Renal effects of aliskiren compared to and in combination with irbesartan in patients with type 2 diabetes, hypertension and albuminuria

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Objective: We investigated if the antiproteinuric effect of the direct renin inhibitor aliskiren is comparable to irbesartan, and the effect of the combination.

Research Design and Methods: Double-blind, randomized, cross-over trial. After a one-month washout period 26 patients with type 2 diabetes, hypertension and albuminuria (>100mg/day) were randomized to four 2-month treatment periods in random order with placebo, aliskiren 300 mg once daily, irbesartan 300 mg once daily or the combination using identical doses. Patients received furosemide in a stable dose throughout the study. Primary endpoint was change in albuminuria. Secondary measures included change in 24h blood pressure (24h BP) and glomerular filtration rate (GFR).

Results: Placebo geometric mean albuminuria was 258 mg/day (range 84-2361), mean 24h BP was 140/73 (SD 15/8) mmHg, GFR was 89 (SD 27) ml/min/1.73 m². Aliskiren treatment reduced albuminuria by 48% (95% confidence interval 27-62) compared to placebo (p<0.001), not significantly different from irbesartan treatment (58% (42-70) (p<0.001 vs. placebo)). Combination treatment reduced albuminuria by 71% (59-79), more than either monotherapy (p<0.001 and p=0.028). Fractional clearances of albumin were significantly reduced (46, 56 and 67% reduction vs. placebo).

24h BP was reduced 3/4 mmHg by aliskiren (NS/p=0.009), 12/5 mmHg by irbesartan (p<0.001/p=0.002) and 10/6 mmHg by the combination (p=0.001/ p<0.001). GFR was significantly reduced 4.6 (0.3, 8.8) ml/min/1.73m² by aliskiren, 8.0 (3.6, 12.3) ml/min/1.73m² by irbesartan and 11.7 (7.4, 15.9) ml/min/1.73m² by the combination.

Conclusions: Combining aliskiren and irbesartan is more antiproteinuric in type 2 diabetic patients with albuminuria as compared to monotherapy. ClinicalTrials.gov ID: NCT00464880
Albuminuria is the best available surrogate parameter in the treatment of diabetic nephropathy. Degree of proteinuria is associated with risk of renal and cardiovascular events\(^1\). Proteinuria reduction is associated with a slowing of the decline in renal function\(^2\). Blockade of the renin-angiotensin-aldosterone system (RAAS) is the cornerstone treatment of incipient and overt diabetic nephropathy, and in type 2 diabetes angiotensin II receptor blockers (ARB) such as irbesartan are considered standard treatment following the IRMA 2\(^3\) and IDNT\(^1\) trials.

Aliskiren represents a new principle of blocking the RAAS, inhibiting renin directly and acting at the rate-limiting step. The drug is approved for treatment of hypertension, but has also shown renoprotective potential in patients with type 2 diabetes and albuminuria\(^4,5\).

Combining an ARB and a direct renin inhibitor could offer improved RAAS blockade by acting both at the receptor level and at the first step of the cascade. We compared the antiproteinuric effect of maximal recommended doses of aliskiren, irbesartan and the combination in patients with type 2 diabetes and albuminuria. We also assessed the impact of the treatments on RAAS components and biomarkers of inflammation, endothelial dysfunction and cardiovascular risk.

**RESEARCH DESIGN AND METHODS**

This was a double-blind, randomized, crossover trial in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). The primary objective was to assess albuminuria during different treatments compared to placebo, secondary objectives were to assess effect on 24h BP, glomerular filtration rate (GFR), biomarkers and RAAS components. Patients were recruited from Steno Diabetes Center, Denmark. The protocol was approved by the local ethics committee and the Danish Medicine Agency. After informed consent patients attended a screening visit comprising laboratory tests and evaluations of inclusion/exclusion criteria. A one-month washout followed, in which all antihypertensive treatment was stopped. Slow-release furosemide in a fixed dose (mean dose 109 mg/24h, range 60-360) was prescribed to prevent blood pressure (BP) elevation and fluid retention. Patients used an electronic blood pressure device (UA 779, A&D Instruments Ltd. Abingdon, UK) to measure home BP throughout the study. Home BP exceeding 170/105 mm Hg, led to exclusion.

