98)	–	22 (36/163 from 4 groups)	NR
–	–		–
–	0.75 (0.49–1.14)	0	–
–	–	0	–
0.36 (0.29–0.45)	–	10 (2/20)	–
–	–	–	–
0.54 (0.39–0.74)	0.65 (0.42–1.00)	9.2 (5/54) at 2 y	−5.3
–	–	14.5 (8/55) at 2 y	–
–	0.65 (0.43–1.00)	3.2 (1/31)	−19.4
–	–	22.6 (7/31)	–
–	0.63 (0.60–0.67)	14.9 (30/194) at 2 y	−4.0
–	–	18.9 (37/201) at 2 y	–
0.48 (0.41–0.56)	–	8.3 (2/24)	–
–	–	–	
0.73 (0.66–0.80)	–	0	–
–	–	0	–
0.69 (0.62–0.77)	–	0	–
–	–	0	–
0.53 (0.42–0.67)	–	4.1 (3/74)	1.4
–	–	2.7 (2/73)	–

the original scale to obtain the final overall estimate of the relative treatment effect.

Several large trials reported estimates of the relative treatment effect (that is, the log-transformed data were analyzed), and these estimates were directly included in the current meta-analysis. We used the result from the reported primary analysis regardless of whether this was adjusted for baseline covariates. For the other trials, we used the following approximations: If mean values and SDs for the original data were reported, the formula of Friedrich and colleagues (10) was used. If medians were reported, they were log-transformed to obtain an average treatment effect estimate on the logarithmic scale. Similarly, quartiles or extreme values were log-transformed and the corresponding log-interquartile range or log range was divided by 1.349 or 4, respectively, to get an estimate of the SD of the treatment effect on the logarithmic scale (11). We also log-transformed the reported results when percent changes from baseline and corresponding (asymmetric) CIs were reported for both groups.

Most crossover trials were small and did not provide relative treatment effects. The trials did not report results for the first period only or provide information on within-patient correlation, thus limiting analysis options. We decided to analyze these trials by assuming independence of the 2 treatment periods (for instance, assuming a within-patient correlation of 0), an approach that is recommended only in exceptional situations. It leads to a consistent estimate of the treatment effect in the absence of carryover; a conservative estimate in the case of a positive carryover effect (for instance, smaller effects in the second period), which is the most frequent form; and an overestimate in the case of a negative carryover (12). Standard errors with this approach will generally be inflated because positive within-patient correlation is ignored, leading to conservative estimates.

We used the I^2 statistic to assess heterogeneity. The I^2 value is an estimate of the amount of variance due to between-study heterogeneity rather than chance (13, 14). It is based on the traditional measure of variance, the Cochran Q statistic (15). Substantial heterogeneity exists when I^2 exceeds 50%. For each of the predefined explanations for heterogeneity, we used a Z test to test the difference in estimates of treatment effect between the 2 subgroups defined by the a priori hypotheses (16), and we considered a P value of 0.05 or less to be statistically significant. All pooled effect estimates are presented with 95% CIs.

We plotted standard error against treatment effect ("funnel plot") for the comparisons at 1 to 4 months to detect publication bias, although we acknowledge the limitations of this method (17). The small number of studies

Table 2. **Angiotensin-Receptor Blockers versus Calcium-Channel Blockers: Included Studies and Outcomes***

Study, Year (Reference)	Population					Intervention			
	Patients, *n*	Age, *y*†	Renal Disease‡	Stage of Chronic Renal Disease§	Baseline Proteinuria†	Treatment Control, *mg*	Use of Diuretics/ Sodium Restriction	Mean Arterial Pressure at End of Treatment, *mm Hg*	Mean Follow-up, *mo*‖
Lewis et al., 2001 (7); Atkins et al., 2005 (29)	579	59	Type 2 DM	2	2.9 g/d**	Irbesartan, 300	Yes/No	98	12
	567	–	–	–	–	Amlodipine, 10	–	98	–
Gartenmann et al., 2003 (23)	13	12**	Other	2	0.5 g/mmol creatinine**	Irbesartan, 75–150	No/No	97	4
	–	11**	–	–	0.4 g/mmol creatinine**	Amlodipine, 5–10	–	100	–
Holdaas et al., 1998 (24)††	15	45**	Other	3–4	4.0 g/d	Losartan, 50–100	Yes/No	113	1
	–	–	–	–	–	Amlodipine, 5–10	–	114	–
Iino et al., 2004 (47)	58	56	Mixed	3–4	2.9 g/d	Losartan, 25–100	Yes/No	102	3 and 12
	59	58	–	–	2.5 g/d	Amlodipine, 2.5–5.0	–	98	–
Nutahara et al., 2005 (48)	24	NR	Other	2	0.1 g/d	Candesartan, 2–8	No/No	98	12
	25	–	–	–	0.1 g/d	Amlodipine, 2.5–10	–	102	–
Park et al., 2003 (25)	20	39	Other	2	2.3 g/d	Losartan, 50	Yes/No	89	3
	16	44	–	–	2.1 g/d	Amlodipine, 5	–	89	–
Praga et al., 2003 (26)	50	48	Other	2	3.1 g/d‡‡	Losartan, 50–100	Yes/No	99	1 and 5
	47	47	–	–	2.5 g/d‡‡	Amlodipine, 5–10	–	102	–
Viberti et al., 2002 (27)	169	59	Type 2 DM	1	57.9 μg/min‡‡	Valsartan, 80	Yes/No	97	3 and 6
	163	57	–	–	55.4 μg/min‡‡	Amlodipine, 5	–	98	–
Yasuda et al., 2005 (28)	44	62	Type 2 DM	1	0.8 g/d‡‡	Losartan, 25–100	No/Yes	108	3
	43	61	–	–	0.8 g/d‡‡	Amlodipine, 2.5–10	–	109	–

* DM = diabetes mellitus; NR = not reported.
† Data are expressed as means, unless indicated otherwise.
‡ "Mixed" includes patients with diabetic and nondiabetic renal disease.
§ Renal impairment according to the classification of the National Kidney Foundation (9): 1 = glomerular filtration rate >90 mL/min (or serum creatinine level <106 μmol/L [<1.2 mg/dL]); 2 = glomerular filtration rate of 90–60 mL/min (or serum creatinine level ≤176 μmol/L [≤2 mg/dL]); 3 = glomerular filtration rate <60 mL/min (or serum creatinine level >176 μmol/L [>2 mg/dL]).
‖ For crossover studies: number of months per treatment period.
¶ Parallel-design studies only, accounting for the unclear denominator in crossover studies in the presence of discontinuation.
** Median.
†† Crossover trial.
‡‡ Geometric mean.

precluded funnel-plot explorations of outcomes at 5 to 12 months.

We used RevMan 4.2 (The Cochrane Collaboration, Oxford, United Kingdom) for statistical analysis. The QUOROM (Quality of Reports of Meta-analyses) statement guided our reporting and discussion of the results (18).

Role of the Funding Source

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RESULTS

Trial Flow

Our final pool of eligible studies included 49 RCTs involving 6181 patients. **Appendix Figure 1** (available at www.annals.org) shows the literature search and the selection flow chart. We excluded 1 eligible trial because of serious implausibilities that contact with the publishing journal could not resolve (19). These included a highly unusual balance in the distribution of 3 key baseline variables across 3 treatment groups, discrepancies between the reported statistical method and the results in the paper, and problems with patient stratification.

Study Characteristics and Quality

Of the 49 RCTs, 12 compared ARBs with placebo (**Table 1**), 9 with calcium-channel blockers (**Table 2**), 23 with ACE inhibitors (**Table 3**), and 16 with the combination of ARBs plus ACE inhibitors (**Table 4**), and 23 trials compared combination therapy with ARBs plus ACE inhibitors with ACE inhibitors alone (**Table 5**). Some of the trials reported results at both 1 to 4 months and 5 to 12 months, whereas others reported results only at 1 to 4 months or 5 to 12 months. Because many studies evaluated 3 or more interventions, we were able to make 72 comparisons at 1 to 4 months (median duration, 3 months [interquartile range, 2 to 3 months]) and 38 comparisons at 5 to 12 months (median duration, 9 months [interquartile range, 6 to 12 months]). The underlying nephropathy was of diabetic origin in 24 comparisons, of nondiabetic origin in 19 comparisons, or of mixed origin in 6 comparisons. Ten studies investigated patients with diabetic microalbuminuria, and 39 studies included patients with proteinuria. The median number of patients in each study group was

Table 2—Continued

Outcome			
Change in Proteinuria Ratio of Means (95% CI)		Discontinuation of Medication for Any Reason, % (n/n)	Risk Difference in Discontinuation Rates (Angiotensin-Receptor Blocker vs. Calcium-Channel Blocker), %¶
Short-Term Follow-up	Extended Follow-up		
–	0.66 (0.60–0.74)	23.7 over 2 y	NR
–	–	–	–
0.62 (0.28–1.38)	–	0	−15.4
–	–	15.4 (2/13)	–
0.69 (0.39–1.22)	–	NR	–
–	–	NR	–
0.79 (0.56–1.10)	0.68 (0.46–1.01)	19 (11/58)	−13.2
–	–	32.2 (19/59)	–
–	0.31 (0.15–0.64)	4.2 (1/24)	−19.8
–	–	24 (6/24)	–
0.55 (0.28–1.05)	–	NR	NR
–	–	NR	–
0.59 (0.48–0.73)	0.56 (0.42–0.75)	6 (3/50)	−6.7
–	–	12.7 (6/47)	–
0.75 (0.63–0.90)	0.6 (0.51–0.70)	13.6 (23/169)	2.6
–	–	11 (18/163)	–
0.72 (048–1.08)	–	8.2 (4/49)	−2.2
–	–	10.4 (5/48)	–

18 (interquartile range, 13 to 44 patients); 5 studies included 100 or more patients per group.

