ORIGINAL ARTICLE

Safety of enhanced renin–angiotensin––aldosterone system inhibition with aliskiren in nondiabetic patients with chronic kidney disease

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KEY WORDS

aliskiren, chronic kidney disease, proteinuria, renin––angiotensin––aldosterone system

ABSTRACT

INTRODUCTION Various methods of combination renin–angiotensin–aldosterone system blockade help achieve more potent antiproteinuric effects, but may be associated with higher risk of side effects. Therapies involving direct renin inhibitor, aliskiren, may promote renal fibrosis by stimulating (pro)renin receptor due to increased renin levels.

OBJECTIVES The aim of the study was to compare the effects of combination treatment with angiotensin receptor blockers, telmisartan (80 mg/d) and aliskiren (300 mg/d) with those of combination treatment with 80 mg/d telmisartan and mineralocorticoid receptor blocker (50 mg/d eplerenone) and telmisartan (160 mg/d) alone on the urinary excretion of transforming growth factor β_1 (TGF-β_1), renal function, and serum potassium levels.

PATIENTS AND METHODS A randomized open-label controlled cross-over study was performed in 18 white patients (7 women and 11 men; mean age, 42.4 ±1.9 years) with proteinuric nondiabetic chronic kidney disease and estimated glomerular filtration rate of 85.2 ±4.6 ml/min.

RESULTS The urinary excretion of TGF-β_1 was stable despite a significant increase in plasma renin levels after treatment with telmisartan and aliskiren. There were no differences in renal function and serum potassium levels between the compared treatments. Moreover, there were no episodes of hypotension or acute renal impairment.

CONCLUSIONS Combination therapy with telmisartan and aliskiren may be safe in young nondiabetic patients with normal renal function at low vascular risk. This treatment may be an alternative for a subset of patients in whom standard RAA system blockade is ineffective.

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Received: March 7, 2013.
Revision accepted: April 25, 2013.
Published online: April 25, 2013.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2013; 123 (5): 221-227

INTRODUCTION Various studies have shown that treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduce proteinuria and the rate of decline in the glomerular filtration rate (GFR) in chronic kidney disease (CKD).[1-3] Direct renin inhibitors (DRIs) have been shown to exert antiproteinuric effects, ameliorate profibrotic signaling in the kidneys, and prevent organ damage.[4-8] Despite a significant progress in this area, there is still no optimal monotherapy that could stop the development of these nephropathies.[9] Different methods of combination renin–angiotensin–aldosterone (RAA) system blockade, involving the simultaneous use of 2 different-class agents inhibiting the RAA system or increasing the dose

TABLE 1 Baseline characteristics of the study group (n = 18)

Parameters		Study group
sex, female/male		4/14
age, y		39.3 ±2.7
mean 24-hour SBP, mmHg		116.8 ±2.4
mean 24-hour DBP, mmHg		73.8 ±1.8
24-hour proteinuria, g		1.62 (0.98–2.26)
serum creatinine, mg/dl		1.1 ±0.11
eGFR CKD-EPI, ml/min/1.73 m^2		85.2 ±6.4
serum potassium, mmol/l		4.47 ±0.1
body mass index, kg/m^2		26.4 ±0.79
background hypotensive therapy, n (%)	ACEIs and ARBs	8 (44.5)
	ACEIs (alone)	4 (22.5)
	ARBs (alone)	2 (11)
	none	4 (22)

Data are expressed as mean ± standard error of the mean or geometric mean (95% confidence interval).

To convert serum creatinine to µmol/l, multiply by 88.4; eGFR in ml/min/1.73 m^2 to ml/s/1.73 m^2, multiply by 0.01667.

Abbreviations: ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin II receptor blocker, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, DBP – diastolic blood pressure, eGFR – estimated glomerular filtration rate, SBP – systolic blood pressure

of ACEIs or ARBs above their therapeutic range, help achieve a more complete RAA system blockade and stronger antiproteinuric effects.[10] However, these strategies are associated with a higher risk of developing severe complications including hyperkalemia, hypotension, and acute renal insufficiency.[11-14] The enhanced RAA system blockade involving DRIs may also lead to an increase in renin and prorenin levels. This could be potentially harmful because high renin and prorenin levels may stimulate the (pro)renin receptor and thus induce profibrotic effects.[15] Recently, we demonstrated that combination therapy with DRIs and ARBs may effectively reduce proteinuria in patients with nondiabetic nephropathies as compared with the combination of ARBs and mineralocorticoid receptor antagonist and monotherapy with ARB in doses 2-fold higher than the maximum.[10] In this study, we focused on the potential side effects of such therapy.

