ORIGINAL ARTICLE

Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

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ABSTRACT

BACKGROUND

Combination therapy with angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) decreases proteinuria; however, its safety and effect on the progression of kidney disease are uncertain.

METHODS

We provided losartan (at a dose of 100 mg per day) to patients with type 2 diabetes, a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300, and an estimated glomerular filtration rate (GFR) of 30.0 to 89.9 ml per minute per 1.73 m^2 of body-surface area and then randomly assigned them to receive lisinopril (at a dose of 10 to 40 mg per day) or placebo. The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m^2 if the initial estimated GFR was ≥60 ml per minute per 1.73 m^2 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m^2), end-stage renal disease (ESRD), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR or ESRD. Safety outcomes included mortality, hyperkalemia, and acute kidney injury.

RESULTS

The study was stopped early owing to safety concerns. Among 1448 randomly assigned patients with a median follow-up of 2.2 years, there were 152 primary end-point events in the monotherapy group and 132 in the combination-therapy group (hazard ratio with combination therapy, 0.88; 95% confidence interval [CI], 0.70 to 1.12; P=0.30). A trend toward a benefit from combination therapy with respect to the secondary end point (hazard ratio, 0.78; 95% CI, 0.58 to 1.05; P=0.10) decreased with time (P=0.02 for nonproportionality). There was no benefit with respect to mortality (hazard ratio for death, 1.04; 95% CI, 0.73 to 1.49; P=0.75) or cardiovascular events. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; P<0.001) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, P<0.001).

CONCLUSIONS

Combination therapy with an ACE inhibitor and an ARB was associated with an increased risk of adverse events among patients with diabetic nephropathy. (Funded by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development; VA NEPHRON-D ClinicalTrials.gov number, NCT00555217.)

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Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States.[1] Persons with diabetes and proteinuria are at high risk for progression to ESRD.[2] Blockade of the renin–angiotensin system decreases the progression of proteinuric kidney disease,[3-5] and the degree of reduction in proteinuria correlates with the extent to which the decrease in the glomerular filtration rate (GFR) is slowed.[2,6] Given these observations, it has been hypothesized that interventions that further lower proteinuria will further reduce the risk of progression.[6] Combination therapy with an angiotensin-converting–enzyme (ACE) inhibitor and an angiotensin II–receptor blocker (ARB) results in a greater decrease in proteinuria than does monotherapy with either type of agent.[7]

In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), a randomized study of combination therapy versus monotherapy in persons at increased cardiovascular risk, no cardiovascular or renal benefits were observed with combination therapy, and there was an increased risk of hyperkalemia and acute kidney injury requiring dialysis.[8,9] However, the benefit of treatment with an ACE inhibitor or an ARB in decreasing the risk of ESRD has been shown only in persons with overt proteinuria,[3-5,10] and the ONTARGET study population had predominantly normal levels of albumin excretion or microalbuminuria.[3-5,10]

The present study was designed to test the safety and efficacy of combination therapy with an ACE inhibitor and an ARB as compared with ARB monotherapy in slowing the progression of proteinuric diabetic nephropathy.

METHODS

STUDY DESIGN AND OVERSIGHT

The Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) study was a multicenter, double-blind, randomized, controlled study designed to test the efficacy of the combination of losartan (an ARB) with lisinopril (an ACE inhibitor), as compared with standard treatment with losartan alone, in slowing the progression of proteinuric diabetic kidney disease. The design of the study has been described previously.[11] There was an initial run-in phase during which treatment with losartan was started or continued and the dose was increased to 100 mg per day, the maximum dose approved by the Food and Drug Administration and the dose used in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study.[3] Patients who did not have any unacceptable adverse events while taking the full dose were eligible for randomization to lisinopril or placebo.

The study was conducted at 32 Department of Veterans Affairs (VA) medical centers. It was approved by the human rights committee at the West Haven VA Cooperative Studies Program Coordinating Center and by the institutional review board at each participating site and was overseen by an independent data and safety monitoring committee chartered by the sponsor (the Cooperative Studies Program of the VA Office of Research and Development). All enrolled patients provided written informed consent. The study protocol is available with the full text of this article at NEJM.org.

The sponsor reviewed the manuscript before it was submitted for publication but did not control the interpretation of the results or the decision to submit the manuscript for publication. The study was designed by the planning committee and executive committee, the participating investigators collected the data, and all the authors wrote the manuscript. The executive committee made the decision to submit the manuscript for publication. The coordinating center had full access to the data and vouches for the accuracy and completeness of the data and analysis. The executive committee and the coordinating center vouch for the fidelity of the study to the protocol. Merck donated losartan and lisinopril for the study but was not involved in the study design, data analysis, or manuscript preparation.