Seven studies met all 3 quality criteria (concealed allocation, blinding, and intention-to-treat analysis), whereas 15 studies met 2 criteria, 12 studies met 1 criterion, and 15 studies met none of the criteria (**Appendix Table 1**, available at www.annals.org). The quality of the studies varied considerably across the 5 main comparisons (**Appendix Figure 2**, available at www.annals.org): 88% to 100% of studies on ARBs versus placebo with 1 to 4 months of follow-up and 5 to 12 months of follow-up fulfilled 2 or 3 quality criteria, followed by 60% of studies of an ARB versus a calcium-channel blocker with 5 to 12 months of follow-up. Of the remaining comparisons, 70% or more of the studies achieved 1 or no quality criterion. All but 3 crossover studies (20–22) reported a prolonged washout period (9 of 21 studies; mean, 4.6 weeks [SD, 2.1]) or tested for carryover with nonsignificant results (12 of 21 studies).

Antiproteinuric Effects of Angiotensin-Receptor Blockers

Figures 1 and **2** provide a graphical summary of the results at 1 to 4 months and at 5 to 12 months, respectively. Compared with placebo, ARBs achieved lower levels of proteinuria: The ratio of means was 0.57 (95% CI, 0.47 to 0.68) for 1 to 4 months of treatment and 0.66 (CI, 0.63 to 0.69) for 5 to 12 months. Compared with calcium-channel blockers, ARBs reduced proteinuria at 1 to 4 months to a ratio of means of 0.69 (CI, 0.62 to 0.77) and at 5 to 12 months to a ratio of means of 0.62 (CI, 0.55 to 0.70). Differences in antiproteinuric effect between ARBs versus placebo and versus calcium-channel blockers were not significant ($P = 0.07$ for 1 to 4 months and $P = 0.30$ for 5 to 12 months). In head-to-head comparisons, ARBs and ACE inhibitors demonstrated similar effectiveness in reducing proteinuria over 1 to 4 months (ratio of means, 0.99 [CI, 0.92 to 1.05]) and 5 to 12 months (ratio of means, 1.08 [CI, 0.96 to 1.22]). Combinations of ARBs with ACE inhibitors had an additional impact in reducing proteinuria beyond the level achieved with ARBs alone: The ratio of means was 0.76 (CI, 0.68 to 0.85) in the 1- to 4-month comparisons and 0.75 (CI, 0.61 to 0.92) in the 5- to 12-month comparisons. The superiority of the combination therapy was similar for ACE inhibitors and ARBs: The 1-to 4-month ratio of means of combination therapy versus ACE inhibitors alone was 0.78 (CI, 0.72 to 0.84), and the 5- to 12-month ratio was 0.82 (CI, 0.67 to 1.01). Including the study by Nakao and colleagues (19) appreciably changed the results for the 5- to 12-month follow-up of an ARB plus an ACE inhibitor versus ARB alone (ratio of means, 0.66 [CI, 0.49 to 0.89]) and an ARB plus an ACE inhibitor versus an ACE inhibitor alone (ratio of means, 0.73 [CI, 0.54 to 0.99]).

Sensitivity Analysis

Substantial between-study heterogeneity ($I^2 > 50\%$) was evident in only 1 of the 10 main comparisons: ARB versus placebo with short-term follow-up ($I^2 = 86\%$). None of the sensitivity analyses using predefined clinical characteristics identified a significant difference in treatment effect for this comparison. The sensitivity analyses evaluating methodological features detected larger treatment effects for studies reporting allocation concealment compared with studies that did not (ratio of means, 0.47 [CI, 0.39 to 0.56] and 0.71 [CI, 0.66 to 0.76], respectively; $P = 0.016$) and larger effects in crossover studies

Table 3. **Angiotensin-Receptor Blockers versus Angiotensin-Converting Enzyme Inhibitors: Included Studies and Outcomes***

Study, Year (Reference)	Population					Intervention			
	Patients, *n*	Age, *y*†	Renal Disease‡	Stage of Chronic Renal Disease§	Baseline Proteinuria†	Comparison, *mg*	Use of Diuretics/ Sodium Restriction	Mean Arterial Pressure at End of Treatment, *mm Hg*	Mean Follow-up, *mo*‖
Andersen et al., 2000 (39)**	16 –	42 –	Type 1 DM –	1 –	1.2 g/d†† –	Losartan, 100 Enalapril, 20	Yes/No –	96 93	2 –
Barnett et al., 2004 (5)	120 130	61 60	Type 2 DM –	1 –	46.2 μg/min‡‡ 60.0 μg/min‡‡	Telmisartan, 80 Enalapril, 20	Yes/No –	NR –	3 and 12 –
Campbell et al., 2003 (49)**	24 –	49 –	Other –	2 –	3.3 g/d –	Valsartan, 160 Benazepril, 20	Yes/No –	95 –	2 –
Cetinkaya et al., 2004 (50)	11 –	55 –	Type 2 DM –	2 –	4.8 g/d –	Losartan, 50 Enalapril, 10	No/Yes –	102 –	3 –
Esnault et al., 2005 (51)**	18 –	49 –	Mixed –	2 –	3.7 g/d –	Valsartan, 160 Ramipril, 10	Yes/No –	104 100	1 –
Ferrari et al., 2002 (52)**	10 –	48 –	Other –	2 –	7.9 g/d –	Irbesartan, 150 Fosinopril, 20	Yes/No –	101 –	1.5 –
Horita et al., 2004 (53)	10 –	43 40	Other –	1 –	0.8 g/d 0.7 g/d	Losartan, 12.5 Temocapril, 1	No/No –	91 86	3 and 6 –
Jacobsen et al., 2003 (41)**	18 –	43 –	Type 1 DM –	NR –	0.4 g/d‡‡ –	Valsartan, 80 Benazepril, 20	Yes/No –	92 –	2 –
Lacourcière et al., 2000 (54)	52 51	59 58	Type 2 DM –	NR –	64.1 μg/min†† 73.9 μg/min††	Losartan, 50–100 Enalapril, 5, 10, or 20	Yes/No –	102 99	3 and 12 –
Luño et al., 2002 (55)	15 14	45 50	Other –	1 –	4.0 g/g creatinine 3.6 g/g creatinine	Candesartan, 8–32 Lisinopril, 10–40	Yes/No –	88 85	3 and 6 –
Matos et al., 2005 (56)**	20 –	54‡‡ –	Type 2 DM –	2 –	1 g/d†† 0.8 g/d††	Irbesartan, 300 Perindopril, 8	Yes/Yes –	101 97	4 –
Matsuda et al., 2003 (57)	15 –	51 –	Other –	1 –	2.5 g/d 2.7 g/d	Losartan, 25 Perindopril, 2	No/Yes –	100 97	3 and 12 –
Matsuda et al., 2003 (57)	17 15	58 50	Other –	1 –	3.0 g/d 2.7 g/d	Candesartan, 4 Trandolapril, 0.5	No/Yes –	99 97	3 and 12 –
Mogensen et al., 2000 (58)	99 98	60 –	Type 2 DM –	1 –	5.9 mg/mmol creatinine†† 6.6 mg/mmol creatinine††	Candesartan, 16 Lisinopril, 20	Yes/No –	107 106	3 and 6 –
Muirhead et al., 1999 (43)	31 29	58 57	Type 2 DM –	2 –	58.1 μg/min†† 40.9 μg/min††	Valsartan, 160 Captopril, 75	Yes/No –	99 100	12 –
Renke et al., 2004 (59)	18 –	40 43	Other –	1 –	2.2 g/d 2.6 g/d	Losartan, 25 Enalapril, 10	No/No –	103 93	3 and 9 –
Russo et al., 2001 (60)**	10 –	25 –	Other –	1 –	1.6 g/d –	Losartan, 100 Enalapril, 20	No/No –	85 83	1 –
Rutkowski et al., 2004 (61)**	30 –	35 –	Other –	2 –	2.1 g/d –	Losartan, 50 Benazepril, 10	No/No –	98 98	4 –
Schulz et al., 2000 (62)	64 65	NR –	Mixed –	3–4 –	0.7g/d 1.0/d	Losartan, 50–100 Captopril, 50–100	No/No –	NR –	3 –
Segura et al., 2003 (63)	12 –	50 –	Other –	2 –	4.6 g/d 3.8 g/d	Valsartan, 80–160 Benazepril, 10–20	Yes/NR –	102 107	3 and 6 –
Sengul et al., 2006 (64)	109 110	59 57	Type 2 DM –	1 –	0.3 g/d‡‡ 2.3 g/d‡‡	Telmisartan, 80 Lisinopril, 20	Yes/Yes –	103 102	3 and 7 –
Song et al., 2006 (65)**	25 –	49 –	Type 2 DM –	3–4 –	4.1 g/d –	Candesartan, 16 Ramipril, 10	Yes/No –	97 98	4 –
Tütüncü et al., 2001 (66)	12 –	58 51	Type 2 DM –	NR –	0.1 g/d 0.08 g/d	Losartan, 50 Enalapril, 5	No/No –	95 93	3 and 12 –
Tylicki et al., 2005 (67)	19 14	41 43	Other –	1 –	1.9 g/d 2.3 g/d	Losartan, 25 Enalapril, 10	No/No –	100 92	12 –