From a list of pre-screened candidates 41 patients were screened for study participation. Nine of these were screen failures mainly due to albuminuria levels below randomization requirement. Thirty-two patients were randomized and 22 patients completed the study. Of the 10 randomized patients that left the study before completion, two died, one was lost to follow-up, four patients had an adverse event that led to exclusion (diarrhoea, severe hypertension, recurrent urinary tract infection and dizziness) and three patients withdrew consent. Twenty-six patients had the primary endpoint: albuminuria assessed after randomization and were included in the final analysis; the remaining six patients dropped out shortly after randomization and were not included in the final analysis. After washout, patients attended a randomization visit prior to two months of treatment with placebo, aliskiren 300 mg once daily, irbesartan 300 mg daily or the combination of the two, in random order. Patients with type 2 diabetes (WHO criteria) aged 30-80 years old were eligible for randomization with baseline urinary albumin excretion rate (UAER) > 100 mg/24h, hypertension (baseline office BP above...
135/85 mm Hg ) and baseline GFR > 40 ml/min/1.73 m². Exclusion criteria included major cardiovascular disease (within 6 months), heart failure (NYHA class II-IV), HbA₁C >11 % and history of malignancy. Cardiovascular history was assessed at screening using medical records and ECG. Seven patients had previously been exposed to aliskiren.

There was no washout of study medication between the treatment periods; rather we used active washout: during the first 14 days of all treatments, every patient received aliskiren 150 mg daily to avoid risk of hypotension or drastic increase in BP when switching from placebo to combination treatment or vice versa.

During the last three days of each treatment, patients collected three consecutive 24h urine samples for assessment of geometric mean UAER. At the last day of each treatment period patients attended our clinic for assessment of GFR and mounting of standard Takeda 24h BP devices (TM2421, version 7, A&D Medical, Tokyo, Japan). Measurements were performed every 15 minutes from 7 to 23 h (daytime) and every 30 minutes from 23 to 7 h (nighttime). Less than 10% difference between daytime and nighttime BP defined non-dipping. GFR was measured as plasma clearance of $^{51}$Cr-EDTA(6).

Urinary albumin and creatinine concentrations were determined on a turbidimetric Hitachi 912 System (Roche Diagnostics, Mannheim, Germany).

Samples for prorenin, plasma renin activity (PRA), high-sensitivity PRA (hsPRA), immunoreactive plasma renin concentration (ir-PRC), angiotensinogen, angiotensin I (Ang I), angiotensin converting enzyme (ACE) activity, angiotensin II (Ang II) and aldosterone levels were taken after 30 minutes of supine rest and the plasma was frozen after centrifugation (−80°C).

RAAS components and biomarkers were measured at baseline and at the end of treatment periods. Biomarkers of inflammation, endothelial dysfunction and cardiovascular risk were measured: high sensitivity C-reactive protein (hsCRP) (EIA, DAKO A/S, Glostrup, Denmark); serum soluble vascular adhesion molecule-1 (sVCAM-1) and serum soluble intercellular adhesion molecule-1 (EIA, Diaclone, Besançon, France); plasma plasminogen activator inhibitor-1 (PAI-1) (HYPHEN BioMed kit, Andresy, France); serum N-terminal-pro brain natriuretic peptide (NT-proBNP) (EIA, Biomedica kit, Wien, Austria), fibrinogen (immunoturbidimetry) and plasma asymmetrical dimethyl arginine (ADMA) (high-performance liquid chromatography). Total renin concentration, prorenin concentration, plasma angiotensinogen, PRA and biomarkers of inflammation and endothelial dysfunction were measured using previously described methodology(4). Ir-PRC was measured with an immunoradiometric kit (Renin III, CisBio, Gif-sur-Yvette, France). hsPRA was measured by in-house radioimmunoassay of Ang I formed during incubation of 25 µl of plasma and 50 pmol of sheep angiotensinogen for 3h at 37° C in a total reaction volume of 100 µl. The assay was double calibrated against Ang I and the international reference preparation of renin, 68/356, from NIBSC, Hertfordshire, UK. Plasma Ang I and Ang II were measured using in-house radioimunoassays and ethanol extraction of plasma samples. Antibodies were raised in rabbits and calibrators were purchased from NIBSC, Hertfordshire, UK. ACE activity was determined using a commercial radioenzymatic assay (ACE direct, Bühlmann-Laboratories AG, Schönenbuch, Switzerland).

