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1.1 TITLE PAGE

Study title:	A prospective, randomized, open label blinded end point (PROBE), crossover study to compare the effects of Telmisartan and Losartan on metabolic profile of renal transplant patients (COSTANT study)
Test drug:	Telmisartan and Losartan
EudraCT:	2008-000822-38
Clinical Trial registration:	NCT01224860
Phase:	II
Date of Ethic Committee	Parere Unico rilasciato dal Comitato Etico Coordinatore (Comitato di Bioetica della ASL di Bergamo) il 22/05/2008
Period covered:	First subject / patient entered: 09/02/2010 Last subject / patient completed: 08/03/2013
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Date: January 8th, 2014

1.2 STUDY ADMINISTRATION AND INVESTIGATORS

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Laboratory of Pharmacokinetics and Clinical Chemistry

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
AII	Angiotensin II
CsA	Cyclosporine
CRF	Case Report Form
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HOMA	Homeostatic Model Assessment
IEC	Independent Ethics Committee
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MNI	Mario Negri Institute
NYHA	New York Health Association
PP	Per Protocol
PPARg	Peroxisome proliferators-activated receptor-g
RPF	Renal Plasma Flow
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SUSAR	Suspected Unexpected Serious Adverse Event Reaction
TEAE	Treatment Emergent Adverse Event
TIA	Transient Ischemic Attack
UAE	Urinary Albumin Excretion
WHO	World Health Organization

2. ETHICS

2.1 Ethical Conduct of the Study

The study was conducted in accordance with Good Clinical Practices (GCP) and the Declaration of Helsinki and its amendments.

All the study documents (protocol, patient information sheet, consent form, etc.) and any amendment have been approved by competent IEC.

The following amendments have been performed:

- Amendment n°1 (April, 27th 2012) approved by Coordinating IEC on June 7th 2012.

Written informed consent was obtained from all participants. The study was coordinated and monitored, according to GCP guidelines, by the Laboratory of Pharmacovigilance and Monitoring for Clinical Investigations of the Clinical Research Centre.

3. INVESTIGATIONAL PLAN

3.1 Introduction

In renal transplant recipients, residual renal insufficiency combined to the effects of immunosuppressive therapy with steroids or calcineurin inhibitors may reduce insulin activity and may contribute to several of the abnormalities associated with the metabolic syndrome, such as hypertension, glucose intolerance and hyperlipidemia (1, 2). In turn, insulin resistance, hypertension, hyperglycemia and dyslipidemia may importantly contribute to the excess cardiovascular risk of renal transplant patients (an excess comparable to that of diabetes subjects with over diabetic nephropathy) and may also accelerate progressive renal function deterioration and promote graft loss (3, 4). Thus, amelioration of the insulin activity and of the related metabolic syndrome is a key component of treatments aimed to improve patient and graft survival in renal transplant recipients.

Recently, drugs such as peroxisome proliferators-activated receptor-g (PPARg) activators, that ameliorate insulin sensitivity and metabolic syndrome, have become available (5, 6). These agents, however, can provoke fluid retention, weight gain, edema and, in some cases, heart failure. Thus, the risk/benefit profile of PPARg activators is still uncertain, in particular in renal transplant patients where the risks of therapy may overwhelm the potential benefits.

Recent studies showed that Telmisartan, an angiotensin II (AII) type 1 receptor antagonist, in addition to block the AII receptor - a key surface receptor involved in the regulation of blood pressure - may also activate PPARg, thus improving some of the features of the metabolic syndrome, such as hyperglycemia and dyslipidemia in people with hypertension and/or diabetes (7, 8).

Thus, in addition to control high blood pressure and to limit some of the adverse effects of angiotensin II, including target organ damage, graft fibrosis and CsA nephrotoxicity (9), Telmisartan may also substantially reduce the overall cardiovascular and renal risk of renal transplant recipients by ameliorating some of the modifiable components of the metabolic syndrome, such as hypertension, glucose intolerance and hyperlipidemia. On the other hand, Telmisartan is devoided of the adverse effects of PPARg activators such as fluid retention, and has therefore a remarkably better risk/benefit profile. Thus, whether Telmisartan in addition to the beneficial effects of a reference AII receptor antagonist (such as Losartan) may offer adjunctive advantages related to improved insulin sensitivity in renal transplant patients on chronic therapy with steroids and/or calcineurin inhibitors, is worth investigating.

3.2 Methods

This academic, prospective, randomized, phase II, open label blinded end point (PROBE) (10), crossover study was primarily aimed at comparing the short-term effects of Telmisartan and Losartan on insulin sensitivity in kidney transplant recipients with stable renal function and concomitant treatment with steroids and/or calcineurin inhibitors. Secondarily the trial compared changes in systemic (sitting systolic/diastolic blood pressure, 24-h blood pressure profile) (11-14), metabolic (morning fasting blood glucose, glucose tolerance test, glycated hemoglobin, morning fasting insulin, HOMA index, lipid profile) (15,16) and renal (UAE, GFR, albumin fractional clearance) variables (17).

3.3 Study population

Study participants were identified among kidney transplant patients referred to the outpatient clinics of the Clinical Research Center for Rare Diseases Aldo and Cele Daccò. > 18 years old consent men and women, with single or dual marginal renal transplant >6 months duration, blood pressure >130/85 mmHg or need for anti-hypertensive therapy, stable renal function (changes in serum creatinine < 30%) and no acute rejection episodes in the last six months, stable for at least six months dual or triple immunosuppressive therapy including corticosteroids or calcineurin inhibitors, were eligible for study

participation. Those with vascular disease of the kidney, heart failure (NYHA classification class III-IV on ACEi or AII receptor inhibitors therapy), cerebral hemorrhage, stroke or TIA, myocardial infarction within three months prior to study enrolment, unstable angina pectoris and severe hepatic disease were excluded as well as patients with overt diabetes or concomitant treatment with oral antidiabetic agents and/or insulin, specific clinical indication to be treated with ACE inhibitors or AII receptor antagonists, specific contraindications or history of hypersensitivity to the study drugs, glitazones, ACE inhibitors or AII receptor antagonists or subjects unable to provide informed consent and pregnant, lactating or potentially childbearing women without adequate contraception.