* ACE = angiotensin-converting enzyme; DM = diabetes mellitus; NR = not reported.
† Data are expressed as means, unless indicated otherwise.
‡ "Mixed" includes patients with diabetic and nondiabetic renal disease.
§ Renal impairment according to the classification of the National Kidney Foundation (9): 1 = glomerular filtration rate >90 mL/min (or serum creatinine level ≤106 μmol/L [≤1.2 mg/dL]); 2 = glomerular filtration rate of 90–60 mL/min (or serum creatinine level ≤176 μmol/L [≤2 mg/dL]); 3 = glomerular filtration rate ≤60 mL/min (or serum creatinine level >176 μmol/L [>2 mg/dL]).
‖ For crossover studies: number of months per treatment period.
¶ Parallel-design studies only, accounting for the unclear denominator in crossover studies in the presence of discontinuation.
** Crossover trial.
†† Geometric mean.
‡‡ Median.

Table 3—**Continued**

Outcome			
Change in Proteinuria Ratio of Means (95% CI)		Discontinuation of Medication for Any Reason, *% (n/n)*	Risk Difference in Discontinuation Rates (Angiotensin-Receptor Blocker vs. ACE Inhibitor), %¶
Short-Term Follow-up	Extended Follow-up		
1.36 (0.59 to 3.18)	–	0	–
–	–	–	–
0.83 (0.70 to 0.99)	0.9 (0.72 to 1.13)	31.7 (38/120)	−2.1
–	–	33.8 (44/130)	–
1.16 (0.62 to 2.18)	–	0	–
–	–	–	–
1.01 (0.84 to 1.22)	–	NR	NR
–	–	–	–
0.84 (0.54 to 1.30)	–	11.1 (2/18)	–
–	–	–	–
0.94 (0.40 to 2.23)	–	9.1 (1/11)	–
–	–	–	–
1.29 (0.22 to 7.64)	1.25 (0.18 to 8.64)	0	−9.1
–	–	9.1 (1/11)	–
0.94 (0.54 to 1.65)	–	10 (2/20)	–
–	–	–	–
1.08 (0.73 to 1.62)	1.24 (0.79 to 1.95)	13.5 (7/52)	3.7
–	–	9.8 (5/51)	–
0.92 (0.48 to 1.76)	1.19 (0.51 to 2.79)	NR	NR
–	–	–	–
1.18 (0.73 to 1.90)	–	25 (5/20)	–
–	–	–	–
1.44 (0.79 to 2.61)	1.67 (1.20 to 2.31)	NR	NR
–	–	–	–
1.06 (0.52 to 2.16)	0.98 (0.69 to 1.39)	NR	NR
–	–	–	–
1.30 (1.00 to 1.69)	1.30 (1.00 to 1.69)	7.1 (14/197)	NR
–	–	–	–
–	1.15 (0.76 to 1.74)	3.2 (1/31)	−10.5
–	–	13.7 (4/29)	–
1.14 (0.60 to 2.15)	0.92 (0.53 to 1.61)	0	0.0
–	–	–	–
1.03 (0.70 to 1.52)	–	47 (9/19)	–
–	–	–	–
0.9 (0.65 to 1.25)	–	20 (6/30)	–
–	–	–	–
0.6 (0.30 to 1.23)	–	12.5 (8/64)	−16.7
–	–	29.2 (19/65)	–
1.14 (0.66 to 1.97)	0.95 (0.50 to 1.82)	NR	NR
–	–	–	–
0.96 (0.87 to 1.07)	0.96 (0.87 to 1.07)	11 (12/109)	−2.6
–	–	13.6 (15/110)	–
0.94 (0.67 to 1.32)	–	20 (5/25)	–
–	–	–	–
1.29 (0.87 to 1.90)	1.29 (0.87 to 1.90)	8 (3/37)	NR
–	–	–	–
–	0.95 (0.57 to 1.61)	17.5 (7/40)	NR
–	–	–	–

compared with parallel-design studies (ratio of means, 0.43 [CI, 0.34 to 0.55] vs. 0.66 [CI, 0.59 to 0.74]; $P = 0.02$).

None of our postulated clinical factors explained differences in the magnitude of the treatment effect between studies for the other 9 comparisons apart from 1 analysis: In this comparison of combination therapy versus an ARB or ACE inhibitor alone for 1 to 4 months, studies of 1079 patients with proteinuria found a significant reduction in proteinuria (ratio of means, 0.77 [CI, 0.73 to 0.82]) compared with 1 negative study on 34 patients with microalbuminuria (ratio of means, 1.03 [CI, 0.87 to 1.21]).

Allocation concealment and blinding affected differences in treatment effect in the comparison of ARB–ACE inhibitor combination therapy versus monotherapy with an ARB or ACE inhibitor. Studies reporting concealed allocation achieved a larger treatment effect than studies that

Table 4. **Combination Therapy versus Angiotensin-Receptor Blockers: Included Studies and Outcomes***

Study/Year (Reference)	Population					Intervention			
	Patients, *n*	Age, *y*†	Renal Disease	Stage of Chronic Renal Disease‡	Baseline Proteinuria†	Comparison, *mg*	Use of Diuretics/ Sodium Restriction	Mean Arterial Pressure at End of Treatment, *mm Hg*	Follow-up, *mo*§
Campbell et al., 2003 (49)¶	24	49	Other	2	3.3 g/d	Valsartan, 80 + benazepril, 10	Yes/No	94	2
	–	–	–	–	–	Valsartan, 160	–	95	–
Esnault et al., 2005 (51)¶	18	49	Other	2	3.7 g/d	Valsartan, 80 + ramipril, 5	Yes/No	100	1
	–	–	–	–	–	Valsartan, 160	–	104	–
Ferrari et al., 2002 (52)¶	10	48	Other	2	7.9 g/d	Irbesartan, 150 + fosinopril, 20	Yes/No	98	1.5
	–	–	–	–	–	Irbesartan, 150	–	101	–
Horita et al., 2004 (53)	11	40	Other	1	0.8 g/d	Losartan, 12.5 + temocapril, 1	No/No	83	3 and 6
	10	43	–	–	–	Losartan, 12.5	–	90	–
Jacobsen et al., 2003 (41)¶	18	43	Type 1 DM	NR	0.4 g/d**	Valsartan, 80 + benazepril, 20	Yes/No	85	2
	–	–	–	–	–	Valsartan, 80	–	92	–
Luño et al., 2002 (55)	16	42	Other	1	3.8 g/g creatinine	Candesartan, 4–16 + lisinopril, 5–20	Yes/No	88	3 and 6
	15	45	–	–	4.0 g/g creatinine	Candesartan, 8–32	–	88	–
Matos et al., 2005 (56)¶	20	54**	Type 2 DM	2	1.0 g/d††	Irbesartan, 300 + perindopril, 8	Yes/Yes	99	4
	–	–	–	–	1.0 g/d††	Irbesartan, 300	Yes/Yes	101	–
Mogensen et al., 2000 (58)	67	60	Type 2 DM	1	5.6 mg/mmol creatinine††	Candesartan, 16 + lisinopril, 20	Yes/No	98	6
	66	–	–	–	7.2 mg/mmol creatinine††	Candesartan, 16	–	107	–
Renke et al., 2004 (59)	16	38	Other	1	3.3 g/d	Losartan, 25 + enalapril, 10	No/No	94	3 and 9
	18	40	–	–	2.2 g/d	Losartan, 25	–	103	–
Ruilope et al., 2000 (68)	44	58	Other	3–4	1.8 g/d	Valsartan, 160 + benazepril, 5–10	Yes/No	101	1.25
	22	57	–	–	–	Valsartan, 160	–	109	–
Russo et al., 2001 (60)¶	10	25	Other	1	1.6 g/d	Losartan, 100 + enalapril, 20	No/No	80	1
	–	–	–	–	–	Losartan, 100	–	85	–
Rutkowski et al., 2004 (61)¶	30	35	Other	1	2.1 g/d	Losartan, 25 + benazepril, 5	No/No	94	1
	–	–	–	–	–	Losartan, 50	–	98	–
Segura et al., 2003 (63)	12	48	Other	2	4.0 g/d	Valsartan, 80–160 + benazepril, 10–20	Yes/No	100	3 and 6
	–	50	–	–	4.6 g/d	Valsartan, 80–160	–	102	–
Sengul et al., 2006 (64)	49	57	Type 2 DM	1	0.2 g/d**	Telmisartan, 80 + lisinopril, 20	Yes/Yes	91	7
	48	56	–	–	0.2 mg/d**	Telmisartan, 80	–	91	–
Song et al., 2006 (65)¶	25	49	Type 2 DM	3–4	4.1 g/d	Candesartan, 8 + ramipril, 5	Yes/No	96	4
	–	–	–	–	–	Candesartan, 16	–	97	–
Tütüncü et al., 2001 (66)	10	58	Type 2 DM	NR	0.1 g/d	Losartan, 50 + enalapril, 5	No/No	87	3 and 12
	12	–	–	–	0.1 g/d	Losartan, 50	–	95	–