PATIENTS AND METHODS

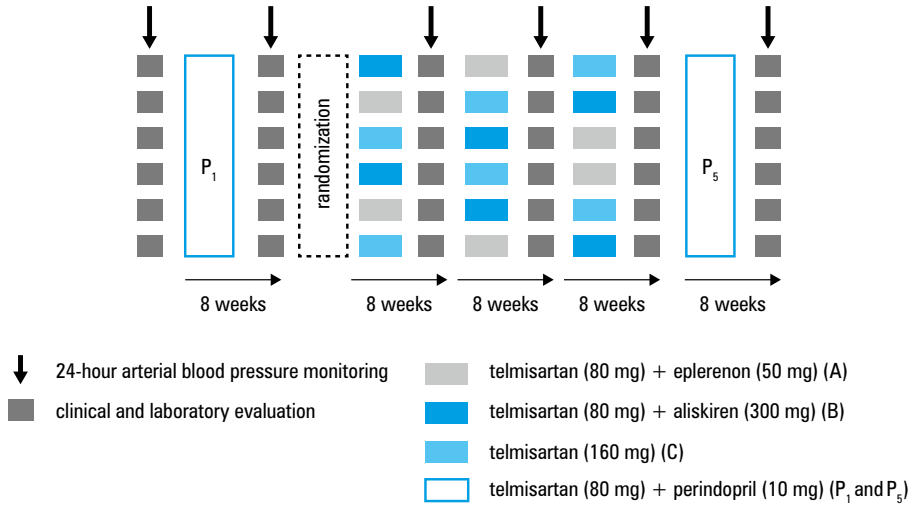
Patients Patients were selected from the cohort that attended the Outpatient Renal Clinic at the Medical University of Gdańsk and Ludwik Rydygier Collegium Medicum of the Nicolaus Copernicus University in Bydgoszcz, Poland. The inclusion criteria were as follows: age 18–65 years, proteinuric nondiabetic CKD stages 1–3, stable proteinuria above 500 mg/24 h in the last 6 months (no variations above 500 mg/24 h), hypertension treated with at least 1 agent or untreated hypertension with blood pressure (BP) above 140/90 mmHg, and no steroids or other immunosuppressive treatment for the minimum of 6 months before the study. Patients with unstable coronary heart disease or decompensated congestive heart failure in the previous 6 months, with an episode of malignant hypertension or stroke in history, with diabetis, and those with estimated GFR (eGFR) of less than 30 ml/min/1.73 m^2 were excluded from the study.

A total of 18 patients were enrolled to the study. CKD was caused by IgA nephropathy in 5 patients, membranous glomerulonephritis in 3 patients, focal segmental glomerulosclerosis in 3 patients, mesangial glomerulonephritis in 1 patient, minimal change nephropathy in 1 patient, and mesangiocapillary glomerulonephritis in 1 patient. In 2 patients, the diagnosis of chronic glomerulonephritis was based on clinical symptoms and laboratory findings. Prior to enrollment, 1 patient was treated with an ACEI, ARB, and diuretic; 7 patients with an ACEI and ARB; 3 patients only with an ACEI; and 3 patients did not receive any hypotensive or renoprotective treatment. Additionally, 6 patients received statins and 2 patients were treated with a β-blocker.

All patients who entered the study completed the study. Baseline clinical characteristics of the patients are presented in TABLE 1.