3.4 Randomization and masking

Patients were randomised on a 1:1 basis to the sequence Telmisartan-Losartan or to sequence Losartan-Telmisartan. Randomisation was performed at the Laboratory of Biostatistics of the Clinical Research Center for Rare Diseases "Aldo e Cele Daccò" Villa Camozzi, Ranica, Bergamo, of the IRCCS - Mario Negri Institute for Pharmacological Research (MNI), under the responsibility of an independent investigator (GAG, see study organization). After baseline evaluation, a central randomisation by telephone was used to allocate study participants to the two sequences using the generated randomisation list by an independent investigator (GAG: see study organization) at the Laboratory of Biostatistics of the Clinical Research Centre for Rare Diseases "Aldo e Cele Daccò" of the Mario Negri Institute for Pharmacological Research (Ranica, Bergamo). The randomisation sequence was created using SAS 9.0 (SAS Institute Inc, Cary, NC) statistical software using random blocks of 4 or 8 sizes. Study physicians, nurses and participants were aware of the allocated arm, whereas outcome assessors were kept blinded to the allocation.

3.5 Study Design

After four weeks wash-out period from previous ACE inhibitors and AII receptor antagonists, and basal evaluation of systolic/diastolic blood pressure, body weight, insulin sensitivity, glucose tolerance, lipid profile, renal hemodynamics, albuminuria, albumin, Na+ and free water fractional clearances and other routine laboratory analyses, eligible patients were randomized to two treatment arms:

1. Telmisartan (one week 40 mg daily, followed by fifteen weeks treatment period with 80 mg daily);
2. Losartan (one week 50 mg daily, followed by fifteen weeks treatment period with 100 mg daily).

At the end of the first treatment period with Telmisartan or Losartan, each patient crossed over to the other treatment. After the second treatment period, there was a four-week recovery period.
Systolic and diastolic blood pressure and routine laboratory tests have been evaluated within one week after each up- or down-titration of the study drugs and whenever deemed appropriate for safety reasons. Should symptomatic hypotension, refractory hyperkalemia (serum potassium >6.0 mEq/L in two consecutive measurements), hemoglobin reduction higher than 1.5 g/dl, relevant water retention, or acute renal function deterioration (serum creatinine increase versus baseline >30%) developed, the dose of Telmisartan or Losartan was reduced to the previous step or the drug was withdrawn.
No major changes in diet and immunosuppressive, antihypertensive and other concomitant treatments were introduced throughout the whole study period. Antihypertensive therapy was adjusted to maintain target blood pressure of SBP <130 mmHg and DPB <85 mmHg. All the baseline evaluations were repeated at the end of each treatment period and of the recovery period.

3.6 Study Materials

Study drugs (Telmisartan and Losartan) were provided as commercial available product (Micardis tablets 40 mg, Losaprex tablets 50 mg, respectively). Commercial boxes were relabelled in compliance with revision of Annex 13.

4. DATA MANAGEMENT PROCEDURES

This was an electronic trial. A computerized system that allows data capture, monitoring and storage of clinical data in spite of the use of carbon copy case report forms (CRF) has been used. The system also named electronic case report form (e-CRF) fulfils all the formal requirements of the GCP and Food and Drug Administration (FDA) Guidance in order to assure adequate standards of data quality, safety and protection, in the absence of paper CRF.
MNI Coordinating Center provided every Investigator with the credentials for the use of computerized system. Demographic, efficacy and safety data have been collected for the purpose of the study, to be documented by the Investigator or his/her designated on the individual e-CRF. This also applies to the data for patients who, after having consented to participate, underwent baseline examinations but were not further recruited.

A reasonable explanation has been given by the Investigator for all missing data. Source documents are available to support all the data recorded in the e-CRFs.

5. STATISTICAL CONSIDERATIONS

5.1 Sample Size estimation

The present trial was a pilot study and the sample size was not calculated on the basis of the expected treatment effect. However, on the basis of previous experimental evidence, a cross-over study on 20 patients has the power to detect a statistically significant difference, defined as $p < 0.05$, in the effect on insulin activity between each treatment period as compared to baseline (7).

5.2 Statistical analysis

Efficacy analyses. To test the hypothesis of no difference in primary and secondary efficacy variables between Telmisartan and Losartan, an analysis of variance (ANOVA – mixed model) with TREATMENT and PERIOD as fixed factor and SUBJECT as random factor was performed on the Intention-To-Treat (ITT) population. This model has no baseline covariate since it is assumed that baseline information is accounted for by adjusting for period and subject effects and all effects of carry-over have disappeared at the time of the baseline for the second treatment period. The Per protocol (PP) population was analyzed using ANOVA similar to that of the ITT population. In addition if more than 50% of the ITT sample does not participate in the second treatment period, then the first treatment period data was analyzed using a two-sample t-test for treatment comparison. Underlying assumptions and carry-over effects were assessed for the primary and secondary efficacy parameters by visual inspection. In case where non-normality is clearly exhibited which could not be accounted for by a transformation of the data (i.e. log-transformation), non-parametric cross-over analysis methods (Koch's adaptation of the Wilcoxon-Mann-Whitney rank sum test) should be used. Within-group and between-groups comparisons for categorical variables were performed by McNemar test and chi-squared test or Fisher's Exact test as appropriate. Normally and not normally distributed data were reported as means±SD or as median and interquartile range (IQR), respectively. Binary data were summarized by counts and percentages. All statistical testing were performed at the two-sided 5% level of significance. SAS (Version 9.1) was used for all statistical analyses.

Safety. The safety was assessed on the population by vital sign measurements, physical examination, laboratory tests, adverse event data, and documented concomitant medications.

Adverse events (AEs) were summarized by MedDRA's system organ class and preferred term. Safety data were summarized using descriptive statistics. For concomitant medication the WHO code was used. For each adverse event, original term, the lowest level term, the preferred term, the high level term, high-level group term and system organ class are presented. In the report tables and listings only the primary system organ class have been presented. The most recent version of the MedDRA dictionary was used (Version 10.1). Adverse event tables have been created per treatment but only for treatment emergent adverse events (TEAE). Normally and not normally distributed data were reported as means±SD or as median and interquartile range (IQR), respectively. Binary data were summarized by counts and percentages.

6. FUNDINGS

This was an academic study supported by a grant of Boehringer Ingelheim Italia S.p.a. (Milan), that also supplied study drugs.