STUDY POPULATION

Veterans with type 2 diabetes, an estimated GFR of 30.0 to 89.9 ml per minute per 1.73 m^2 of body-surface area (calculated with the use of the four-variable Modification of Diet in Renal Disease formula[12]), and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 300 in a random sample were eligible to participate. We excluded patients with known nondiabetic kidney disease, a serum potassium level of more than 5.5 mmol per liter, current treatment with sodium polystyrene sulfonate, or an inability to stop proscribed medications that increase the risk of hyperkalemia. The urinary albumin-to-creatinine ratio was measured locally; a urinary

protein-to-creatinine ratio (with both protein and creatinine measured in grams) of more than 0.5 was used to define eligibility at a few sites in which local laboratories did not quantify the urinary albumin-to-creatinine ratio if it exceeded 300.

INTERVENTION

After obtaining informed consent, we provided patients with 50 mg of losartan per day and increased the dose to 100 mg per day if the potassium level remained below 5.5 mmol per liter and the creatinine level did not rise by more than 30% from the time of enrollment. If renin–angiotensin–aldosterone system blockers were being used at the time of enrollment, they were discontinued. Once patients had been taking 100 mg of losartan per day for at least 30 days, we randomly assigned them in a 1:1 ratio to receive lisinopril or placebo, with stratification according to site, the estimated GFR (<60 or ≥60 ml per minute per 1.73 m²), proteinuria (albumin-to-creatinine ratio of ≤1000 or >1000 or protein-to-creatinine ratio of ≤1.5 or >1.5), and use or nonuse of combination therapy with an ACE inhibitor and an ARB at enrollment. We increased the dose of lisinopril or placebo every 2 weeks, from 10 mg to 20 mg to 40 mg per day as long as there were no unacceptable side effects, checking potassium and creatinine levels 10 to 14 days after each increase to ensure that the potassium level remained below 5.5 mmol per liter and that the creatinine level did not rise by more than 30% from the value at randomization.

Once patients reached a maintenance dose, we evaluated them every 3 months. We adjusted blood-pressure medications to target a systolic pressure of 110 to 130 mm Hg and a diastolic pressure of less than 80 mm Hg. To decrease the risk of major hyperkalemia, elevations in the potassium level (5.0 to 6.0 mmol per liter) were managed by means of dietary modification and adjustment in diuretics and other medications, as described previously.[11] Serum creatinine and potassium levels were measured at the local VA laboratory; at randomization and every 3 months, the creatinine level was measured at a central laboratory, with the use of an isotope-dilution mass-spectroscopy traceable assay, for assessment of the primary end point.

END POINTS

The primary end point was the first occurrence of a decline in the estimated GFR (an absolute decrease of ≥30 ml per minute per 1.73 m² if the estimated GFR was ≥60 ml per minute per 1.73 m² at randomization or a relative decrease of ≥50% if the estimated GFR was <60 ml per minute per 1.73 m²), ESRD (defined by the initiation of maintenance dialysis or an estimated GFR of <15 ml per minute per 1.73 m²), or death. The secondary renal end point was the first occurrence of a decline in the estimated GFR (as defined above) or ESRD. Changes in the estimated GFR were confirmed at least 4 weeks after treatment of potentially reversible factors. Patients who reached the primary end point on the basis of the estimated GFR continued to receive study medications until the occurrence of ESRD or death. Tertiary end points included cardiovascular events (myocardial infarction, stroke, or hospitalization for congestive heart failure), the slope of change in the estimated GFR, and the change in albuminuria at 1 year.

ADVERSE EVENTS AND SAFETY

Safety outcomes were all-cause mortality, serious adverse events, hyperkalemia, and acute kidney injury. Hyperkalemia was defined as a potassium concentration that was more than 6 mmol per liter or that required an emergency room visit, hospitalization, or dialysis. Acute kidney injury events were serious adverse events requiring hospitalization or occurring during hospitalization.

Serious adverse events were defined according to the globally accepted definitions in the International Conference on Harmonization Guideline for Clinical Safety Data Management.[13] Serious adverse events were recorded from the time the patient consented to be in the study through 30 days after study exit.