Randomization was performed blinded to all investigators and the study drugs were packed and labelled prior to delivery to the
site. Treatment code was revealed only after database lock.

**Statistical analysis:** It was estimated that 20 completed patients could provide 80% power to demonstrate a significant difference between two treatments in antiproteinuric effect (UAER) if the true difference was 15%. This was based on the assumption that intra-subject coefficient of variation (CV) for the UAER was 13%. The log-transformed values of UAER were analyzed by a PROC MIXED model with sequence, treatment, and period as fixed factors and subject (nested in sequence) as a random factor. For 24h BP data, daytime average, nighttime average, and 24h average values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were analyzed using a PROC MIXED model with sequence, treatment, and period as fixed factors and subject (nested in sequence) as a random factor. Extra analyses were performed to test the assumption of no carryover effect by fitting a carryover effect term into the model. GFR results and all other laboratory assessment data were analyzed similarly as for BP data. A two-sided p-value <0.05 was considered significant.

The correlation between changes in albuminuria and changes in hsPRA or Ang II were assessed by the non-parametric Spearman’s correlation coefficient. Correlations between changes in albuminuria and changes in ir-PRC were assessed by linear regression analysis within each active treatment (aliskiren, irbesartan, and aliskiren/irbesartan combination) and for all active treatments combined. Fractional clearance was calculated using urine samples collected during GFR measurements (urinary albumin excretion/serum albumin concentration x GFR) and log transformed levels were compared using the paired T-test. Statistical analyses were performed using SAS version 8.2 or higher (SAS Institute Inc., Cary, North Carolina, USA) and SPSS version 14.0 (Chicago, Illinois).

**RESULTS**

Baseline demographic data are shown in Table 1. Primary and secondary objectives were met. During placebo treatment geometric mean UAER was 258 mg/day (range 84-2361), mean 24h BP was 140/73 (SD 15/8) mmHg, daytime BP was 144/76 (SD 17/9) and nighttime BP 130/68 (SD 17/9). Eleven patients were defined as non-dippers. GFR was 89 (SD 27) ml/min/1.73 m² and mean serum creatinine 88 µmol/l.

Aliskiren treatment led to significant albuminuria reduction by 48% (95% CI 27-62) compared to placebo (p<0.001), not significantly different from irbesartan, lowering UAER by 58% (42-70) (p<0.001 vs. placebo). Combination treatment reduced albuminuria with 71% (59-79) (p<0.001) compared to placebo, significantly more than with either monotherapy (p<0.001 and p=0.028). The relative difference between aliskiren and combination treatment was 31%. To adjust for treatment induced changes in GFR, and potential influence on albuminuria reduction, we calculated fractional clearance, which was reduced by 46% vs. placebo during aliskiren treatment (p=0.021), by 56% vs. placebo during irbesartan treatment (p=0.002) and by 67% vs. placebo during combination treatment (p=0.001). There were no indications of carry-over effects on the results.

Systolic/diastolic 24h BP was reduced vs. placebo 3/4 mmHg by aliskiren (NS/p=0.009), 12/5 mmHg by irbesartan (p<0.001/p=0.002) and 10/6 mmHg by the combination (p=0.001/ p<0.001). There was no significant change in 24h BP from irbesartan to combination therapy. A correlation was found between change in albuminuria and change in 24h diastolic BP during all treatments (p=0.039).

Seated office systolic/diastolic BP was reduced 7/4 mmHg by aliskiren, 6/4 mmHg by irbesartan and 12/8 mmHg by the combination, all statistically significant
compared to placebo, except for diastolic BP during irbesartan treatment.

Compared to placebo GFR was significantly reduced 4.6 (95% CI 8.8, 0.3) ml/min/1.73m\(^2\) by aliskiren (p=0.037), 8.0 (12.3, 3.6) ml/min/1.73m\(^2\) by irbesartan (p<0.001) and 11.7 (15.9, 7.4) ml/min/1.73m\(^2\) by the combination (p<0.001).