7. RESULTS

7.1 Study subjects

a) Disposition of subjects

A total of 26-hypertensive kidney transplant patients who had stable renal function and were on dual or triple immunosuppressive therapy that included steroids and/or calcineurin inhibitors were selected for study participation between October 2009 and May 2012. All patients gave written informed consent before inclusion in the study. Of screened patients, six were excluded and not randomized. The non-randomization reasons were: not meeting inclusion criteria (n=2), withdrawal of consent (n=1), and therapeutic medical decisions (n=3). Of note, medical indications for not including the last group were taken in agreement between the transplant team that regularly followed these patients and the principal investigator of the study. These indications were: not stopping double RAS blockade with ACE inhibitors/AII receptor antagonists that had been suitably indicated for proteinuria, uncontrolled arterial blood pressure during the programmed wash-out period from ACE inhibitors/AII receptor antagonists

and the impossibility to interrupt concomitant antihypertensive drugs that had been started for specific cardiovascular indications. Thus, a total of 20 subjects fulfilled the selection criteria, were randomized and considered for the final analysis. Four patients withdrew from the study after they had been randomized. Since they had received at least one dose of study drug, they were included in the analysis up to the last available visit. Reasons for exclusion were: withdrawal of consent (n=3) and adverse event (n=1). A summary description of the disposition of subjects is shown in Figure 1.

b) Protocol deviations

One substantial protocol amendment was made.

1. Amendment 1 (May 07th, 2012) was aimed at also allowing the inclusion in the study of patients that for specific conditions and indications had received a double marginal kidney transplant.

The amendment was approved by the Ethics Committee.

c) Protocol Major Violation

One patient that had been initially randomized to the Losartan – Telmisartan sequence started on the Telmisartan – Losartan one. This major violation was due to an unintentional mistake after randomization. However, since the patient had started with study medication before the Coordinating Center had been notified about the protocol violation, he was maintained on the investigational treatment sequence that had already begun and was considered for the final analysis.

7.2 Efficacy evaluation

Data sets analyzed

A baseline characteristics analysis was performed in 20 patients. Ten patients were randomly assigned to Telmisartan followed by Losartan and the other 10 to Losartan followed by Telmisartan.

Demographic characteristics

All patients were Caucasian. Sixteen patients (80%) were males and were equally distributed (8/8) in both randomization sequences Telmisartan - Losartan and Losartan - Telmisartan. Overall mean age at inclusion was 53±8.8 years and tended to be higher (56±10.5 years) in the Telmisartan-Losartan sequence when compared to Losartan - Telmisartan (51±5.9 years). Three (15%) patients were current smokers, seven (35%) were former smokers and 10 (50%) patients had never smoked. Never smokers

were more frequent in the Telmisartan – Losartan sequence, whereas former smokers were more frequent in the Losartan – Telmisartan one. None of the patients had diabetes.

Clinical and laboratory characteristics

The main demographic, clinical and laboratory characteristics of the participants at baseline are shown in Table 1.

Overall mean BMI was 26.37±3.1 kg/m² at baseline and was similar between both randomization sequences. On average participants were enrolled at 11 years after renal transplantation and had stable graft function at inclusion with an overall mean serum creatinine of 1.2±0.4 mg/dl. At baseline, mean adjusted GFR in the study group as a whole, measured by iohexol plasma clearance technique (17), was 71.71±20.61 ml/min per 1.73 m². Moreover, for these renal parameters, serum creatinine and GFR, no significant differences were present when both randomization sequences were compared at baseline. Overall, mean serum glucose and glycosylated hemoglobin, measured by ion-exchanged high-performance liquid chromatography (normal ranges: 3.53-5.21 percentage), averaged at baseline 98.65±8.80 mg/dl and 3.77±0.47 %, respectively. Differences between randomization sequences were not significant. Indices of insulin sensitivity were evaluated by measurement of Total-body Glucose Disposal Rate (GDR), HOMA IR and oral glucose tolerance test. Overall mean GDR, assessed by means of hyperinsulinemic-euglycemic clamp, HOMA IR and serum glucose levels at 120 min (glucose tolerance test) at baseline were 9.98±3.42 mg. Kg -1.min -1, 1.53±0.89 and 131.75±47.04 mg/dl, respectively (Table 2). Of note, when the baseline Telmisartan – Losartan randomization sequence was compared with the Losartan – Telmisartan, mean GDR tended to be lower (8.7±3.45 vs. 11.14±3.11 mg . Kg -1 . min -1) but HOMA IR, glycosylated hemoglobin and serum glucose levels at 120 min were higher [1.995±1.02, 3.94±0.34% and 138.10±43.50 mg/dl vs. 1.06±0.39, 3.59±0.53% and 125.40±51.86 mg/dl], respectively. However, differences between randomization sequences were not statistically significant.

Despite 18 (90%) of the 20 included patients were on concomitant treatment with blood pressure lowering medications, mean diastolic blood pressure at inclusion was 87.2±6.11 mmHg and exceeded the recommended target of ≤ 80 mmHg in most patients. Mean office systolic blood pressure and MAP were 136.6±16.53 and 103.7±8.76 mmHg, respectively (Table 3). Although office diastolic and systolic blood pressure tended to be higher in the Losartan – Telmisartan sequence, no significant differences in blood pressure parameters were observed between sequences at baseline.

Median baseline 24-hour urinary albumin excretion rate (24-h AER) and 24-hour proteinuria in the study group as a whole were 18.50 (8.17 – 83.17) μg/min and 0.16 (0.1 – 0.29) g/24 hours, respectively. Of note, baseline 24-h AER and 24-hour proteinuria were lower in the Telmisartan – Losartan than in the Losartan – Telmisartan sequence [9.5 (6 – 19) μg/min and 0.14 (0.09 – 0.16) g/24 hours vs. 64 (16.33 – 194.5) μg/min and 0.24 (0.1 – 0.44) g/24 hours], respectively. Differences between sequences were not statistically significant (Table 2).

Overall, mean serum triglycerides, apolipoprotein (a) and apolipoprotein (b), were in the recommended target ranges in most cases at baseline; however, serum total cholesterol and LDL levels tended to be above and HDL below optimum levels. No significant differences in serum total cholesterol; cholesterol fractions, triglycerides and apolipoproteins were observed between randomization sequences at baseline (Table 1 and Table 3).