STATISTICAL ANALYSIS

Assuming a 45% cumulative event rate and a 10% loss to follow-up, we initially calculated that we would need to enroll 1850 patients over a period of 3 years, with a minimum follow-up of 2 years, for the study to have 85% power to detect an 18% relative reduction in the primary end point at a two-sided alpha level of 0.05. In 2010, the enrollment period was extended to 4.25 years; a minimum follow-up of 2 years was maintained. Assuming a higher (51%) cumulative event rate in the monotherapy group with longer follow-up and a dropout rate of 12%, we estimated that we would need to enroll 1644 participants to have a total of 759 primary end-point events, with the

same power, alpha level, and relative risk reduction maintained. The data and safety monitoring committee monitored safety every 6 months. We planned for two interim efficacy analyses, after 50% and 75% of the expected number of primary end-point events had occurred.

We analyzed primary and secondary end points with the use of a stratified log-rank test based on the randomization strata, according to the intention-to-treat principle. We calculated cumulative event rates using the Kaplan–Meier method. Data on patients lost to follow-up or lost to surveillance of the estimated GFR or ESRD were censored at the date of the last visit; for the secondary end point, data were censored at death. We calculated hazard ratios with the use of Cox regression, adjusting for estimated-GFR and albuminuria strata. Exploratory analyses evaluated hazard ratios in prespecified subgroups (according to albuminuria stratum, estimated-GFR stratum, age, race, sex, and use or nonuse of combination therapy with an ACE inhibitor and an ARB at enrollment). We also analyzed each component of the composite primary end point separately and performed similar analyses for cardiovascular events, hyperkalemia, and acute kidney injury.

We analyzed changes in the estimated GFR and albuminuria using a linear mixed model with repeated measures. Because the distribution of albuminuria values was skewed, we analyzed geometric means using log-transformed values. We compared the proportions of patients in the two study groups who had serious adverse events with the use of a chi-square test and compared the summarized rates of serious adverse events with the assumption of a Poisson distribution.

P values for all end points are two-sided; P values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS

Between July 2008 and September 2012, a total of 4346 patients were screened, 1648 were enrolled, and 1448 underwent randomization (724 in each group). Reasons for nonenrollment and nonrandomization are summarized in Figure S1 in the Supplementary Appendix, available at NEJM.org. A total of 182 randomly assigned patients died or had progression to ESRD (60 patients in the monotherapy group and 63 patients in the combination-therapy group died), and 143 exited the study before it was closed (66 withdrew, 39 were lost to follow-up, 26 were at study sites that stopped participating in the study, and 12 had other reasons).

Baseline characteristics in the two groups were similar (Table 1). The median urinary albumin-to-creatinine ratio was 847 at enrollment; 662 patients (336 in the monotherapy group and 326 in the combination-therapy group) had a urinary albumin-to-creatinine ratio of 1000 or higher.

Fewer patients in the combination-therapy group than in the monotherapy group were able to reach the full target dose of lisinopril or placebo (589 vs. 629); 89.6% of the patients in the combination-therapy group and 93.4% of the patients in the monotherapy group were taking at least 10 mg of lisinopril or placebo per day at the end of the dose-adjustment period. At the end of the study, 83.9% of patients in the monotherapy group and 79.3% of patients in the combination-therapy group were taking at least 10 mg of lisinopril or placebo per day. Only 74 patients (40 in the monotherapy group and 34 in the combination-therapy group) were no longer taking losartan. Blood-pressure control was similar in the two groups at enrollment, during adjustment of the losartan dose, and at randomization. After adjustment of the lisinopril or placebo dose, the combination-therapy group had a slightly lower blood pressure than the monotherapy group (within 2 mm Hg) (Fig. S2 in the Supplementary Appendix). The change in the estimated GFR from randomization to 3 months was similar in the two groups (from 55±18 to 53±18 ml per minute per 1.73 m^2 in the combination-therapy group and from 57±19 to 54±19 ml per minute per 1.73 m^2 in the monotherapy group).

In October 2012, the data and safety monitoring committee recommended to the sponsor that the study treatment be stopped, primarily on account of safety concerns due to increased rates of serious adverse events, hyperkalemia, and acute kidney injury in the combination-therapy group as compared with the monotherapy group, along with low conditional power (<5% for the observed trend) to detect a treatment effect on the primary end point. The data and safety

monitoring committee concluded that the absolute risk of serious adverse events appeared to be greater than the potential benefit of reducing primary end-point events, even if the hypothesized treatment effect emerged later in follow-up. The sponsor accepted the recommendation and instructed the executive committee to stop the study treatment. At study closure, the median patient follow-up was 2.2 years.