General protocol This was a double-center, prospective, randomized, double-blind, cross-over study assessing the safety of an 8-week combination of telmisartan (80 mg) and eplerenone (50 mg) once a day (OD) (A) as compared with the combination of telmisartan (80 mg) and aliskiren (300 mg) OD (B) and telmisartan (160 mg) OD (C). Initially, subjects who met the inclusion criteria entered the 8 week run-in period during which any hypotensive agents previously used were stopped and BP was controlled by the background therapy with combination of telmisartan (80 mg) and perindopril (10 mg) OD (P1 period). At the end of the run-in period, subjects were randomly allocated to 1 of 6 treatment sequences: ABC, ACB, BAC, BCA, CAB, CBA (FIGURE 1). For ethical reasons, there was no washout between the run-in period and 3 treatment therapies or between the treatments in each sequence. At the end, the same 8-week background therapy as in the run-in period was administered (P5 period). Preparing, labeling, and blinding of the study medications was performed by the Department of Pharmaceutical Technology, Medical University of Gdańsk. Patients were instructed to take the study medication once a day in the morning. The doses were not changed. Patients were recommended not to change their usual daily protein and sodium intake during the study period. At the end of each of the 3 treatment periods (A, B, C) and after both background therapies (P1 and P5), urine excretion of transforming growth factor β_1 (TGF-β_1), 24-hour ambulatory BP, serum concentration of creatinine and potassium, plasma concentration of prorenin and renin were measured and eGFR was calculated. Patients discontinued the trial in the case of consent withdrawal, noncompliance, hyperkalemia above 6.0 mmol/l,

FIGURE 1 Study protocol



worsening of renal function defined by a decrease from baseline eGFR greater than 30% and confirmed on 2 occasions, any other severe adverse events associated with treatment, for example, cough or angioedema on ACEI therapy. The study was approved by the local ethics committee, and all patients provided written informed consent. The study was registered at www.clinicaltrial.gov (identifier: NCT 01541267).

Procedures and laboratory analyses The morning urine sample was collected to measure TGF-β_1. The samples were stored at –75°C until assayed. The urinary concentration of TGF-β_1 was measured by an enzyme-linked immunosorbent assay (ELISA) (DRG Diagnostics, Germany). The DRG TGF-β_1 ELISA kit was based on the sandwich principle. The analytical sensitivity was calculated by adding 2 standard deviations to the mean of 20 replicate analyses with a standard of 0; it was found to be 1.9 pg/ml. The creatinine level was measured in the same urine samples using a modified kinetic Jaffe method. Urinary TGF-β_1 concentrations were normalized based on the urinary creatinine concentration.

The plasma concentration of renin was measured by the ELISA method (DRG Diagnostics). The microliter wells were coated with a monoclonal (mouse) antibody directed towards a unique antigenic site on the human active renin molecule. An aliquot of a patient's sample containing endogenous renin was incubated in the coated well with the assay buffer. After incubation, unbound components were washed off. Finally, the enzyme conjugate, which was a monoclonal antirenin antibody conjugated with horseradish peroxidase, was added. After incubation, the unbound enzyme conjugate was washed off. The amount of bound peroxidase was proportional to the concentration of renin in the sample. Having added the substrate solution, the color intensity was proportional to the concentration of active renin in the patient's sample. The range of assay was between 0.81 and 128 pg/ml. The analytical sensitivity was calculated by adding 2 standard deviations to the mean of 20 replicate analyses with a standard of 0; it was found to be 0.81 pg/ml. Intra-assay reproducibility was 4.2%, and interassay reproducibility was 6.27%.

The plasma concentration of prorenin was measured by the ELISA (BioVendor Research and Diagnostic Products, Czech Republic). Human prorenin binds to the capture antibody coated on the microtiter plate. After appropriate washing steps, antihuman prorenin primary antibody was bound to the captured protein. Only prorenin and inactive renin was detected by the primary antibody. The excess antibody was washed away, and the bound primary antibody was then reacted with the secondary antibody conjugated to the horseradish peroxidase. The TMB (3,3',5,5'-tetramethylbenzidine) substrate was used for color development at 450 nm. A standard calibration curve was prepared along with the samples using dilutions of prorenin. The amount of color development was directly proportional to the concentration of prorenin in the sample. The assay measures human prorenin in the range of 0.01–10 ng/ml.

Creatinine and potassium levels were measured using standard methods. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Side effects of therapies were monitored by questionnaires.

Ambulatory BP was measured continuously for 24 hours using the Mobil-o-graph (version 12) monitoring system. BP was measured every 15 minutes during the day (from 7:00 a.m. to 10:00 p.m.) and every 30 minutes during the night (from 10:00 p.m. to 7:00 a.m.). The results of ambulatory BP measurements were presented as the mean arterial pressure (MAP).