Concomitant medications

All patients were on cyclosporine A that was used in combination with azathioprine (n=13) or mycophenolate mofetil (n=5) as maintenance immunosuppressive therapy. From these 18 patients, 11 had associated corticosteroids and seven were on a free steroid regime. The remaining two patients were on cyclosporine A and steroids only. Therefore, a total of 13 patients had steroids included in the immunosuppressive therapy and were distributed eight on the Telmisartan – Losartan and five in the Losartan – Telmisartan randomization sequences. Of note, before the wash-out period, seven (35%) patients were on RAS inhibitor therapy, two on ARBs and five on ACE inhibitors. Four of these seven were initially randomized to the Telmisartan – Losartan sequence. No patient was on dual RAS blockade therapy at baseline. The anti-hypertensive agents more frequently used at baseline were beta-blockers and calcium channel blockers followed by diuretics. Six (30%) patients were treated with lipid lowering agents at randomization and all of them were on therapy with statins, either alone (n=4) or in combination with omega 3 polyunsaturated fatty acids (n=2). None of the patients was on therapy with fibrates, hypoglycemic drugs or insulin. Both antihypertensive and lipid lowering agents were evenly distributed between randomization sequences.

Efficacy results

Primary efficacy variable

Insulin sensitivity (i.e. glucose disposal rate as assessed by an euglycemic hyperinsulinemic clamp)

We screened 26 patients, of whom 20 were randomized, 10 assigned to Telmisartan then Losartan and 10 assigned to Losartan then Telmisartan (Figure 1). Four patients withdrew during the study. Thus, 16 patients were included for primary analysis. Of note, one patient that had been randomized to the Telmisartan – Losartan treatment sequence couldn't perform the euglycemic hyperinsulinemic clamp test due to the complete absence of a venous access on the left arm. Thus, analysis for primary outcome (insulin sensitivity) was available in 15 patients. Baseline characteristics were much the same between randomization sequences (Table 1).

GDR values were available for comparative analysis in eight patients included in the Telmisartan – Losartan and seven in the Losartan – Telmisartan sequence, respectively. Overall mean GDR fell from 9.98±3.42 to 9.44±3.37 and 9.21±3.94 mg. Kg -1.min -1, after 16-weeks of treatment with Losartan and Telmisartan, respectively (Figure 2). Multivariable longitudinal analysis showed that changes between both treatments were not significant.

Secondary efficacy variables

Sitting systolic/diastolic blood pressure and 24-hour blood pressure profile

Complete office and 24-hour blood pressure recordings were available in 16 patients. Office and 24-hour, day-time and night-time systolic, diastolic, mean and pulse blood pressure decreased during both treatment periods. The reduction was significant for office, 24-hour, day-time and night-time systolic blood pressure, and 24-hour mean and day-time pulse blood pressure during Telmisartan therapy, and for mean office and night-time blood pressure as well as for office diastolic blood pressure during Losartan therapy. Differences in changes in all considered parameters between the two treatment periods were never significant (Table 2).

Metabolic Parameters

Sixteen patients were available for metabolic parameters and underwent comparative analyses after 16 weeks of treatment period. No parameters significantly changed during each treatment period with the only exception of HbA1c that significantly increased on Losartan vs. baseline. Changes in any considered parameter were never significantly different between the two treatment periods (Table 3).

Serum Lipids

Serum lipids did not significantly change during both treatment periods with the exception of serum apolipoprotein (a) that significantly decreased during Losartan therapy vs. baseline. Differences in changes during the two treatment periods were never significant with the only exception for changes in serum total cholesterol levels that, because of the opposite trends to increase on Telmisartan and decrease on Losartan, were significantly different between the two treatment periods (Table 3).

Other End Points

Renal outcomes

Twenty four-hour urinary sodium excretion and creatinine clearance did not change significantly during each treatment period. Median 24-h AER and GFR significantly decreased during both Telmisartan and Losartan treatment periods vs. baseline, whereas albumin fractional clearance decreased significantly only during Telmisartan treatment. Differences between changes during the two treatment periods were never significant (Table 3).

7.3 Safety Evaluation

Safety data are presented under the following headings:

- Summary of safety
- Exposure
- AEs
- ADRs
- SAEs
- Cardiovascular events (CV), deaths and discontinuation of medication or the study due to adverse events
- Safety conclusions

a) Summary of safety

- Considering the study group as a whole, there were 32 treatment-emergent AEs (including SAEs) during both study periods.

- Overall, the frequency of treatment-emergent AEs (including SAEs) was equally distributed with 50% of events that occurred during Telmisartan and the other 50% of events during the Losartan treatment period.
- Considering separated time-treatment periods after randomization, irrespectively of the therapy assigned, total AEs were higher during the first 16-week treatment period (71.9%) when compared with the last 16-week period (28.1%).
- There were only four treatment-emergent SAEs during the whole study period. No treatment-emergent SAEs were considered by the investigator to be related to study drugs.
- Overall, there were 28 non-serious treatment-emergent AEs and 11 of them were related to study drug (ADR).
- There were no major cardiovascular (MCV) events during the whole study period.
- The observed AEs were consistent with the known safety profile of ARBs in this kind of patients. Most events were transient and fully recovered with concomitant treatment or study drug modifications. None of these events required trial discontinuation.

b) Extent of exposure

Safety results are limited to the available follow-up period, ranging from 0 to 32 weeks after the first dose intake of study medication in 20 randomized patients. The occurrence of adverse events was evaluated on the full analysis set. Thus, all 20 patients randomized were included in this analysis.

Patients were randomized to receive over a 32-week follow-up one of the following treatment sequences: Telmisartan – Losartan or Losartan – Telmisartan. In the middle of the sequence, after 16 weeks of treatment, each patient underwent cross-over to the other treatment. Both treatment sequences were exposed to a half-dose (Telmisartan 40 mg or Losartan 50 mg) for the first 7 days and to the full (Telmisartan 80 mg or Losartan 100 mg) dose for the remaining follow-up after a tolerability check (biochemistry, acid-base balance and vital signs). In some cases, study dosages were increased more slowly than planned in the study protocol (however within the first month after randomization) because of concern of symptomatic hypotension.

c) Adverse events and most common adverse events

- Considering the study group as a whole, the proportion of patients experiencing any AEs (not including SAEs) was marginally lower during Losartan (46.4%) than Telmisartan (53.6%) treatment. However; difference between treatment periods failed to achieve statistical significance.
- During the first 16-week treatment period, AEs were slightly more frequent in those treated with Telmisartan (56.5%) than in those treated with Losartan (43.5%).
- Overall, treatment-emergent AEs were reported most frequently in the system organ classes as metabolism and endocrine (39.3%), followed by skin, muscular and skeletal (21.4%) and cardiovascular disorders (17.9%).
- A significant proportion of AEs in system organ class consisted in isolated, transient alterations in blood laboratory parameters.