* DM = diabetes mellitus; NR = not reported.
† Data are expressed as means, unless indicated otherwise.
‡ Renal impairment according to the classification of the National Kidney Foundation (9): 1 = glomerular filtration rate >90 mL/min (or serum creatinine level ≤106 μmol/L [≤1.2 mg/dL]); 2 = glomerular filtration rate of 90–60 mL/min (or serum creatinine level ≤176 μmol/L [≤2 mg/dL]); 3 = glomerular filtration rate <60 mL/min (or serum creatinine level >176 μmol/L [>2 mg/dL]).
§ For crossover studies: number of months per treatment period.
‖ Parallel-design studies only, accounting for the unclear denominator in crossover studies in the presence of discontinuation.
¶ Crossover trial.
** Median.
†† Geometric mean.

lacked reports on concealment ($P < 0.01$; ratio of means, 0.72 [CI, 0.67 to 0.78] for concealment vs. 0.89 [CI, 0.80 to 0.96] for lack of reporting on concealment). Blinding resulted in larger treatment effects than lack of blinding ($P = 0.04$; ratio of means, 0.75 [CI, 0.69 to 0.80] for blinding vs. 0.89 [CI, 0.79 to 0.99] for no blinding). Otherwise,

Table 4—Continued

Outcome			
Change in Proteinuria Ratio of Means (95% CI)		Discontinuation of Medication for Any Reason, % *(n/n)*	Risk Difference in Discontinuation Rates (Angiotensin-Receptor Blocker vs. ACE Inhibitor), %‖
Short-Term Follow-up	Extended Follow-up		
0.68 (0.36–1.29)	–	0	–
–	–	0	–
1 (0.67–1.48)	–	11.1 (2/18)	–
–	–	–	–
0.66 (0.26–1.66)	–	9.1 (1/11)	–
–	–	–	–
0.81 (0.17–3.81)	0.51 (0.07–3.57)	8.3 (1/12)	8.3
–	–	0	–
0.61 (0.49–0.76)	–	10 (2/20)	–
–	–	–	–
0.81 (0.43–1.52)	0.46 (0.24–0.87)	NR	NR
–	–	–	–
0.86 (0.55–1.33)	–	25 (5/20)	–
–	–	–	–
–	0.66 (0.45–0.97)	7.1 (14/197)	NR
–	–	–	–
0.71 (0.43–1.18)	1.21 (0.74–2.00)	12.5 (2/16)	12.5
–	–	0	–
0.57 (0.23–1.41)	–	9.1 (6/66)	NR
–	–	–	–
0.56 (0.34–0.92)	–	47 (9/19)	–
–	–	–	–
0.76 (0.54–1.06)	–	20 (6/30)	–
–	–	–	–
0.84 (0.45–1.55)	0.51 (0.23–1.12)	NR	NR
–	–	–	–
–	0.74 (0.62–0.89)	NR	NR
–	–	11 (12/109)	–
0.88 (0.63–1.22)	–	20 (5/25)	–
–	–	–	–
0.96 (0.70–1.33)	0.99 (0.58–1.68)	8 (3/37)	NR
–	–	–	–

we observed consistent effects on proteinuria in patients with microalbuminuria, proteinuria, diabetic and nondiabetic nephropathy, and design features, independent of the duration of follow-up.

We assessed the impact of blood pressure on the antiproteinuric effect. Although both ARBs and calcium-channel blockers decreased blood pressure to a similar extent, ARBs showed a greater antiproteinuric effect than the active comparator, calcium-channel blockers, over 1 to 4 months (ratio of means, 0.68 [CI, 0.60 to 0.77]) (23–28) and during extended follow-up (ratio of means, 0.64 [CI, 0.58 to 0.69]) (26, 27, 29).

Funnel plots did not suggest presence of publication bias in any analysis.

Adverse Effects

Only 33% of studies reported detailed methods of assessing adverse drug reactions, 26% noted the timing of

Table 5. **Combination Therapy versus Angiotensin-Converting Enzyme Inhibitor: Included Studies and Outcomes***

Study/Year (Reference)	Population					Intervention			
	Patients, *n*	Age, *y*†	Renal Disease‡	Stage of Chronic Renal Disease§	Baseline Proteinuria†	Comparison, *mg*	Use of Diuretics/ Sodium Restriction	Mean Arterial Pressure at End of Treatment, *mm Hg*	Follow-up, *mo*‖
Agarwal, 2001 (69)**	16	53	Mixed	2	3.6 g/d	Lisinopril, 40 + losartan, 50	Yes/No	106	1
	–	–	–	–	–	Lisinopril, 40 + placebo	–	104	–
Berger et al., 2002 (70)**	12	52	Other	2	2.0 g/d	ACEI + candesartan, 8	Yes/No	92	2
	–	–	–	–	1.8 g/d	ACEI, "low dose" + placebo	–	95	–
Campbell et al., 2003 (49)**	24	49	Other	2	3.3 g/d	Benazepril, 10 + valsartan, 80	Yes/No	94	2
	–	–	–	–	–	Benazepril, 20	–	95	–
Esnault et al., 2005 (51)**	18	49	Other	2	3.7 g/d	Ramipril, 5 + valsartan, 80	Yes/No	100	1
	–	–	–	–	–	Ramipril, 10	–	100	–
Ferrari et al., 2002 (52)**	10	48	Other	2	7.9 g/d	Fosinopril, 20 + irbesartan, 150	Yes/No	98	1.5
	–	–	–	–	–	Fosinopril, 20	–	101	–
Horita et al., 2004 (53)	11	40	Other	1	0.8 g/d	Temocapril, 1 + losartan, 12.5	No/No	83	3 and 6
	10	–	–	–	0.7 g/d	Temocapril, 1	–	86	–
Jacobsen et al., 2002 (71)**	21	45	Type 1 DM	NR	1.9 g/d††	ACEI + irbesartan, 300	Yes/No	96	2
	–	–	–	–	–	ACEI, various + placebo	–	102	–
Jacobsen et al., 2003 (41)**	18	43	Type 1 DM	NR	0.4 mg/d‡‡	Benazepril, 20 + valsartan, 80	Yes/No	85	2
	–	–	–	–	–	Benazepril, 20	–	92	–
Jacobsen et al., 2003 (72)**	24	42	Type 1 DM	NR	NR	Enalapril, 40 + irbesartan, 300	Yes/No	88	2
	–	–	–	–	–	Enalapril, 40 + placebo	–	93	–
Kim et al., 2003 (21)**	41	34	Mixed	2	3.9 g/d	Ramipril, about 5.7 + candesartan, 4	Yes/Yes	91	3
	–	–	–	–	–	Ramipril, about 5.7 + placebo	–	92	–
Kincaid-Smith et al., 2002 (20)**	60	NR	Mixed	3–4	2.3g/d	ACEI, various + candesartan, 8	No/No	99	3
	–	–	–	–	–	ACEI, various	–	96	–
Luño et al., 2002 (55)	16	42	Other	1	3.8 g/g creatinine	Lisinopril, 5–20 + candesartan, 4–16	Yes/No	88	3 and 6
	14	50	–	–	3.6 g/g creatinine	Lisinopril, 10–40	–	85	–
Matos et al., 2005 (56)**	20	54‡‡	Type 2 DM	2	1.0 g/d††	Perindopril, 8 + irbesartan, 300	Yes/Yes	99	4
	–	–	–	–	0.9 g/d††	Perindopril, 8	–	97	–
Mogensen et al., 2000 (58)	67	60	Type 2 DM	1	5.6 mg/ mmol creatinine††	Lisinopril, 20 + candesartan, 16	Yes/No	98	6
	64	–	–	–	5.9 mg/ mmol creatinine††	Lisinopril, 20	–	106	–
Renke et al., 2004 (59)	16	38	Other	1	3.3 g/d	Enalapril, 10 + losartan, 25	No/No	94	3 and 9
	18	43	–	–	2.6 g/d	Enalapril, 10	–	93	–
Rossing et al., 2002 (73)**	17	58	Type 2 DM	NR	1.8 g/d††	ACEI + candesartan, 8	Yes/No	93	2
	–	–	–	–	–	ACEI various + placebo	–	99	–
Rossing et al., 2003 (74)**	20	62	Type 2 DM	1	NR	ACEI + candesartan, 16	Yes/No	92	2
	–	–	–	–	–	ACEI various + placebo	–	94	–
Russo et al., 2001 (60)**	10	25	Other	1	1.6 g/d	Enalapril, 20 + losartan, 100	No/No	80	1
	–	–	–	–	–	Enalapril, 20	–	83	–
Rutkowski et al., 2004 (61)**	30	35	Other	2	2.1 g/d	Benazepril, 5 + losartan, 25	No/No	94	4
	–	–	–	–	–	Benazepril, 10	–	98	–
Segura et al., 2003 (63)	12	48	Other	2	4.0 g/d	Benazepril, 10–20 + valsartan, 80–160	Yes/No	100	3 and 6
	–	50	–	–	3.8 g/d	Benazepril, 10–20	–	107	–
Sengul et al., 2006 (64)	47	57	Type 2 DM	1	0.2 g/d‡‡	Lisinopril, 20 + telmisartan, 80	Yes/Yes	83	7
	48	–	–	–	0.2 g/d‡‡	Lisinopril, 20	–	89	–
Song et al., 2006 (65)**	25	49	Type 2 DM	3–4	4.1 g/d	Ramipril, 5 + candesartan, 8	Yes/No	96	4
	–	–	–	–	–	Ramipril, 10	–	98	–
Tutüncü et al., 2001 (66)	10	58	Type 2 DM	NR	0.1 g/d	Enalapril, 5 + losartan, 50	No/No	87	3 and 12
	12	51	–	–	0.1 g/d	Enalapril, 5	–	93	–