Statistics In the per-protocol design, the variable differences were assessed by the analysis of variance (ANOVA) for repeated measurements with the Bonferroni corrections for paired comparisons. Head-to-head comparisons between study therapies and background treatment with

TABLE 2 Plasma renin and prorenin concentrations and urinary transforming growth factor β_1 / creatinine during the study

Variable	Telmisartan + perindopril (P1)	Telmisartan + eplerenone (A)	Telmisartan + aliskiren (B)	Telmisartan 160 mg (C)	Telmisartan + perindopril (P2)	ANOVA (A vs. B vs. C)
plasma prorenin, ng/ml	3.59 (2.0–9.84)	2.74 (1.78–7.57)	2.98 (2.41–5.17)	3.16 (2.43–6.15)	2.86 (2.23–5.32)	NS (P = 058)
plasma renin, pg/ml	154[c,d,e] (358–751)	73[a] 176–369)	469 (418–875)	90[b] (192–403)	133[c,d] (324–679)	P <0.001
urinary TGF-β_1 / creatinine, pg/mg	17.2 (5.2–10.9)	14.5 6.3–13.1)	16.7 (6.0–12.6)	17.0 (6.2–13.1)	14.9 (7.3–15.2)	NS (P = 0.27)

Data are expressed as the geometric mean (95% confidence interval).

a post-hoc P <0.001 (A vs. B), **b** post-hoc P <0.001 (C vs. B), **c** significant vs. A (t test; P <0.05), **d** significant vs. B (t test; P <0.05), **e** significant vs. C (t test; P <0.05)

Abbreviations: ANOVA – analysis of variance, NS – nonsignificant, TGF-β_1 – transforming growth factor β_1

telmisartan plus perindopril, as secondary analyses, were performed using the t test. A P less than 0.05 (2-tailed) was considered statistically significant. Data were evaluated using a STATISTICA software package (version 9.0 Stat Soft Inc.). The results were expressed as means ± standard error of the mean.

To prevent or limit the risk of a "carry-over effect", we planned each treatment period for 8 weeks. Previous studies demonstrated that the effects of RAA system blocking agents on the kidney are fully reversible within 4 weeks.[15] Thus, prolonging each treatment period to 8 weeks allowed us to rule out any residual effect of previous treatment at the end of the eighth week, when analyses were performed. To prevent or limit the possibility of a "period effect", we introduced a degree of balance into the study design, with a scheme of randomization allowing every treatment sequence to be represented in every period with the same frequency. Overall, we had 6 different therapy sequences with 3 treatment periods (FIGURE 1). Equal numbers of patients (n = 3) per sequence were randomized. Since no patients were prematurely withdrawn, this balance was fully respected at the end of the study.

RESULTS We observed no differences in the urinary excretion of TGF-β_1 between the therapies (TABLE 2, FIGURE 2). Moreover, there were no differences in plasma prorenin concentrations between treatments, while plasma renin concentration was significantly higher after therapy with aliskiren 300 and telmisartan 80 mg as compared with other therapies (ANOVA, P <0.001) (TABLE 2). Renal function assessed by eGFR remained stable during the study. There were no episodes of acute impairment of renal function. No differences in serum potassium concentrations were observed between the treatments (TABLE 3). There were no differences in MAP between the treatments. BP was stable during the entire study and no hyper- or hypotonic episodes were observed (TABLE 3). All therapies were well-tolerated by patients. Adverse effects were not reported in questionnaires.