Table 4 summarizes the number of patients experiencing AEs.

d) Treatment-related adverse events or drug adverse reactions (ADRs)

- The frequency of treatment-emergent, drug-related AEs was 34.38% (n=11) in the study group as a whole. Four events were during the Telmisartan and seven during the Losartan treatment period and represented 36.4% and 63.6% of all ADRs, respectively.
- All drug-related AEs were of mild intensity and consisted in acute renal failure (n=3), mild anemia (n=4), peripheral edema (n=1), hypotension (n=1), asthenia (n=1) and headache (n=1).
- Four patients did not up-titrated study drug due to ADRs. The reasons for Telmisartan were: hypotension (n=1) and anemia (n=1) and for Losartan: acute renal failure (n=2).
- One of the three patients that developed acute renal failure during the Losartan treatment completed the period with the full dose of 100 mg but up-titration was not made with Telmisartan (40 mg) after cross-over due to a medical decision of the transplant team that followed the patient and the principal investigator of the study to avoid a possible recurrence of acute renal failure. Correspondingly, in a patient who developed anemia during Telminsartan, up-titration of Losartan was not performed (50 mg) after he was crossed over to prevent worsening of symptoms**.**
- Interestingly, two patients had peripheral edema, one during Losartan and the other during Telmisartan treatment; however, neither of two was considered ADR.
- The remaining patients underwent up-titration and completed the follow-up period with the recommended dose of both treatments

e) Serious adverse events (SAEs)

- Considering the study group as a whole, there were four SAEs during both treatment periods. Three SAEs occurred during the Losartan (urinary tract infection, squamous cell carcinoma of the skin and periorbital cellulitis) and one during the Telmisartan (adenogastric carcinoma) treatment period; however, differences among groups were not statistically significant.
- No treatment-emergent SAEs were considered by the investigator to be related to study drugs. The SAEs observed are commonly seen in a population of diabetic patients of similar age and duration of disease followed for a similar time period.

Table 4 summarizes the number of patients experiencing SAEs.

f) Cardiovascular events (CV), deaths and discontinuation of study medications or the study due to adverse events

- There were no major cardiovascular (MCV) events during the whole study period. The only two minor CV events were peripheral edema and hypotension and occurred one during the Telmisartan and the other during the Losartan treatment period, respectively.
- No patient had to discontinued the study medication due to adverse event.
- One patient that had discontinued the study drug due to adenogastric carcinoma died of complications from stroke after had dropped out of the study. None of these events was drug-related.

Safety conclusions

- Treatment with Telmisartan 80 mg or Losartan 100 mg was well tolerated.
- Drug-related AEs tended to occur more frequently during the Losartan than the Telmisartan treatment period. However, they were transient and generally of mild or moderate intensity. In only 1 case the event led to study drug discontinuation with subsequent recovery.
- None of the SAEs was fatal.

8. DISCUSSION AND OVERALL CONCLUSIONS

We found that in 20 kidney transplant recipients 16-week treatment with full dose Telmisartan did not appreciably affect insulin sensitivity, glucose tolerance, metabolic control and serum lipids, but effectively ameliorated blood pressure control with significant reduction in office, 24-hour, day-time

and night-time systolic blood pressure compared to baseline. Losartan therapy significantly reduced serum apolipoprotein(a) and increased HbA1C levels, but did not significantly affect other considered parameters with the exception of marginal reductions in office diastolic and office and night time mean blood pressure. However, changes in all the above considered parameters never significantly differed between the two treatment periods with the only exception in serum cholesterol levels that showed significantly different opposite trends to increase with Telmisartan and to decrease with Losartan. Due to the small sample size, the wide variability of data and, most important, the non-significant changes within each treatment period, the possibility that the above difference could be an effect of chance cannot be definitively excluded.

Incidence of cardiovascular events was relatively low despite the high prevalence of risk factors such as reduced insulin sensitivity, hypertension, obesity and dyslipidemia in this population and, at least in a subgroup, smoking habits and no fatal cardiovascular event was observed throughout the whole observation period. No difference in cardiovascular event rates was observed among treatment periods. Our present study, however, was underpowered to evaluate treatment effect on this outcome.

Both treatments significantly reduced 24-hour urinary albumin excretion and GFR, while Telmisartan also reduced albumin fractional clearance. Twenty four hour urinary sodium excretion as stable over time providing evidence that albuminuria reduction was not explained by reduced salt intake. Thus, reduction in albuminuria can be explained by reduction in arterial blood pressure and/or concomitant changes in glomerular hemodynamics and sieving function mediated by treatment induced inhibition of the renin-angiotensin system (18). Thus, because of their blood pressure and albuminuria lowering effect, both Telmisartan and Losartan appear to be valuable options for nephro and cardio-protective therapy in this population. Whether reduced albumin fractional clearance with Telmisartan therapy may reflect a superior, specific antiproteinuric effect of Telmisartan compared to Losartan may merit further investigation.

Of note, Telmisartan and Losartan were both well tolerated and in no case treatment related serious adverse events were observed requiring treatment interruption and patient withdrawal.

To the best of our knowledge, this is the first randomized clinical trial that compared the effect of Telmisartan with that of Losartan in kidney transplant patients.

These findings were obtained in well-characterized patients through gold standard procedures not only for the evaluation of the insulin sensitivity by hyperinsulinemic euglycemic clamp, but also for the measurement of GFR by iohexol plasma clearance, centralyzed laboratory analyses and albuminuria in

repeated urinary collections. The study patients are representative of those who normally attend the Transplant Nephrology Unit of Azienda Ospedaliera "Papa Giovanni XXIII" of Bergamo in every day clinical practice and are expected to represent the average population of stable renal transplant recipients referred to a transplant unit. Data were not affected by concomitant medications since no systemic change in concomitant treatment was introduced throughout the study and only small adjustments were allowed to optimize blood pressure control. Salt exposure was not an issue as well, since no changes in salt intake were introduced and systemic 24-h urinary sodium excretion was stable during the whole study period.