* ACEI = angiotensin-converting enzyme inhibitor; DM = diabetes mellitus; NR = not reported.
† Data are expressed as means, unless indicated otherwise.
‡ "Mixed" includes patients with diabetic and nondiabetic renal disease.
§ Renal impairment according to the classification of the National Kidney Foundation (9): 1 = glomerular filtration rate >90 mL/min (or serum creatinine level ≤106 μmol/L [≤1.2 mg/dL]); 2 = glomerular filtration rate of 90–60 mL/min (or serum creatinine level ≤176 μmol/L [≤2 mg/dL]); 3 = glomerular filtration rate <60 mL/min (or serum creatinine level >176 μmol/L [>2 mg/dL]).
‖ For crossover studies: number of months per treatment period.
¶ Parallel-design studies only, accounting for the unclear denominator in crossover studies in the presence of discontinuation.
** Crossover trial.
†† Geometric mean.
‡‡ Median.

Table 5—**Continued**

Outcome			
Change in Proteinuria Ratio of Means (95% CI)		Discontinuation of Medication for Any Reason, % *(n/n)*	Risk Difference in Discontinuation Rates (Angiotensin-Receptor Blocker vs. ACEI), %¶
Short-Term Follow-up	Extended Follow-up		
1.01 (0.80–1.28)	–	5.9 (1/17)	–
–	–	0	–
0.68 (0.40–1.18)	–	0	–
–	–	0	–
0.79 (0.43–1.46)	–	0	–
–	–	0	–
0.84 (0.51–1.37)	–	11.1 (2/18)	–
–	–	–	–
1.61 (0.64–4.04)	–	9.1 (1/11)	–
–	–	–	–
1.04 (0.27–3.98)	0.64 (0.09–4.55)	9.1 (1/11)	0
–	–	9.1 (1/11)	–
0.63 (0.51–0.78)	–	9.5 (2/21)	–
–	–	0	–
0.75 (0.66–0.85)	–	10 (2/20)	–
–	–	–	–
0.63 (0.51–0.78)	–	0	–
–	–	0	–
0.85 (0.71–1.02)	–	NR	–
–	–	–	–
0.81 (0.54–1.22)	–	13.3 (8/60)	–
–	–	–	–
0.74 (0.35–1.58)	0.55 (0.23–1.29)	NR	NR
–	–	–	–
1.02 (0.66–1.56)	–	25 (5/20)	–
–	–	–	–
–	0.82 (0.56–1.20)	7.1 (14/197)	NR
–	–	–	–
0.81 (0.44–1.49)	1.31 (0.77–2.26)	12.5 (2/16)	12.5
–	–	0	–
0.72 (0.62–0.83)	–	5.9 (1/17)	–
–	–	0	–
0.76 (0.58–0.98)	–	0	–
–	–	0	–
0.58 (0.35–0.95)	–	47 (9/19)	–
–	–	–	–
0.68 (0.49–0.95)	–	20 (6/30)	–
–	–	–	–
0.73 (0.40–1.34)	0.48 (0.24–0.99)	NR	NR
–	–	–	–
–	0.76 (0.64–0.92)	NR	NR
–	–	13.6 (15/110)	–
0.83 (0.61–1.12)	–	20 (5/25)	–
–	–	–	–
1.24 (0.85–1.80)	1.15 (0.66–1.99)	8 (3/37)	8
–	–	–	

assessments, and 16% described reproducible assessment methods. Studies rarely presented adverse drug reactions in a structured manner that allowed us to make causal inferences (for example, certain, probable, or possible adverse drug reactions). Ninety-two percent (45 of 49) of the studies, including the large registration studies (6–8), lacked quantitative data even on more common but less severe adverse drug reactions, prohibiting a reliable estimate of their incidence.

Eighty-six percent of the studies listed adverse drug reactions, including dizziness, hyperkalemia, cough, allergies, or hypertensive episodes, as reasons for patients to discontinue use of study drugs. Headache, fatigue, nausea or vomiting, and hyper- or hypoglycemic episodes were among the less-frequent severe adverse drug reactions.

The majority of studies (29 of 49) reported medication discontinuation rates by group, 13 of 49 reported only total discontinuation rates of all study patients, and 7 of 49