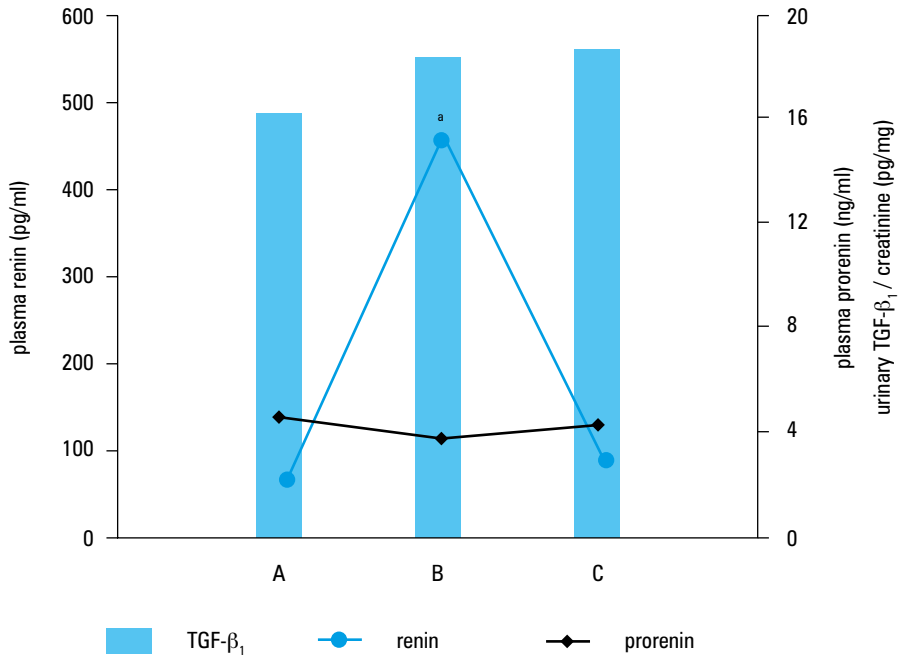


FIGURE 2 Plasma renin and prorenin concentrations and urinary transforming growth factor β_1 (TGF-β_1) / creatinine during the study
a P <0.001 vs. A vs. C

TABLE 3 Mean arterial pressure and laboratory tests during the study

Variable	Telmisartan + perindopril (P1)	Telmisartan + eplerenone (A)	Telmisartan + aliskiren (B)	Telmisartan 160 mg (C)	Telmisartan + perindopril (P2)	ANOVA (A vs. B vs. C)
24-hour MAP, mmHg	102.5 ±8.6	106.5 ±9.4	104.5 ±10.2	105.7 ±8.8	103.8 ±8.2	NS
24-hour proteinuria, g	1.63 (0.92–1.93)	2.18 (0.94–1.97)	1.77 (0.85–1.78)	1.98 (0.86–1.81)	1.84 (1.09–2.28)	NS
eGFR CKD-EPI, ml/min	86.7 ±6.9	90.7 ±7.1	89.7 ±7.1	90.4 ±7.0	90.2 ±7.6	NS
serum potassium, mmol/l	4.47 ±0.1	4.28 ±0.08[a]	4.56 ±0.13	4.45 ±0.1	4.43 ±0.11	NS

Data are expressed as mean ± standard error of the mean.

eGFR CKD-EPI = 141 × min(Scr/κ,1) α × max(Scr/κ,1)–1.209 × 0.993 age × 1.018 [if female] × 1.159 [if black]

P – telmisartan (80 mg) + perindopril (10 mg)

A – telmisartan (80 mg) + eplerenone (50 mg)

B – telmisartan (80 mg) + aliskiren (300 mg)

C – telmisartan (160 mg)

Abbreviations: MAP – mean arterial pressure, others – see TABLES 1 and 2

DISCUSSION In 2008, the ONTARGET study demonstrated that dual therapy with ACEIs and ARBs had no additional cardiovascular benefit, did not reduce chronic dialysis or doubling of serum creatinine but exhibited infrequent but life-threatening adverse events, including acute kidney injury and hyperkalemia in patients at high vascular risk.[17] Similarly, the recently conducted Quite ALTITUDE study performed in diabetics was terminated prematurely due to lack of efficacy and risk of renal impairment, hyperkalemia, and nonfatal stroke in patients taking aliskiren plus ACEIs or ARBs.[18] Therefore, the effect of our intervention with aliskiren on BP, renal function, and potassium concentration in nondiabetic patients with CKD is particularly interesting. We demonstrated that all combination RAA system blockades did not cause significant hyperkalemia, episodes of hypotonia, or acute fall in the eGFR. These therapies were also quite well-tolerated and no significant side effects were reported. Therefore, they may be alternative strategies in the population of patients in whom standard RAA system blockade does not produce a sufficient renal effect.

However, our study have several limitations including a small sample size, a relatively short follow-up, and selected population of only young nondiabetic individuals with quite good renal function and without cardiovascular complications.