PRIMARY END POINT

There were 152 primary end-point events in the monotherapy group (21.0%) and 132 in the combination-therapy group (18.2%) (Table 2 and Fig. 1A). The overall event rate was 10.8 events per 100 person-years of follow-up in the monotherapy group and 9.5 events per 100 person-years of follow-up in the combination-therapy group. The composition of first events was as follows: in the

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)
Age — yr	64.7±7.7	64.5±7.9
Male sex — no. (%)	721 (99.6)	715 (98.8)
Race — no. (%)†		
White	528 (72.9)	523 (72.2)
Black	173 (23.9)	172 (23.8)
Other	23 (3.2)	29 (4.0)
Hispanic ethnic group — no. (%)†	75 (10.4)	71 (9.8)
Body-mass index‡	34.3±6.9	34.9±6.7
Coronary artery disease — %	167 (23.1)	159 (22.0)
Congestive heart failure — %	110 (15.2)	116 (16.0)
Retinopathy — %	310 (42.8)	309 (42.7)
Blood pressure — mm Hg		
Systolic	137.0±16.0	136.9±16.5
Diastolic	72.8±9.9	72.5±10.6
Cholesterol — mg/dl		
Total	159.0±40.5	157.9±43.6
LDL	84.3±35.0	81.6±32.4
HDL	38.7±11.3	37.7±11.0
Triglycerides — mg/dl		
Median	162	165
Interquartile range	111–235	111–260
Glycated hemoglobin — %	7.8±1.3	7.8±1.2
Serum creatinine — mg/dl§	1.5±0.4	1.5±0.4
Serum potassium — mmol/liter	4.3±0.5	4.3±0.5
Estimated GFR		
Mean — ml/min/1.73 m^2	53.7±16.2	53.6±15.5
Category — no./total no. (%)		
30.0–44.9 ml/min/1.73 m^2	211/721 (29.3)	227/712 (31.9)
45.0–59.9 ml/min/1.73 m^2	236/721 (32.7)	220/712 (30.9)
≥60.0 ml/min/1.73 m^2	274/721 (38.0)	265/712 (37.2)
Urinary albumin-to-creatinine ratio¶		
Median	862	842
Interquartile range	488–1789	495–1698

Table 1. (Continued.)

Characteristic	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)
Urinary protein-to-creatinine ratio‖		
Median	1.6	2.1
Interquartile range	0.9–3.0	1.1–3.2
Use of ACE inhibitor, ARB, or both — no. (%)		
ACE inhibitor monotherapy	510 (70.4)	482 (66.6)
ARB monotherapy	118 (16.3)	141 (19.5)
Both ACE inhibitor and ARB	37 (5.1)	42 (5.8)
Neither ACE inhibitor nor ARB	59 (8.1)	59 (8.1)
Blood-pressure medications at randomization — no./total no. (%)		
Diuretic	508/723 (70.3)	516/724 (71.3)
Calcium-channel blocker	413/723 (57.1)	429/723 (59.3)
Beta-blocker	497/723 (68.7)	506/724 (69.9)
Alpha-blocker	158/723 (21.9)	152/724 (21.0)
Other	147/723 (20.3)	147/724 (20.3)

* Plus–minus values are means ±SD. There were no significant differences between the two groups in any of the characteristics listed. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein.
† Race and ethnic group were self-reported. If multiple races were reported, the first response was counted.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ To convert the values for creatinine to micromoles per liter, multiply by 88.4.
¶ Albumin was measured in milligrams, and creatinine was measured in grams.
‖ The urinary protein-to-creatinine ratio (with both protein and creatinine measured in grams) was measured in 187 patients (101 in the monotherapy group and 86 in the combination-therapy group) at sites that did not measure the urinary albumin-to-creatinine ratio in patients with overt proteinuria.

monotherapy group, 78 patients had a change in the estimated GFR (31 patients with a decline of ≥30 ml per minute per 1.73 m² and 47 patients with a decline of ≥50%), 23 had ESRD, and 51 died; in the combination-therapy group, 59 patients had a change in the estimated GFR (23 patients with a decline of ≥30 ml per minute per 1.73 m² and 36 patients with a decline of ≥50%), 18 had ESRD, and 55 died. The risk of the primary end point did not differ significantly between the two groups. There was also no significant difference in the hazard ratios among prespecified subgroups (P>0.10 for all interactions) (Fig. S3 in the Supplementary Appendix).

SECONDARY END POINT

There were 101 secondary end-point events (a decline in the estimated GFR or ESRD) in the monotherapy group (14.0%) and 77 events in the combination-therapy group (10.6%) (Table 2 and Fig. 1B). The overall event rate was 7.2 events per 100 person-years of follow-up in the monotherapy group and 5.5 events per 100 person-years of follow-up in the combination-therapy group. There was a lag in the treatment effect, with an effect emerging after about 6 to 12 months, but it was not sustained with longer follow-up (P=0.02 for the test of nonproportionality). There was no significant between-group difference in mortality (Table 2 and Fig. 1C) or ESRD (Table 2), though the number of ESRD events was small.