Figure 1. **Reduction in proteinuria at 1 to 4 months.**

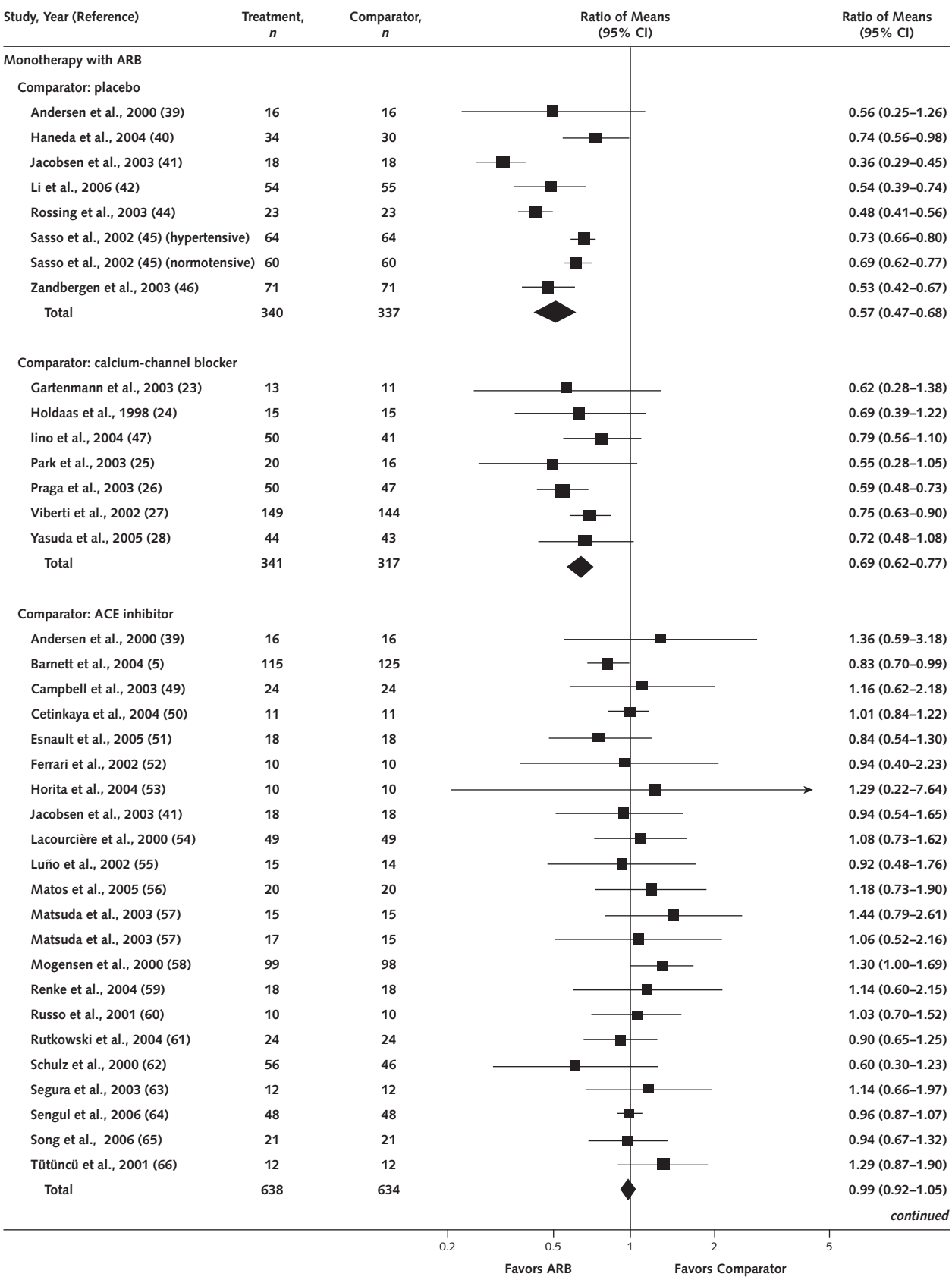
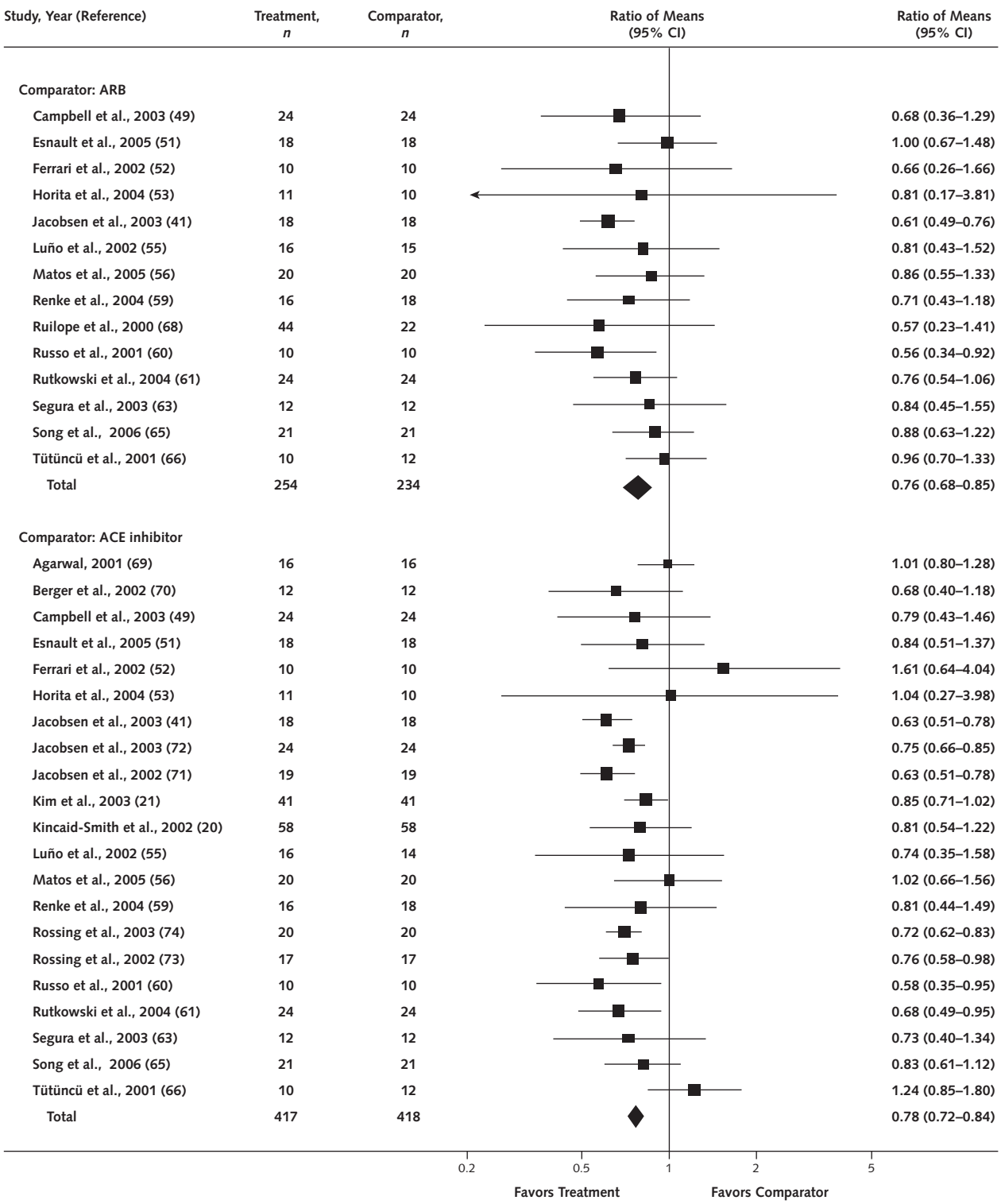


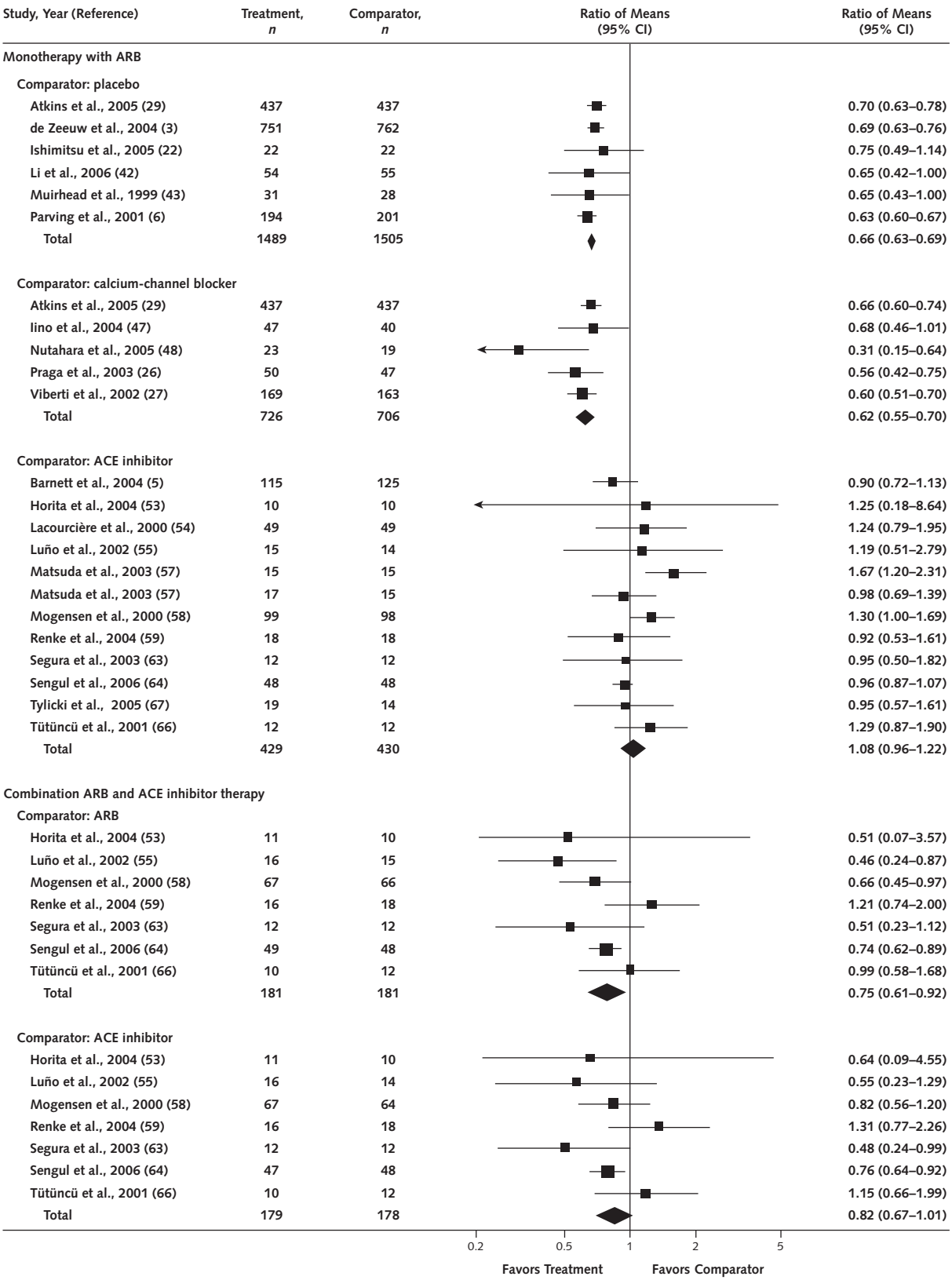
Figure 1—**Continued**



ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.

did not report on discontinuation at all (**Tables 1** to **5**). **Table 6** summarizes the risk for discontinuation for the 5 main comparisons of the meta-analysis: ARBs resulted in fewer discontinuations than placebo and a tendency for fewer discontinuations than calcium-channel blockers and ACE inhibitors ($P = 0.16$ for both comparisons). The low

Figure 2. **Reduction in proteinuria at 5 to 12 months.**



ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.