The present study was designed to determine if Telmisartan, in addition to block angiotensin II type 1 receptor, may also act as a partial agonist of PPARg receptor and consequently improve some of the features of metabolic syndrome, such as hyperglycemia and dyslipidemia, as suggested by previous studies. In particular, Vitale et al. reported that Telmisartan, but not Losartan, significantly reduced HOMA-IR, free plasma glucose, free plasma insulin and HbA1c in hypertensive patients with the metabolic syndrome (7). In this study, baseline HOMA-IR was greater than 3.5 in all patients, a finding consistent with severe insulin resistance in the population. Other studies in patients with less severe insulin resistance failed to demonstrate any specific insulin-sensitizing effect of Telmisartan (19). On the basis of GDR and HOMA-IR index data, also patients included in our present study had a relatively mild insulin resistance. Altogether, the results of the above studies combined to our present data, converge to indicate that Telmisartan may have some specific insulin-sensitizing effect, but that this partial PPARg agonist activity may be appreciated only in patients with more severe insulin resistance. Consistently, another study showed that Telmisartan treatment reduced HOMA IR in hypertensive patients with insulin resistance, but not in those with preserved insulin sensitivity (20).

To some extent unexpected was the inability to demonstrate significantly better blood pressure control with Telmisartan as compared to Losartan, even if Telmisartan, unlike Losartan, significantly improved office and ambulatory systolic blood pressure recordings compared to baseline. Recent meta-analyses documented a superior control of office and ambulatory blood pressure with Telmisartan than Losartan in patients with hypertension (21, 22). Differences in the pharmacokinetics of the two drugs might explain the lack of additional benefits of Telmisartan over Losartan, resulting in a selectively increased bioavailability of Losartan in the kidney transplant population (23, 24). This increased bioavailability in vivo could be explained by cyclosporine A mediated impaired intestinal secretion of Losartan trough

inhibition of the p-glycoprotein transported (25). Moreover, the small sample size of this pilot study might have reduced the power to detect statistically significant differences between treatments.

In conclusion, in the context of a formal study to compare the effect of Telmisartan, an angiotensin II receptor antagonist with peroxisome proliferators-activated receptor-g (PPARg) agonistic effect with those of Losartan, the ancestor of Angiotensin II receptor antagonists, our data showed that Telmisartan failed to improve glucose disposal rate and other major features of the metabolic syndrome as compared to Losartan. However, this study provided some evidence in favor of a superior antihypertensive effect of Telmisartan that was in harmony with previous data in the non-transplant population. This finding can be clinically relevant since systolic blood pressure is one of the strongest risk factors for cardiovascular morbidity and mortality in the average population, as well in patients with renal disease (26, 27). Of note, both medications were remarkably safe and well tolerated and can be therefore considered as a valuable option for the treatment of arterial hypertension and protection of target organs in the renal transplant population.

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10. FIGURES AND TABLES

Figure 1. COSTANT CONSORT 2010 Flow Diagram

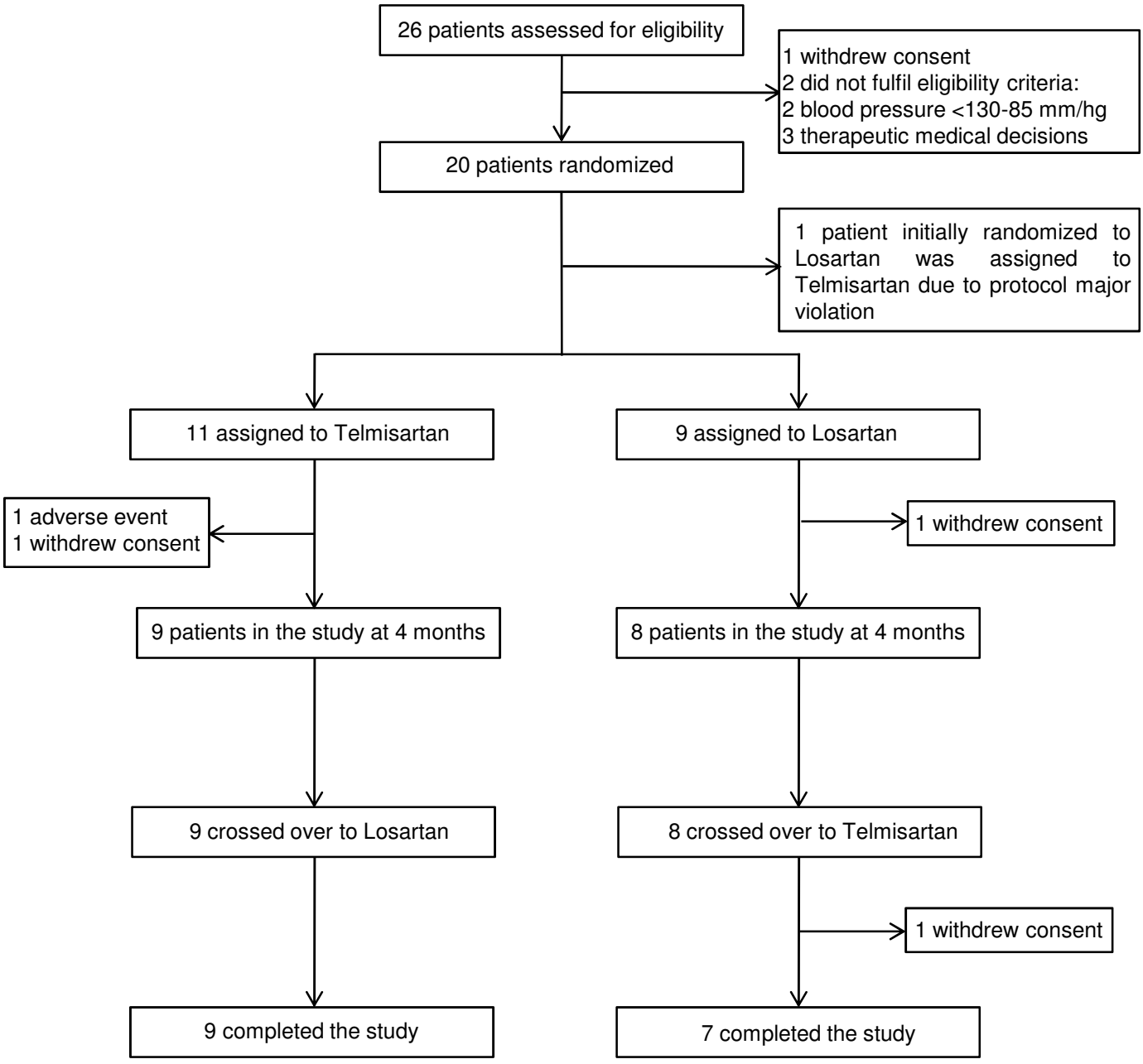
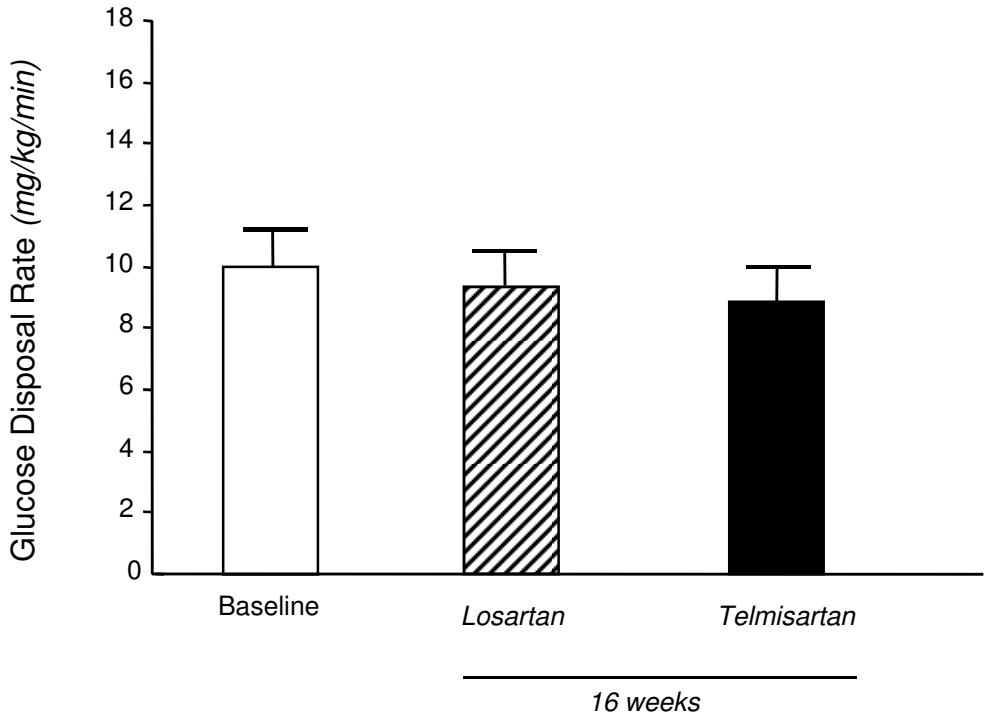