Aliskiren significantly reduced hsPRA, Ang I and Ang II by 87%, 75% and 52% respectively compared to placebo; irbesartan had the opposite effect (Table 2). When combined, the activating effect of irbesartan was counteracted by aliskiren reducing hsPRA, Ang I and Ang II by 88%, 78% and 56%, respectively compared to irbesartan monotherapy. While combination treatment caused a 1068% increase in ir-PRC versus a 279% increase during aliskiren monotherapy and a 178% increase during irbesartan monotherapy, hsPRA was reduced 47% compared to placebo after combination therapy. PRA measured by a conventional method was affected similarly as hsPRA, although the changes were smaller (Table 2). The renin specific activity (renin bioactivity/total renin mass) was 3% and 4% after aliskiren and combination therapy compared to placebo respectively thereby confirming that 96-97% of renin was aliskiren-bound. During irbesartan monotherapy renin specific activity increased 52% compared to placebo.

A significant correlation between reduction in albuminuria and increase in ir-PRC was observed for all active treatments combined (r\(^2\)=0.597, p=0.0001). There was a significant correlation between changes in albuminuria and increase in Ang II during irbesartan treatment (correlation coefficient - 0.486, p=0.022); no significant correlations were observed in the other treatment groups.

Table 2 depicts changes in cardiovascular biomarkers compared to placebo. HsCRP was reduced 35% from placebo with aliskiren (p=0.047), and 35% with irbesartan (p=0.043). Other statistically significant changes from placebo levels were a 6% reduction in sICAM-1 (p=0.017) observed with the combination treatment and a 7% reduction in fibrinogen during aliskiren treatment (p=0.037). No treatment led to significant changes from placebo in any of the other cardiovascular biomarkers (Table 2).

The most frequent adverse events were urinary tract infection (four patients, one male), pneumonia (three patients) and cough (three patients), occurring during different treatments. Anemia and hypomagnesemia were detected in two patients during the combination treatment. Compared to each monotherapy combination treatment showed an increase in plasma potassium by 0.2 mmol/L (p=0.036). No patients developed hyperkalemia (defined as plasma potassium >5.5 mmol/L). There were no incidences of hypotension. One patient dropped out in during the placebo period after several systolic BP readings above 180 mm Hg.

Two patients died before first measurement of albuminuria after the randomization, and were not included in the final endpoint analysis. The first death was a 42-year old obese male (BMI 42) with a history of ischemic heart disease, myocardial infarction and hypertension four years prior to study entry. The patient experienced sudden cardiac arrest, seemingly after a myocardial infarction during aliskiren treatment. The second death was a hypertensive, obese 73-year old male with 16 years diabetes duration. Sudden death was possibly caused by a pulmonary embolism during the placebo period. The deaths were instantly reported to relevant authorities and were not suspected as being related to any of the drugs studied. Subsequently, home BP measurement frequency was increased from twice weekly to twice daily and patients were instructed to contact the investigator by direct phone (available around the clock), if any measurement was above 160/100 mm Hg.
Extra measurements of sodium, potassium and creatinine were introduced three weeks into each treatment period.

CONCLUSIONS

In this exploratory study we demonstrated that treatment with aliskiren 300 mg once daily was as efficient in reducing albuminuria as standard therapy with irbesartan 300 mg once daily. When combining the two treatments at the same doses, the reduction in albuminuria was improved. The added antiproteinuric effect with combination treatment compared to aliskiren alone was about 31% higher.

Given that the reductions in 24h systolic BP with aliskiren compared to placebo were unexpectedly small relative to 24h diastolic BP changes and substantially lower than the office systolic BP measurements in this study, we conducted a thorough review of potential flaws in data collection, storage, device calibration, reporting, and calculation. There was no evidence to indicate that the ambulatory data collection, storage, or reporting was flawed, and the unexpected results could be a play of chance.

Our study suggested that the combination of aliskiren and irbesartan had additional RAAS blocking effect compared to monotherapy since a synergistic increase in ir-PRC was observed with the combination, which was related to the antiproteinuric effect, whereas hsPRA was reduced 50% compared to placebo.