Table 6. **Risk for Medication Discontinuation***

Comparison	Discontinuation Rates for Each Treatment Group/ All Studies, *n/n*	Patients Who Discontinued Therapy/ All Patients, *n/n (%)*		Pooled Rate of Discontinuation (95% CI)
		Experimental Group	Comparator Group	
ARB vs. placebo	5/13	388/1104 (35.1)	462/1122 (41.2)	0.86 (0.78–0.95)
ARB vs. CCB	6/9	42/363 (11.6)	56/355 (15.8)	0.71 (0.43–1.15)
ARB vs. ACE inhibitor	10/23	66/404 (16.3)	88/414 (21.1)	0.78 (0.55–1.11)
Combination therapy vs. ARB	2/16	3/27 (11.1)	0/68 (0)	3.98 (0.47–33.85)
Combination therapy vs. ACE inhibitor	1/23	2/16 (12.5)	0/18 (0)	5.59 (0.29–108.38)

* Numbers sum to the discontinuation of medication with direct link to drug exposure (severe adverse effects), indirect link to drug exposure (malcompliance, withdrawal of consent), and no link to drug exposure (protocol violations, ineligibility, or pregnancy). Only parallel-group trials were included. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker.

proportion of combination trials with parallel-group design reporting discontinuation rates in the individual groups and the implausibly low number of events raise serious doubts about how representative these findings are.

Discussion

Small randomized trials with inconclusive results have perpetuated controversy regarding whether ARBs are as effective as antiproteinuric agents, such as ACE inhibitors, and whether the combination of ARBs and ACE inhibitors is superior to monotherapy. Our systematic review and meta-analysis has addressed both issues. First, ARBs seem to have similar effectiveness as ACE inhibitors in reducing urinary protein excretion. Second, our results suggest that concomitant therapy with an ARB and an ACE inhibitor leads to greater reductions in proteinuria than monotherapy. Our meta-analysis also establishes that ARBs reduce urinary protein excretion by approximately 35% compared with placebo and calcium-channel blockers.

The antiproteinuric effect of ARBs was consistent across clinical subgroups—patients with more or less proteinuria, and patients with and without diabetes—and the different observation periods. Although 1 main comparison (combination therapy versus ACE inhibitor) was nonsignificant for follow-up at 5 to 12 months, this may be because of small sample sizes and the resulting inadequacy of power.

Despite our findings, the inference that patients with renal proteinuria will benefit from combination therapy with ACE inhibitors and ARBs is not certain. First, the available studies did not assess safety well, a finding that is consistent with a recent systematic review (30). Limitations include lack of systematic assessment methods and inadequate reporting. Second, although ARBs and ACE inhibitors have an established safety profile and are generally well tolerated, their tolerance and safety are less well documented in high-risk patients with renal disease and significant comorbid conditions. Most studies used a highly selected middle-aged patient population that probably had few comorbid conditions, previous exposure to ARBs or ACE inhibitors, proven tolerance to maximum dosage, and established drug adherence. Patients lacking these features may have a higher incidence of toxicity, in particular hyperkalemia.

A previous experience emphasizes the importance of this cautionary note: Following a successful trial of add-on therapy of spironolactone to routine ACE inhibition in patients with severe heart failure (31), in which few hyperkalemic episodes were reported, investigators observed a striking increase in hyperkalemia-associated hospital admissions and deaths when the drug combination was administered in routine care (32). This increase was probably the result of less rigorous monitoring of potassium compared with during the trial, a more diverse sample with more predisposing factors for hyperkalemia, and failure to note renal dysfunction that developed during treatment.

Most drugs that reduce blood pressure also reduce urinary protein excretion (1, 2). Therefore, the blood pressure–independent renal protection from ARBs is a matter of ongoing debate (4). In the contrast we set up, studies comparing ARB versus calcium-channel blockers in which both treatment groups achieved similar blood pressure, patients receiving ARBs experienced a more pronounced reduction in urinary protein excretion than did patients receiving calcium-channel blockers (ratio of means, 0.65). This difference probably reflects the specific effect of ARBs on the renin–angiotensin system.

Inhibitors of the renin–angiotensin system reduce proteinuria by decreasing the systemic arterial pressure and the intraglomerular filtration pressure and by changing pore size and charge of the glomerular filter (1–4). Angiotensin-converting enzyme inhibitors block the formation of angiotensin II, the main effector peptide of the renin–angiotensin system, but do so incompletely (4), whereas ARBs do not block all angiotensin II type 1 receptors at clinically recommended doses (4). Combining both drugs might therefore achieve more complete blockage of the renin–angiotensin system. The superiority of combination therapy with an ARB plus an ACE inhibitor may be restricted to conventional doses; monotherapy may be equally effective if either drug is administered at doses higher than those approved by drug regulatory agencies (33, 34). Our

analysis could not address the latter strategy because data were lacking.

Experimental studies suggest that proteinuria is not only a predictor of renal outcome, but also acts as a pathogenic factor for the progression of renal disease, at least within the proteinuric range (2). Recent post hoc data suggest a linear relationship between reduction in urinary protein excretion and protection of renal function (3). Because proteinuria fulfills many criteria of a reliable surrogate marker (35), the additional reduction in proteinuria achieved by combining an ARB and an ACE inhibitor may be of direct relevance to the patient's renal prognosis. A long-term RCT in patients with proteinuria studying the effect of combination versus monotherapy on end-stage renal disease would provide the most compelling evidence but has not yet been done.

Strengths of our systematic review and meta-analysis include the comprehensive search, a priori hypotheses to explain heterogeneity, interpretability of analyses, and consistency and congruity of the results. Limitations include poor reporting of adverse effects; the small sample size of most studies, which led to some statistically nonsignificant results from pooled studies with 5- to 12-month follow-up; and the poor methodological quality of some studies.

The high proportion of studies with a crossover design may also raise concern, in part because carryover effects in crossover trials can seriously bias treatment estimates. Evidence indicates, however, that the antiproteinuric effect of ARBs and ACE inhibitors is fully reversible within 28 days (36). The washout period in many studies and the nonsignificant tests for carryover decrease the likelihood of sizeable carryover effects, even though tests for carryover have low power. Furthermore, the similar treatment effect in crossover and parallel-design studies for all but 1 comparison makes the presence of bias less likely. This 1 short-term comparison of ARB versus placebo detected larger effects for crossover trials than for parallel-group RCTs. The latter result is inconsistent with theoretical considerations that would predict smaller effects in crossover trials due to a positive residual effect from carryover (37). The consistent effects across studies, study designs, and clinical subgroups, and the analysis of studies with 5- to 12-month follow-up that included far more patients, suggest that the 1 anomalous analysis should elicit little concern.

Our sensitivity analysis showed 5 statistically significant comparisons. However, even though we restricted the clinical and methodological factors we tested as explanations of effect, the 5 main factors we investigated for which data were available at 1 to 4 months and 5 to 12 months of follow-up resulted in a large number of comparisons. The result is a large risk for spurious effects. Therefore, we consider all findings from our sensitivity analyses to be of uncertain validity.

The promising but preliminary findings of our meta-analysis call for a long-term trial of combination therapy versus monotherapy with an ARB or an ACE inhibitor in patients with proteinuria who are representative of those seen in general clinical practice. Such a study should address outcomes that are important to patients, including end-stage renal disease. It should include different target values for proteinuria to determine whether aiming for low levels of proteinuria blunts progression of renal disease. Such a trial must further ensure a systematic assessment and reporting of adverse drug reactions.

The clinician thus faces a dilemma. Indirect evidence from a compelling, but still surrogate, outcome suggests the merit of combining an ACE inhibitor and ARB in patients with proteinuric renal disease. However, the impact on patient-important outcomes, in particular the need for renal replacement therapy, remains unproven. Combination therapy carries disadvantages of cost and great potential for toxicity, although the evidence is sparse. Antiproteinuric therapy targets proteinuria less than 0.5 g/d (1, 38). In patients for whom therapy with ARBs or ACE inhibitors fails to reduce proteinuria to less than 0.5 g/d, begin antiproteinuric therapy and closely monitor results, including proteinuria reduction, serum potassium level, and other adverse effects.