Figure 2. GDR at baseline and after treatment with Losartan and Telmisartan



Data are shown as mean and SE

Table 1. Demographic, clinical and laboratory characteristics of patients at baseline

Parameter	Overall	Telmisartan to Losartan	Losartan to Telmisartan
Age *(years)*	53 ± 8.8	56 ± 10.5	51 ± 5.9
Gender *(M/F)*	16/4	8/2	8/2
BMI *(Kg/m^2)*	26.37 ± 3.1	27.12 ± 3.3	25.61 ± 2.8
Time since Tx *(months)*	132 ± 156	128 ± 120	169 ± 149
Smokers *N (%)*			
Never	10 (50%)	7 (70%)	3 (30%)
Former	7 (35%)	1 (10%)	6 (60%)
Current	3 (15%)	2 (20%)	1 (10%)
Steroids included in IST *N (%)*	13 (65%)	8 (80%)	5 (50%)
Lipid Lowering Treatments *N (%)*	6 (30%)	3 (30%)	3 (30%)
Patients taking BP-lowering drugs *N (%)*	18 (90%)	9 (90%)	9 (90%)
ACEi or ARB *N (%)*	7 (35%)	4 (40%)	3 (30%)
ARB *N (%)*	2 (10%)	1 (10%)	1 (10%)
ACEi *N°(%)*	5 (25%)	3 (30%)	2 (20%)
Combination of ACEi and ARB *N°(%)*	0	0	0
Not on ARB, ACE, or other RAAS inhibitor *N°(%)*	13 (65%)	7 (70%)	6 (60%)
Diuretics *N°(%)*	5 (25%)	3 (30%)	2 (20%)
Calcium channel blockers *N°(%)*	8 (40%)	4 (40%)	4 (40%)
Beta-blockers *N°(%)*	9 (45%)	4 (40%)	5 (50%)
Other antihypertensives *N°(%)*	3 (15%)	2 (20%)	1 (10%)
Systolic Office Blood Pressure *(mm/Hg)*	136.6 ± 16.53	134.4 ± 18.49	139.9 ± 14.95
Diastolic Office Blood Pressure *(mm/Hg)*	87.2 ± 6.11	85.4 ± 5.96	89.0 ± 5.98
s. creatinine *(mg/dl)*	1.20 ± 0.36	1.19 ± 0.43	1.21 ± 0.19
GFR *(ml/min per 1.73 m^2)*	71.71 ± 20.61	75.27 ± 21.95	68.14 ± 19.67
Proteinuria *(g/24-h)*	0.16 (0.1-0.29)	9.5 (6-19)	64 (16.33-194.5)
Glucose *(mg/dl)*	98.65 ± 8.80	98 ± 7.41	99.3 ± 10.37
HbA_{1c} *(%)*	3.77 ± 0.47	3.94 ± 0.34	3.59 ± 0.53
HOMA IR index	1.53 ± 0.89	1.995 ± 1.02	1.06 ± 0.39
GDR *(mg . Kg^{-1} . min^{-1})*	9.98 ± 3.42	8.70 ± 3.42	11.14 ± 3.42
Serum Total Cholesterol *(mg/dl)*	204 ± 33.56	201 ± 29.05	208 ± 38.77
Triglycerides *(mg/dl)*	117 ± 54.9	110 ± 25.39	124 ± 74.98

Data are numbers and percentages, mean ± SD or median and interquartile range, as appropriate.