Our results are interesting also from another point of view. Although RAA system blocking agents were confirmed to have a potent antiproteinuric effect in CKD, a question has been raised whether the increased concentration of renin induced by enhanced RAA system blockade, notably involving DRI, might promote renal fibrosis via the activation of (pro)renin receptors. Both prorenin and renin were found to stimulate TGF-β_1 production via MAPK p42/p44 in this way, which subsequently resulted in the upregulation of profibrotic and prothrombotic molecules such as fibronectin, collagen-1, and plasminogen-activator inhibitor.[19] All RAA system blockers cause a reactive rise in renin and prorenin concentrations, but the largest increase is observed with DRI therapy.[15] In the present study, the highest values of plasma renin were also observed during the combination therapy with ARB (telmisartan) and DRI (aliskiren). One might expect that this would result in increased (pro)renin receptor activation, leading to potential detrimental effects. However, no such effects were observed in the study. Urinary TGF-β_1 excretion did not change during any of the treatments.

Previously, the authors did not show an increase of TGF-β_1 synthesis in patients with CKD treated with aliskiren as monotherapy.[4] A possible explanation for the lack of such detrimental effects was provided by Schefe et al.[20] who showed that on activation of the (pro)renin receptor, the transcription factor promyelocytic zinc finger is translocated to the nucleus and represses the transcription of the (pro)renin receptor itself, thus creating a short negative feedback loop.[20] In other words, high (pro)renin levels, as occurring during the RAA system blockade, will suppress (pro)renin receptor expression, thereby preventing excessive receptor activation. In addition, aliskiren was shown to reduce the expression of (pro)renin receptors.

In conclusion, we demonstrated that enhanced RAA system blockade with telmisartan and aliskiren may be safe in young nondiabetic patients with CKD stages 1 and 2 and low cardiovascular risk.

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Bezpieczeństwo skojarzonej blokady układu renina–angiotensyna–aldosteron z zastosowaniem aliskirenu u chorych z niecukrzycową przewlekłą chorobą nerek

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SŁOWA KLUCZOWE

aliskiren, białkomocz, przewlekła choroba nerek, układ renina–angiotensyna–aldostero

STRESZCZENIE

WPROWADZENIE Różne metody skojarzonej blokady układu renina-angiotensyna-aldosteron (RAA) pozwalają zwiększyć redukcji białkomoczu, ale mogą się wiązać ze zwiększonym ryzykiem wystąpienia objawów ubocznych. Terapia z zastosowaniem bezpośredniego inhibitora reniny, aliskirenu, może predysponować do włóknienia nerek poprzez pobudzenie receptora dla (pro)reniny w następstwie zwiększonego stężenia reniny.

CELE Celem badania było porównanie wpływu łączonej terapii blokerem receptora dla angiotensyny II (telmisartanem 80 mg/d i aliskirenem 300 mg/d) ze skojarzoną terapią temisartanem 80 mg/d z blokerem receptora mineralokortykoidowego (eplerenonem 50 mg/d) oraz samym telmisartanem 160 mg/d na wydalanie z moczem transformującego czynnika wzrostu β_1 (*transforming growth factor* β_1 – TGF-β_1), funkcję nerek i stężenie potasu w surowicy.

PACJENCI I METODY Randomizowane, kontrolowane, podwójnie ślepe badanie typu *cross-over* przeprowadzono u 18 chorych rasy białej (7 kobiet i 11 mężczyzn; średnia wieku 42,4 ±1,9 roku) z niecukrzycową przewlekłą chorobą nerek oraz szacowanym współczynnikiem przesączania kłębuszkowego 85,2 ±4,6 ml/min.

WYNIKI Wydalanie z moczem TGF-β_1 było stabilne w trakcie badania mimo znaczącego wzrostu stężenia reniny w surowicy w czasie skojarzonej terapii telmisartanem i aliskirenem. Nie stwierdzono różnic w funkcji nerek, stężeniu potasu oraz wartości ciśnienia tętniczego między porównywanymi terapiami. Ponadto nie obserwowano epizodów niedociśnienia oraz ostrej niewydolności nerek.

WNIOSKI Łączona terapia telmisartanem i aliskirenem jest bezpieczna u młodych pacjentów z cukrzycą z prawidłową funkcją nerek i małym ryzykiem naczyniowym. Leczenie to może być alternatywą dla wybranej grupy chorych, u których standardowa blokada układu RAA nie jest skuteczna.

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Praca wpłynęła: 07.03.2013.
Przyjęta do druku: 25.04.2013.
Publikacja *online*: 25.04.2013.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2013; 123 (5): 221-227