As opposed to the AVOID study(5), which found an additional 20% albuminuria reduction after 24 weeks of treatment with aliskiren compared to placebo added to the maximal recommended dose of losartan and optimal antihypertensive therapy, this is the first study with a head-to-head comparison between aliskiren and irbesartan treatment. No other antihypertensives except furosemide were allowed in our study, thereby offering a clearer picture of the effect of the two compounds used, compared to the AVOID study where aliskiren was combined with losartan and a mixture of other antihypertensive drugs. This study is different with regards to patient population, with a lower mean baseline UAER compared to the AVOID study. In addition, we assessed the effect of renin inhibition on GFR, measurements that are more precise than the estimated GFR used in the AVOID study.

The effect of RAAS blockade is believed to reduce proteinuria through several different mechanisms - the mean transcapillary hydraulic-pressure difference, the glomerular surface area and the size and charge selectivity of the glomerular filter. In diabetic nephropathy several of these variables are abnormal, and RAAS blockade has been demonstrated to normalize directly measured or estimated glomerular hydraulic pressure (7-9), to reduce the shunt-like defects in the membrane, at least in part(10), and to restore the charge-selectivity-properties of the glomerular membrane(11).

Aliskiren is thought to reduce albuminuria by the same mechanism as during treatment with ACE-inhibitors or ARBs. Recently, Fisher et al. have shown that aliskiren treatment increases renal plasma flow to a larger extent than the ACE inhibitor captopril(12). The increase in renal plasma flow may be a response to AT1-receptor-dependent reduction of the vascular tone in the efferent arteriole. Reduced vascular tone in the efferent glomerular arteriole could be responsible for the decrease in intraglomerular pressure leading to the reduction in albuminuria and GFR as demonstrated in our study. Combination treatment may reduce vascular tone to a greater extent than monotherapy. More research on the impact of renin inhibition on renal physiology is needed.

GFR changes seemed dependent on treatment during the study. Although the
combination reduced GFR up to 12 ml/min (15.9, 7.4), we interpret this as an reversible hemodynamic change and not as an indication of nephrotoxicity(13). In fact, it has been shown that an early hemodynamic reduction in GFR can translate into long-term renoprotection(13). When adjusting the albuminuria reduction during combination treatment for changes in GFR (fractional clearance) it was 11% higher than during irbesartan treatment, non-significant, possibly due to a small sample number.

Signs of more effective RAAS blockade were evident from the synergistic effect of combination treatment on ir-PRC. This conclusion is based on the fact that renin release into plasma is proportional to the interruption of the permanent negative feedback loop of angiotensin II on renin secretion (14). Combining aliskiren with irbesartan provided a 12-fold increase in ir-PRC, but still with a 50% reduction in hsPRA compared to the placebo period. This renin rise could reflect a high degree of intra-renal RAAS blockade during combination treatment as compared to the monotherapies, as has been suggested in non-diabetic patients(15). The reductions in albuminuria in our study were correlated to the rise in ir-PRC, supporting the concept of increased intrarenal RAAS blockade underlying the additional effects observed during combination treatment. In comparison with other studies of dual RAAS blockade, the rise in ir-PRC is higher in dual RAAS blockade using aliskiren than in dual RAAS blockade with an ACE inhibitor and an ARB(5,16,17). Such marked rises in renin during aliskiren treatment have been noted before(18). Apart from reflecting more complete (intrarenal) RAAS blockade, they may also be due to the detection of prorenin as renin(19) or a change in the renin half life following its binding to aliskiren(20).

Plasma renin activity was measured both by a conventional method (PRA) and by a new high sensitivity assay (hsPRA), which is independent of endogenous substrate variation(21). As high PRA levels confer risk of cardiovascular disease(22), it will be interesting to evaluate long-term effects of direct renin inhibition in the ongoing ALTITUDE study, providing data on hard cardiovascular and renal endpoints(23).

The antihypertensive effect of aliskiren was smaller than found in previous larger studies(16), although the office BP reduction did not differ from that caused by irbesartan. More research on the possible differential dosing of aliskiren treatment is warranted.