Table 2. Blood pressure at baseline, after treatment with Losartan and Telmisartan and differences between treatments

		16 weeks		Telmisartan vs Losartan	
	Baseline	**Losartan**	**Telmisartan**	**Absolute difference**	***P value**
Blood Pressure Profile					
Office					
Systolic	136.6 ± 16.5	130.1 ± 9.9	130.3 ± 12.5[b]	0.19	1.0000
Diastolic	87.2 ± 6.1	83.0 ± 7.5[b]	84.2 ± 10.4	1.27	0.6991
PP	65.0 ± 11.4	60.8 ± 9.7	61.4 ± 8.8	0.68	0.9893
Mean	103.7 ± 8.8	98.7 ± 7.4[b]	99.6 ± 10.5	0.91	0.8059
24-h					
Systolic	140.3 ± 13.2	135.0 ± 14.3	134.5 ± 14.5[a]	0.46	0.7281
Diastolic	83.6 ± 6.3	81.6 ± 6.8	81.9 ± 7.8	0.32	0.8857
PP	69.0 ± 9.1	69.4 ± 9.6	72.0 ± 9.4	2.58	0.3337
Mean	102.1 ± 7.7	99.2 ± 8.3	99.3 ± 9.4[b]	0.10	0.6218
Day-time					
Systolic	141. ± 11.9	136.9 ± 13.0	136.7 ± 13.9[b]	0.2	0.8472
Diastolic	84.7 ± 6.4	83.4 ± 5.9	83.2 ± 7.0	0.18	0.8363
Pulse	70.6 ± 9.9	71.3 ± 10.0	74.0 ± 9.7[b]	2.7	0.2393
Mean	103.5 ± 7.1	101.0 ± 7.3	100.6 ± 8.4[b]	0.4	0.4878
Night-time					
Systolic	133.3 ± 19.3	127.6 ± 22.5	127.2 ± 22.4[b]	0.45	0.7127
Diastolic	78.7 ± 8.8	75.3 ± 10.8	77.3 ± 12.7	2.04	0.3015
Pulse	63.5 ± 6.3	63.2 ± 8.5	62.0 ± 7.7	1.24	0.2551
Mean	96.5 ± 11.7	89.8 ± 13.1[b]	94.5 ± 15.6	4.71	0.2177

Data are presented as mean (SD) *Repeated measures ANOVA: Losartan vs Telmisartan. Repeated measures ANOVA: Telisartan or Losartan vs Baseline. [a] P< 0.01 vs baseline; [b] P< 0.05 vs baseline.

Table 3. Clinical secondary outcomes at baseline, after treatment with Losartan and Telmisartan and differences between treatments

		16 weeks		Telmisartan vs Losartan	
	Baseline	**Losartan**	**Telmisartan**	**Absolute difference**	***P value**
Lipid profile					
Total Cholesterol *(mg/dl)*	204.45 ± 33.56	196.53 ± 27.61	212.13 ± 31.10	15.60	0.0352
Triglycerides *(mg/dl)*	116.90 ± 54.9	124.94 ± 60.84	149.19 ± 141.58	24.25	0.5378
HDL *(mg/dl)*	49.25 ± 20.29	46.18 ± 14.12	47.63 ± 17.11	1.45	0.4875
LDL *(mg/dl)*	129.70 ± 23.76	123.41 ± 23.48	133.06 ± 18.62	9.65	0.1197
Apolipoprotein (a) *(mg/dl)*	145.10 ± 40.09	132.06±20.59[b]	132.38±23.08	0.32	0.9816
Apolipoprotein (b) *(mg/dl)*	100.39 ± 19.27	97.14 ± 17.64	104.01 ± 17.72	6.87	0.2564
Other metabolic parameters					
Morning fasting glucose *(mg/dl)*	98.65 ± 8.80	96.76 ± 9.80	99.88 ± 9.23	3.12	0.1474
HbA1c *(%)*	3.77 ± 0.47	3.93 ± 0.46[b]	3.93 ± 0.49	0.002	0.9629
HOMA IR index	1.53 ± 0.89	1.37 ± 0.52	1.75 ± 1.21	0.38	0.2543
Glucose at 120 min (tolerance test)	131.75 ± 47.04	115.71 ± 37.83	114.81 ± 33.30	0.90	0.9738
Kidney function parameters					
GFR (ml/min per 1.73 m2)	71.71 ± 20.61	67.10±19.86[b]	66.94±18.11[a]	0.16	0.9759
24-h AER (µg/min)	18.50 (8.17 – 83.17)	10.67 (6.00 – 42.67)[a]	12.67 (8.17 – 43.50)[b]	2	0,5986
Albumin Fraction Clearence (x 10^5)	194.34 (38.16 – 570.11)	53.40 (31.05 – 329.95)	50.04 (27.97 – 172.99)[b]	3.36	0.7558
Creatinine Clearance (ml/min)	85.58 ± 25.57	82.47 ± 29.72	82.18 ± 24.99	0.29	0.7443
Urinary Sodium Excretion (mEq/24-h)	179.28 (139.07 – 216.15)	177.86 (131.66 – 196.57)	172.32 (138.43 – 183.47)	5.54	0.9582

Data are presented as mean (SD) or median [IQR], as appropriate. *Repeated measures ANOVA: Losartan vs Telmisartan. Repeated measures ANOVA: Losartan or Telmisartan vs baseline. [a] P< 0.01 vs baseline; [b] P< 0.05 vs baseline.

Table 4. Overview of adverse events during consecutive treatment periods with Telmisartan or Losartan

		First treatment period (16 weeks)			Last treatment period (16 weeks)		
Adverse events	**Overall**	**Telmisartan**	**Losartan**	**P value**	**Telmisartan**	**Losartan**	**P value**
Total	32	13	10	1.000	3	6	1.000
Serious	4	1	–	1.000	–	3	1.000
Non Serious	28	12	10	0.751	3	3	1.000
Cardiac and vascular	5	2	3	1.000	–	–	–
Liver and gastrointestinal	1	1	–	1.000	–	–	–
Metabolism and endocrine	11	4	4	1.000	1	2	1.000
Nervous system	1	1	–	1.000	–	–	–
Respiratory	4	1	1	1.000	2	–	0.487
Skin, subcutaneous and muscoloskeletal	6	3	2	1.000	–	1	1.000