TERTIARY END POINTS

There was no significant difference in the rate of cardiovascular events between the two groups. The number of patients with myocardial infarction was higher and the number of patients with congestive heart failure was lower in the combination-therapy group than in the monotherapy group, but the differences were not significant (Table 2). The rate of stroke was the same in the two groups.

Over time, the estimated GFR declined in both groups; the estimated GFR slope was –2.7 ml per

Table 2. Efficacy End Points and Mortality.*

End Point	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
	no. of patients (%)			
Primary end point†	152 (21.0)	132 (18.2)	0.88 (0.70–1.12)	0.30
Secondary end point‡	101 (14.0)	77 (10.6)	0.78 (0.58–1.05)	0.10
ESRD	43 (5.9)	27 (3.7)	0.66 (0.41–1.07)	0.07
Death	60 (8.3)	63 (8.7)	1.04 (0.73–1.49)	0.75
Myocardial infarction, heart failure, or stroke	136 (18.8)	134 (18.5)	0.97 (0.76–1.23)	0.79
Myocardial infarction	40 (5.5)	52 (7.2)	1.30 (0.87–1.97)	0.20
Congestive heart failure	106 (14.6)	89 (12.3)	0.82 (0.62–1.09)	0.17
Stroke	18 (2.5)	18 (2.5)	0.98 (0.52–1.85)	0.95

* CI denotes confidence interval, and ESRD end-stage renal disease.
† The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m^2 if the initial estimated GFR was ≥60 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m^2), ESRD, or death.
‡ The secondary end point was the first occurrence of a change in the estimated GFR (as defined above) or ESRD.

minute per 1.73 m^2 per year in the combination-therapy group and –2.9 ml per minute per 1.73 m^2 per year in the monotherapy group (Fig. S4 in the Supplementary Appendix). There was no significant difference in treatment effect on the decline in the estimated GFR (P=0.17). During adjustment of the losartan dose, the median urinary albumin-to-creatinine ratio declined from 959 to 807 (P=0.001). There was a further decline from randomization to 1 year, with a greater decline in the combination-therapy group (from 786 to 517) than in the monotherapy group (from 829 to 701) (P<0.001) (Fig. S5 in the Supplementary Appendix).

ADVERSE EVENTS AND SAFETY

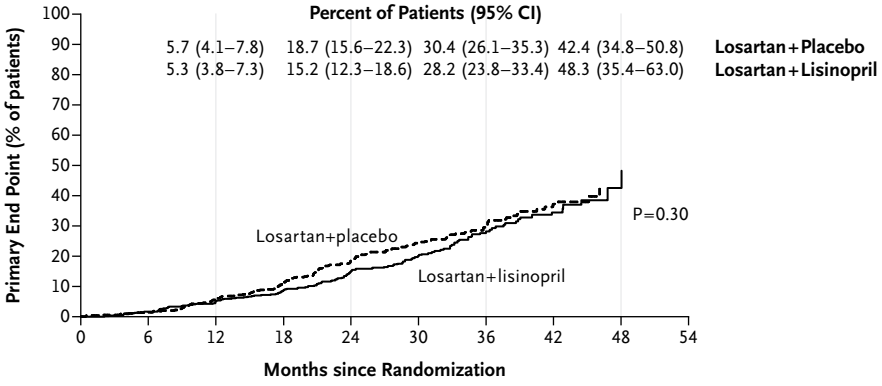
Serious adverse events occurred in more patients in the combination-therapy group than in the monotherapy group (Table 3, and Table S1 in the Supplementary Appendix). The rate of serious adverse events was 98 events per 100 person-years in the combination-therapy group versus 82 events per 100 person-years in the monotherapy group. The proportion of serious adverse events attributed to study medication by the site investigators was higher in the combination-therapy group than in the monotherapy group.

Acute kidney injury was the main reason for the higher rate of serious adverse events in the combination-therapy group, with 190 acute kidney injury events in 130 patients in the combination-therapy group (12.2 events per 100 person-years) as compared with 105 acute kidney injury events in 80 patients in the monotherapy group (6.7 events per 100 person-years). Figure 2A shows the cumulative probability of acute kidney injury during the study. The hazard ratio with combination therapy was 1.7 (95% confidence interval [CI], 1.3 to 2.2; P<0.001).