The ONTARGET study investigators(24) concluded that in a cardiovascular risk population, dual RAAS blockade with the ARB telmisartan and the ACE inhibitor ramipril, is equivalent in reducing cardiovascular events as compared to either monotherapy, although with more frequent adverse events, including renal adverse events. Almost 3,000 of the participating 25,260 patients had microalbuminuria at baseline, and substudies of albuminuria effects are expected. Several short-term studies using dual RAAS blockade in diabetic nephropathy have shown promising antiproteinuric effects, as reviewed by Rossing(17), but the largest study so far(25), did not show additional benefit of combination with ramipril and irbesartan, as compared to ramipril monotherapy, in terms of albuminuria reduction after 20 weeks.

The only biomarker showing a systematic reduction during treatment was hsCRP.

The sample size and the short treatment periods are obvious limitations to the study. The size is however sufficient to demonstrate the likely beneficial effect of combination therapy with aliskiren and irbesartan, although we evaluate a surrogate endpoint. In addition, the discrepancy between 24h and office BP readings
complicates interpretation of the results. Studies evaluating mortality and morbidity are ongoing and will provide further information on dual RAAS blockade with aliskiren.

In conclusion, we demonstrate an antiproteinuric effect of dual RAAS blockade with aliskiren and irbesartan in combination compared to either treatment alone in patients with type 2 diabetes, hypertension and albuminuria. The synergistic effect on ir-PRC illustrates a higher degree of intra-renal RAAS blockade during combination treatment.

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DISCLOSURE
Dr. Persson reports having received lecture fees from Novartis and having equity interest in NovoNordisk. Dr. Rossing reports having received lecture fees from Novartis, and Boehringer Ingelheim, and research grant from Novartis, has served as a consultant for Merck, and having equity interest in NovoNordisk. Dr. Danser reports having received research grant from Novartis and having served as a consultant to Novartis. Dr. Parving reports having served as a consultant for Novartis, Merck, Pfizer and Sanofi-Aventis, having equity interest in Merck and NovoNordisk and having received lecture fees from Novartis, Merck, Pfizer and Sanofi-Aventis. Dr. Parving has received grant support from Novartis, AstraZeneca and Sanofi-Aventis.

FIGURE LEGEND
**Figure 1.** Change in urinary albumin excretion rate (%) vs. placebo during treatment with aliskiren 300 mg daily, irbesartan 300 mg daily or the combination
REFERENCES


Table 1. Demographics of the 32 randomized patients with type 2 diabetes, hypertension and albuminuria and the 26 included in the final analysis.

<table>
<thead>
<tr>
<th></th>
<th>Total randomized population (N=32)</th>
<th>Included in analysis (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.3 (9.0)</td>
<td>59.8 (9.2)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>25 (78)</td>
<td>20 (77)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>32 (100)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 (9)</td>
<td>175 (10)</td>
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<tr>
<td>Weight (Kg)</td>
<td>99.9 (20.6)</td>
<td>100.9 (21.4)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>32.3 (5.4)</td>
<td>32.7 (5.5)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 (1.3)</td>
<td>8.2 (1.3)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>3.7 (0.8)</td>
<td>3.8 (0.8)</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>10</td>
<td>8</td>
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<tr>
<td>CVD history (n)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>BP medications prior to study inclusion (n)</td>
<td>2.5 (0.8)</td>
<td>2.3 (0.8)</td>
</tr>
<tr>
<td>RAAS blocking treatment prior to study inclusion (n)</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Baseline† 24h BP (mmHg)</td>
<td>142/74 (12/8)</td>
<td>141/74 (12/7)</td>
</tr>
<tr>
<td>Baseline† UAER (mg/d)</td>
<td>307 (87-1378*)</td>
<td>275 (103-1088*)</td>
</tr>
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</table>