In conclusion, our meta-analysis provides high-quality evidence that monotherapy with ARBs and ACE inhibitors achieves similar reductions in proteinuria in patients with microalbuminuria and proteinuria regardless of the cause of renal disease, and evidence is encouraging that the combination of the 2 drugs is more effective, at usual doses, than either drug alone. Remaining uncertainty regarding benefits that are important to patients and the risk for adverse effects limits the implications of the results for clinical practice, particularly in populations at high risk for adverse effects.

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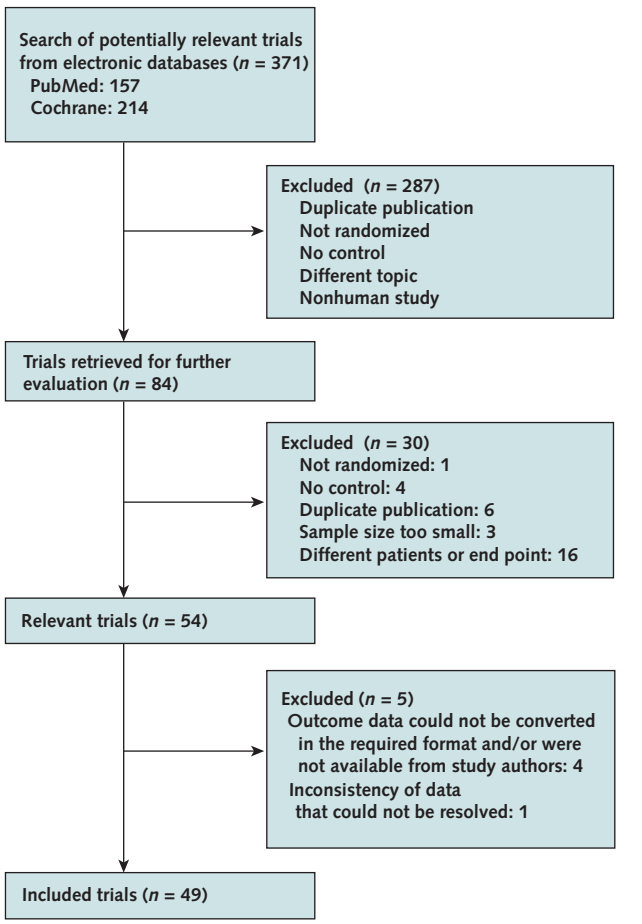
Appendix Figure 1. **Study flow diagram.**

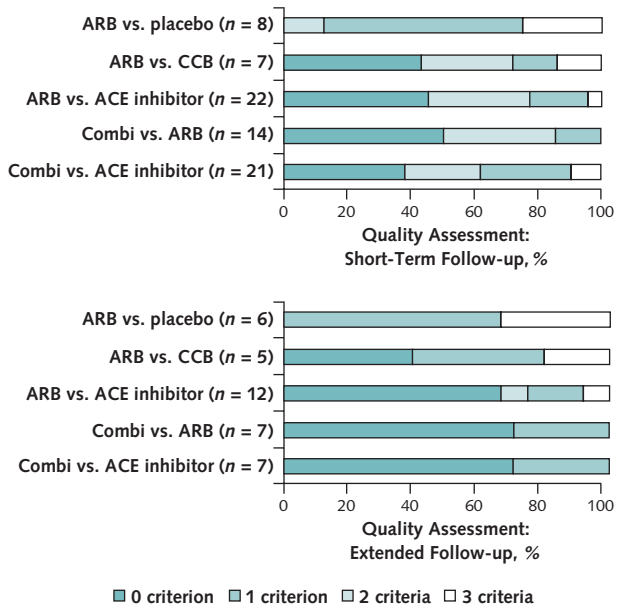


Appendix Table. **Methodological Quality of the Included Studies***

Study, Year (Reference)	Design	Allocation Concealment	Blinding	ITT/PP Analysis	Carryover Effect	Washout between Study Periods
Agarwal, 2001 (69)	Crossover	NR	No blinding	PP	Not detected	2 wk
Andersen et al., 2000 (39)	Crossover	NR	Blinding	PP = ITT†	Not detected	0
Atkins et al., 2005 (29)	Parallel	Concealed	Blinding	PP	NA	NA
Barnett et al., 2004 (5)	Parallel	Concealed	Blinding	ITT	NA	NA
Berger et al., 2002 (70)	Crossover	Concealed	Blinding	PP = ITT†	NR	4 wk
Campbell et al., 2003 (49)	Crossover	NR	No blinding	PP = ITT†	Not detected	0
Cetinkaya et al., 2004 (50)	Parallel	NR	No blinding	PP = ITT†	NA	NA
de Zeeuw et al., 2004 (3)	Parallel	Concealed	Blinding	ITT	NA	NA
Esnault et al., 2005 (51)	Crossover	NR	No blinding	ITT	Not detected	4 wk
Ferrari et al., 2002 (52)	Crossover	Concealed	Unclear	PP	NR	4 wk
Gartenmann et al., 2003 (23)	Parallel	NR	No blinding	PP	NA	NA
Haneda et al., 2004 (40)	Parallel	NR	Blinding	PP	NA	NA
Holdaas et al., 1998 (24)	Crossover	NR	Blinding	PP	Not detected	6 wk
Horita et al., 2004 (53)	Parallel	NR	No blinding	PP	NA	NA
Iino et al., 2004 (47)	Parallel	NR	No blinding	PP	NA	NA
Ishimitsu et al., 2005 (22)	Crossover	Concealed	No blinding	PP = ITT†	NR	0
Jacobsen et al., 2002 (71)	Crossover	Concealed	Blinding	PP	Not detected	0
Jacobsen et al., 2003 (41)	Crossover	Concealed	Blinding	PP	Not detected	0
Jacobsen et al., 2003 (72)	Crossover	Concealed	Blinding	PP = ITT†	Not detected	0
Kim et al., 2003 (21)	Crossover	NR	Blinding	PP	NR	0
Kincaid-Smith et al., 2002 (20)	Crossover	Concealed	No blinding	ITT	NR	0
Lacourcière et al., 2000 (54)	Parallel	NR	Blinding	Unclear	NA	NA
Li et al., 2006 (42)	Parallel	Concealed	Blinding	ITT	NA	NA
Luño et al., 2002 (55)	Parallel	Concealed	No blinding	ITT	NA	NA
Matos et al., 2005 (56)	Crossover	NR	No blinding	Unclear	NR	4 wk
Matsuda et al., 2003 (57)	Parallel	NR	No blinding	Unclear	NA	NA
Mogensen et al., 2000 (58)	Parallel	NR	Blinding	ITT	NA	NA
Muirhead et al., 1999 (43)	Parallel	NR	Blinding	ITT	NA	NA
Nutahara et al., 2005 (48)	Parallel	NR	No blinding	PP	NA	NA
Park et al., 2003 (25)	Parallel	NR	No blinding	PP	NA	NA
Parving et al., 2001 (6)	Parallel	NR	Blinding	ITT	NA	NA
Praga et al., 2003 (26)	Parallel	NR	Blinding	ITT	NA	NA
Renke et al., 2004 (59)	Parallel	NR	No blinding	PP	NA	NA
Rossing et al., 2002 (73)	Crossover	Concealed	Blinding	PP	Not detected	0
Rossing et al., 2003 (74)	Crossover	Concealed	Blinding	PP	Not detected	0
Rossing et al., 2003 (44)	Crossover	Concealed	Blinding	PP	Not detected	0
Ruilope et al., 2000 (68)	Parallel	NR	No blinding	ITT	NA	NA
Russo et al., 2001 (60)	Crossover	NR	No blinding	PP	NR	4 wk
Rutkowski et al., 2004 (61)	Crossover	NR	No blinding	PP	Not detected	0
Sasso et al., 2002 (45)	Crossover	NR	Blinding	PP = ITT†	NR	2 wk
Schulz et al., 2000 (62)	Parallel	NR	Blinding	PP	NA	NA
Segura et al., 2003 (63)	Parallel	NR	No blinding	PP	NA	NA
Sengul et al., 2006 (64)	Parallel	NR	No blinding	PP	NA	NA
Song et al., 2006 (65)	Crossover	NR	Blinding	PP	NR	8 wk
Tutüncü et al., 2001 (66)	Parallel	NR	No blinding	PP	NA	NA
Tylicki et al., 2005 (67)	Parallel	NR	No blinding	PP	NA	NA
Viberti et al., 2002 (27)	Parallel	Concealed	Blinding	12 wk: PP; 24 wk: ITT	NA	NA
Yasuda et al., 2005 (28)	Parallel	NR	No blinding	ITT	NA	NA
Zandbergen et al., 2003 (46)	Parallel	Concealed	Blinding	ITT	NA	NA

* ITT = intention to treat; NA = not applicable; NR = not reported; PP = per protocol.
† Complete follow-up of all patients who entered the trial.

Appendix Figure 2. **Quality assessment.**



ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; Combi = combination therapy.