Figure 1 (facing page). Kaplan–Meier Plot of Cumulative Probabilities of the Primary and Secondary End Points and Death.

The primary end point was the first occurrence of a change in the estimated glomerular filtration rate (GFR) (a decline of ≥30 ml per minute per 1.73 m^2 of body-surface area if the initial estimated GFR was ≥60 ml per minute per 1.73 m^2 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m^2), end-stage renal disease, or death. The secondary end point was the first occurrence of a change in the estimated GFR (as defined above) or end-stage renal disease. Death was defined as death from any cause. The P values with calculated with the use of a stratified log-rank test. CI denotes confidence interval.

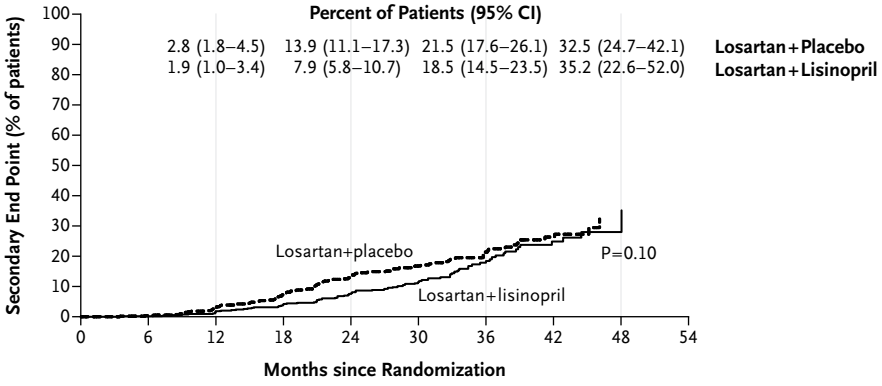
A Primary End Point



No. at Risk

Losartan+placebo	724	641	543	453	335	238	149	75	14
Losartan+lisinopril	724	631	534	457	347	245	139	69	10

B Secondary End Point



No. at Risk

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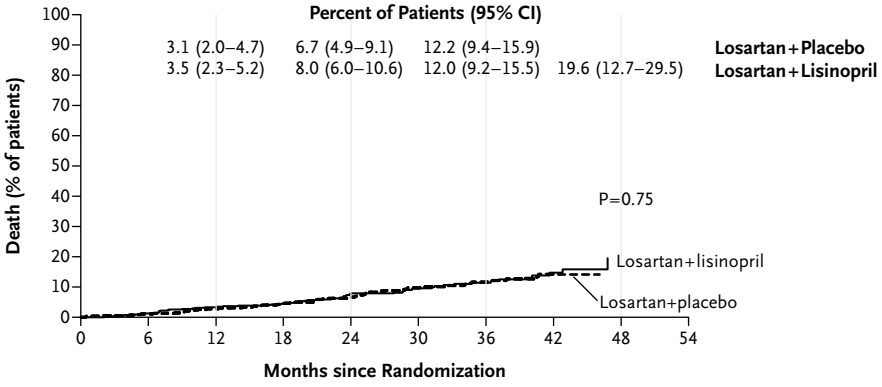
Losartan+lisinopril	724	631	534	457	347	245	139	69	10

C Death



No. at Risk

Losartan+placebo	724	654	573	499	389	281	183	96	21
Losartan+lisinopril	724	658	575	505	393	297	185	93	13

Table 3. Safety Outcomes.*

Outcome	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
Patients with serious adverse events — no. (%)	380 (52.5)	416 (57.5)	NA	0.06
No. of serious adverse events	1274	1539†	NA	
Attribution of serious adverse events to study drugs — no. of events (%)†				0.049
Not attributed	1159 (91.0)	1365 (88.7)	NA	
Possibly attributed	104 (8.2)	146 (9.5)	NA	
Attributed	11 (0.9)	27 (1.8)	NA	
Acute kidney injury — no. of patients (%)	80 (11.0)	130 (18.0)	1.7 (1.3–2.2)	<0.001
Hyperkalemia — no. of patients (%)	32 (4.4)	72 (9.9)	2.8 (1.8–4.3)	<0.001

* NA denotes not applicable.
† For one of the serious adverse events in the monotherapy group, information was not available to determine whether the event was attributable to study medications. The percentages are based on the total number of serious adverse events in each group.