Values in brackets are SD except * range.
† Baseline defined as day of randomization. Values from placebo treatment period used in endpoint analysis.
Table 2. Changes in RAAS components and cardiovascular biomarkers versus placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Aliskiren</th>
<th>Irbesartan</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean (range)</td>
<td>Geometric mean (range)</td>
<td>Ratio (95% CI) vs placebo</td>
<td>Geometric mean (range)</td>
<td>Ratio (95% CI) vs placebo</td>
</tr>
<tr>
<td>Angiotensinogen (nmol/L)</td>
<td>969 (726-2686)</td>
<td>956 (500-2505)</td>
<td>(0.99 (0.90, 1.08))</td>
<td>719 (317-2480)</td>
</tr>
<tr>
<td>Plasma prorenin concentration (ng/L)</td>
<td>295 (75-1646)</td>
<td>336 (85-1600)</td>
<td>1.14 (0.99, 1.30)</td>
<td>406 (107-2386)</td>
</tr>
<tr>
<td>Plasma renin concentration (ng/L)</td>
<td>29 (6-180)</td>
<td>110 (18-1024)</td>
<td>3.79 (2.79, 5.17)†</td>
<td>80 (9-868)</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.44 (0.63-3.18)</td>
<td>0.40 (0.03-1.24)</td>
<td>0.36 (0.26, 0.49)†</td>
<td>2.69 (0.43-13.67)</td>
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<tr>
<td>hsPRA (ng/ml/h)</td>
<td>4.5 (1.1-15.3)</td>
<td>0.6 (0.2-3)</td>
<td>0.13 (0.09, 0.21)†</td>
<td>18.7 (2.5-113)</td>
</tr>
<tr>
<td>ACE activity (U)</td>
<td>43 (32-57)</td>
<td>44 (32-57)</td>
<td>1.02 (0.97, 1.07)</td>
<td>45 (29-61)</td>
</tr>
<tr>
<td>Angiotensin I (pmol/L)</td>
<td>19 (7.6-76)</td>
<td>4.9 (0.9-19)</td>
<td>0.25 (0.17, 0.36)†</td>
<td>60 (5.5-408)</td>
</tr>
<tr>
<td>Angiotensin II (pmol/L)</td>
<td>10 (3-33)</td>
<td>4.8 (1.1-27)</td>
<td>0.48 (0.32, 0.72)†</td>
<td>33 (3.7-199)</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>2.5 (0.1-12)</td>
<td>1.6 (0.1-19)</td>
<td>0.65 (0.43, 0.99)*</td>
<td>1.6 (0.1-17)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.9 (2.6-5.5)</td>
<td>3.7 (2.4-5.2)</td>
<td>0.93 (0.87, 1.00)*</td>
<td>3.7 (2.8-5.1)</td>
</tr>
<tr>
<td>VWF (%)</td>
<td>184 (98-289)</td>
<td>172 (76-297)</td>
<td>0.94 (0.81, 1.09)</td>
<td>175 (107-282)</td>
</tr>
<tr>
<td>ICAM-1 (µg/l)</td>
<td>636 (397-1643)</td>
<td>632 (408-1825)</td>
<td>1.00 (0.94, 1.05)</td>
<td>637 (425-2137)</td>
</tr>
<tr>
<td>VCAM-1 (µg/l)</td>
<td>937 (661-1588)</td>
<td>937 (693-1890)</td>
<td>1.00 (0.96, 1.04)</td>
<td>954 (685-1747)</td>
</tr>
<tr>
<td>Aldosterone (ng/l)</td>
<td>52 (8-200)</td>
<td>40 (1-150)</td>
<td>0.77 (0.51, 1.17)</td>
<td>47 (1-656)</td>
</tr>
<tr>
<td>ADMA (µmol/l)</td>
<td>0.49 (0.40-0.60)</td>
<td>0.50 (0.40-0.60)</td>
<td>1.01 (0.96, 1.07)</td>
<td>0.50 (0.40-0.60)</td>
</tr>
<tr>
<td>PAI-1 (µg/l)</td>
<td>75 (26-267)</td>
<td>80 (34-282)</td>
<td>1.05 (0.81, 1.37)</td>
<td>76 (17-324)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>268 (129-995)</td>
<td>258 (119-881)</td>
<td>0.96 (0.84, 1.10)</td>
<td>251 (93-965)</td>
</tr>
</tbody>
</table>

*p<0.05; †p<0.001; ‡p<0.01. All treatments were administered once daily.