The rate of hyperkalemia in the combination-therapy group was more than double the rate in the monotherapy group (Table 3 and Fig. 2B). After randomization, there were 139 total events in 104 patients (98 events in the combination-therapy group [6.3 events per 100 person-years] and 41 events in the monotherapy group [2.6 events per 100 person-years]). The hazard ratio for hyperkalemia with combination therapy was 2.8 (95% CI, 1.8 to 4.3; P<0.001). Mean potassium levels at scheduled follow-up visits over time are shown in Figure S6 in the Supplementary Appendix.

DISCUSSION

We found that combination therapy with an ARB and an ACE inhibitor, as compared with monotherapy, was associated with an increased risk of serious adverse events — acute kidney injury and hyperkalemia. The higher risk of acute kidney injury with combination therapy was evident from the time of treatment initiation through 42 months of follow-up. Combination therapy did not provide a significant benefit with respect to the primary end point (renal-disease progression or death), mortality, or cardiovascular disease. Because the study was stopped early with a fraction of the planned accrued events, one cannot definitively rule out a potential benefit of combined therapy. The point estimates for the effect on the primary end point were less than 1, though the estimated effect size was smaller than initially hypothesized during trial design. Conditional power calculations suggest that even if the study had been completed as planned, the observed effects on the primary end point would not have been significant.

For the secondary end point, there was an overall trend toward a lower risk in the combination-therapy group than in the monotherapy group. However, the nonproportional hazard ratio (P=0.02 for the test of nonproportionality) suggests a varying treatment effect (a lower risk with combination therapy than with monotherapy at 24 months but a similar risk at 42 months). This change may be artifactual, because relatively few patients were at risk at later time points, despite the significant P value for the test of proportionality.

The results of this trial are generally consistent with those of ONTARGET[8,9] and the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE),[14] which showed increased harms and no cardiovascular or renal benefit with combination therapies that block the renin–angiotensin system. Monotherapy with ACE inhibitors or ARBs slows the progression of proteinuric diabetic nephropathy[3-5] but has not been shown to slow the progression of nonproteinuric kidney disease.[15] We postulated that a

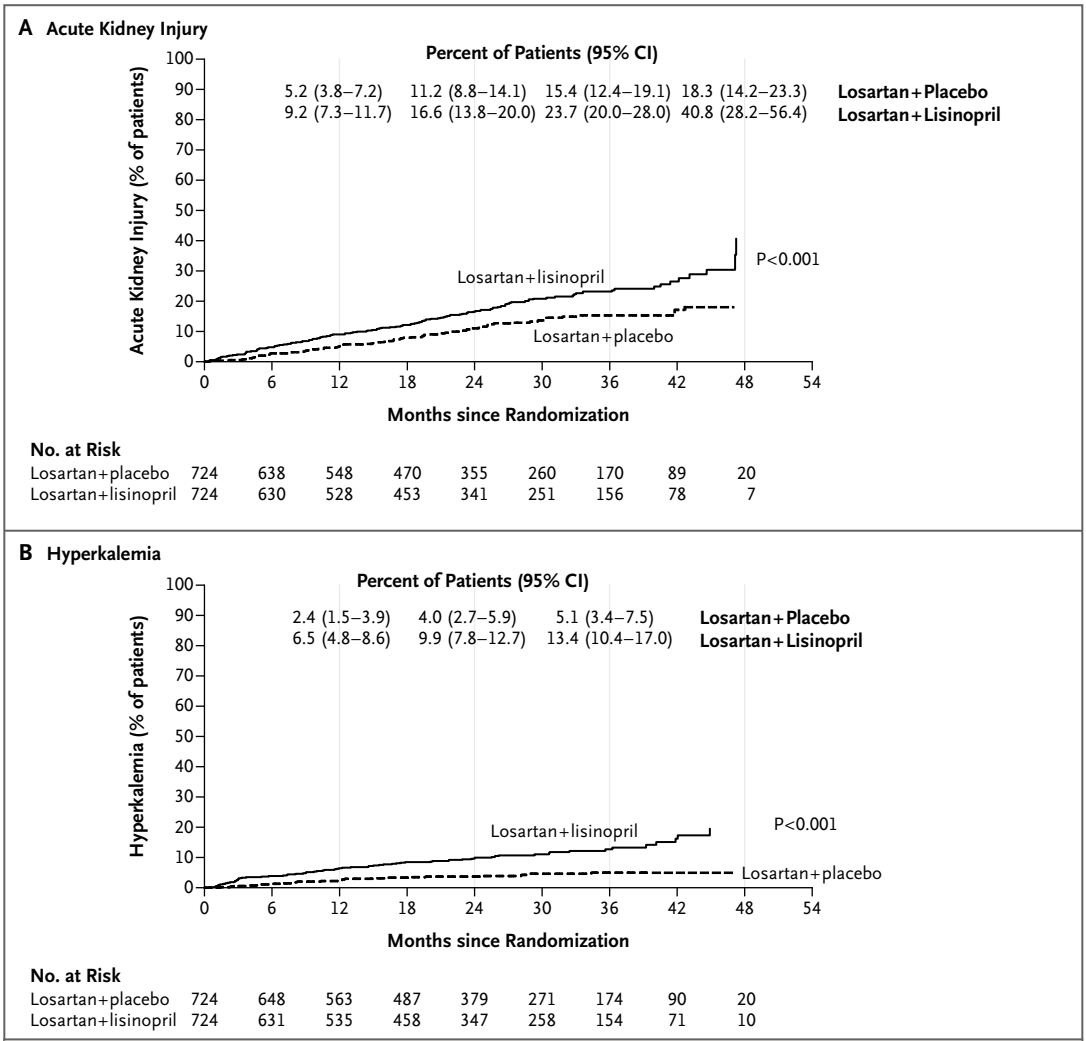


Figure 2. Kaplan–Meier Plot of Cumulative Probabilities of Acute Kidney Injury and Hyperkalemia.

Acute kidney injury was defined as acute kidney injury requiring hospitalization or occurring during a hospitalization. Hyperkalemia was defined as a potassium level that was more than 6.0 mmol per liter or that required an emergency room visit, hospitalization, or dialysis. The P values were calculated with the use of a stratified log-rank test.

complete blockade of the renin–angiotensin system with combination therapy might be more effective than monotherapy among patients with proteinuric kidney disease. In ONTARGET, there was an increased risk of a need for dialysis, a doubling of the serum creatinine level, or death in the combination-therapy group, owing to an increased risk of acute kidney injury requiring dialysis.[8] In that study, the excess renal risk was greatest among patients without albuminuria; in those with overt diabetic kidney disease, the hazard ratio with combination therapy was slightly less than 1.00.

The patients in our trial represent a high-risk population with residual proteinuria, despite the use of a full dose of an ARB. We had hypothesized that the benefit in slowing the progression of kidney disease would outweigh the risks of hyperkalemia and acute kidney injury associated with more intensive blockade of the renin–angiotensin system. However, the significant increase in risk overshadowed a nonsignificant trend toward a benefit with respect to the primary and secondary end points. As compared with monotherapy, combination therapy was associated with 17 more serious adverse events per 100 person-

years. The risk of hyperkalemia was more than twice as high in the combination-therapy group as in the monotherapy group. ALTITUDE, a trial of aliskiren added to an ACE inhibitor or an ARB in patients with diabetes and kidney disease, was also stopped early because of safety concerns, including an increased number of strokes and serious adverse renal events.[14]

In our study, acute kidney injury events primarily accounted for the increased rates of serious adverse events with combination therapy. When renal perfusion is reduced (e.g., because of volume depletion), angiotensin II constricts the efferent glomerular arteriole and stimulates proximal tubular sodium reabsorption and aldosterone secretion.[16,17] These actions lead to restoration of plasma volume and maintenance of the GFR. Angiotensin blockade decreases the ability to respond to stresses such as volume depletion. Chronically increased angiotensin activation worsens diseases such as heart failure and renal disease[18,19]; angiotensin blockade improves outcomes, but our study suggests that there may be a point beyond which further blockade is unsafe and without additional benefit. Acute kidney injury is associated with an increased risk of subsequent progression of chronic kidney disease[20]; whether the increased risk of acute kidney injury from intensive angiotensin blockade counteracts the beneficial effects with respect to progression and the risk of ESRD is not known. It is possible that the cumulative effect of greater acute kidney injury in the combination-therapy group than in the monotherapy group explains the narrowing of the survival curves for the progression of kidney disease.

As in ONTARGET[8] and ALTITUDE,[14] combination therapy decreased albuminuria in our study, without slowing long-term progression. However, neither our study nor the other two studies specifically targeted albuminuria. Whether this discrepancy indicates that albuminuria is not an appropriate surrogate or whether it is appropriate but adverse effects of combination therapy offset any benefit is unknown. In addition, our results illustrate that studies showing a treatment benefit with respect to intermediate outcomes may have insufficient power to identify a safety signal that can be detected only in larger, long-term studies.

In conclusion, the results of our study show that the use of combination therapy with an ACE inhibitor and an ARB in patients with proteinuric diabetic kidney disease does not provide an overall clinical benefit.

The opinions expressed in this article are those of the authors and do not necessarily represent those of the Department of Veterans Affairs or Merck.

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