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RESEARCH LETTER

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Effect of gender on transition of normo- to microalbuminuria under angiotensin receptor blocker therapy in diabetes

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KEYWORDS

albuminuria, diabetes mellitus, diabetic nephropathy, gender, renin-angiotensin-aldosterone-system

Highlights

- In normoalbuminuric diabetic patients at low cardiovascular risk, the risk of transition from normo- to microalbuminuria is lower in women, despite the nonprotective effects of the angiotensin receptor blocker olmesartan.
- Additional methods of assessment of albuminuria in clinical studies (eg, measurements of albumin and creatinine excretion rate) should be implemented or the actually accepted higher urine albumin creatinine ratio (UACR) cutoff values for microalbuminuria in women reconsidered.

To the Editor

There are differences in the prevalence, clinical manifestations, complications, and response to treatment of cardiovascular disease between women and men with diabetes.[1] In particular, women lose the cardiovascular protection of their gender if type 2 diabetes occurs.[2] The underlying mechanisms have not been fully understood and are attributed to biological and behavioral traits.[3,4]

Gender-related differences on cardiovascular outcomes are obviously a result of the differential impact of risk factors. Concerning this matter, uncertainty exists about the effects of albuminuria, one of the strongest cardiovascular and renal disease risk factors.[5] Studies with renin-angiotensin-aldosterone system (RAAS) blockers, a medication class with indisputable antiproteinuric properties, showed better cardiovascular protection in women,[6] despite their diminished efficacy and increased adverse event rate.[7] The reasons for this apparent

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paradox in the pharmacodynamic actions of RAAS blockers in females have not been elucidated.

In the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) study, females were significantly protected from progression of albuminuria.[8] In this report we try to approach the gender-related disparities regarding the primary endpoint and present an analysis of the relationship between treatment with olmesartan, gender, and albuminuria levels at baseline.

1 | METHODS

ROADMAP (ClinicalTrials.gov number NCT00185159) was a randomized, double-blind, placebo-controlled, parallel-group study, conducted at 262 collaborating centers in 19 European countries. It was designed to test whether an angiotensin receptor blocker (ARB), olmesartan medoxomil 40 mg once daily, is superior to placebo in preventing the onset of microalbuminuria (MA) in a diabetic population at low cardiovascular risk. MA was defined as an urinary albumin creatinine ratio (UACR) above 35 mg/g in women and above 25 mg/g in men.[9]

In the present paper MA was compared between treatment groups stratified by gender and differences in response to treatment with olmesartan were sought. The Restricted Full Analysis Set of ROADMAP study was used.

Statistical analyses were performed using SAS software version 9.1. The primary efficacy endpoint "time to onset of microalbuminuria" was analyzed using a Cox proportional hazard model with treatment as a fixed effect and the log10 transformed baseline UACR as covariate. Baseline UACR stratified by gender was categorized in quartiles and related to MA.

2 | RESULTS

At baseline, there were statistically significant differences in nearly all risk factors for MA between women and men (Table S1). Baseline characteristics of patients stratified by gender and treatment arm are presented in Table 1 and results illustrated in Figure 1. In both sexes MA risk increased as baseline UACR increased, but there was a difference regarding treatment with olmesartan. In women no protective effects were observed independently of baseline UACR, whereas men belonging to the highest UACR quartile (15-25 mg/g) showed a significant reduction in MA if treated with olmesartan (Figure S1).

3 | COMMENT

Studies have shown gender-related differences in cardiovascular disease outcomes, risk factors, efficacy of medication, and progression of chronic kidney disease[7,10] or have explored potential underlying mechanisms.[10,11] To the best of our knowledge, gender-specific differences in the effects of RAAS blockers on diabetic patients with normoalbuminuria have not been investigated.

In this subanalysis of the ROADMAP study we tested if an interaction between progression of albuminuria and gender exists. The disparity in the antialbuminuric effects of olmesartan at the expense of women did not got lost in the multivariate analysis and was most obvious in the quartiles with baseline UACR between 15 and 25 mg/g.

In our previous publication dealing with correlations between risk factors and albuminuria at baseline significantly higher albumin excretion rates were observed in females, probably owing to the dysbalance in the respective risk factors, favoring men.[12] This analysis showed that after multifactorial goal-directed therapy for a few years the initial association inverted. Albuminuria progression occurred less frequently in women than men, whereas olmesartan exerted protective effects foremost in men. The interpretation of these discrepant data is mostly speculative. First, it is another example of the differences in results between associative and causative studies. Second, it could point to genuine gender-specific differences in the pathophysiologic mechanisms of diabetic nephropathy or on pharmacodynamic effects of ARBs. Third, the lower risk in women may simply reflect better compliance after randomization or is the result of the higher cutoff value for MA (35 mg/g).

The strength of our report was that the data were derived from a large randomized, controlled study. A major drawback is that an analysis omitting the confounding effects of gender on creatinine by using albumine excretion rate urine albumin excretion (UAE) only instead of UACR was not conducted. We did not know if the gender differences of UACR disappear when albumin excretion is not featured for creatinine excretion rate, which is different in men and women. Moreover, because UACR accounts for dilution effects (mg/g) whereas UAE (μg/min) does not, we could not draw conclusions about the superiority of the one or the other urine collection method.[13] Another limitation was that random urinary creatinine, which reflects disease-associated sarcopenia and emerges as a significant chronic kidney disease risk factor, was not compared between genders or evaluated as a predictor of MA.[14] Lastly, because the mean UACR in all groups at baseline ranged from 5.2-6.8 mg/g, case numbers in the upper UACR quartile may be limited compated with those from

TABLE 1 Demographic data at baseline stratified by gender and treatment arm

	Female			Male		
	Placebo (n = 1165)	Olmesartan (n = 1142)	*P* Value	Placebo (n = 974)	Olmesartan (n = 1018)	*P* Value
Age, y	58.4 ± 8.3	58.4 ± 8.6	>0.9999	57.1 ± 9.0	56.8 ± 9.0	0.4572
Elderly (≥ 65 y), n (%)	304 (26.1)	316 (27.7)	0.3863	234 (24.0)	226 (22.2)	0.3407
BMI, kg/mP^2	31.6± 5.2	31.7 ± 5.3	0.6474	30.0 ± 4.3	30.4 ± 4.2	**0.0358**
Duration of diabetes, months	75.2 ± 73.9	78.4 ± 74.6	0.3008	70.3 ± 71.7	68.5 ± 69.6	0.5697
Smoking history, n (%)						
Nonsmoker	896 (76.9)	903 (79.1)	0.2024	400 (41.1)	422 (41.5)	0.8562
Ex-smoker	107 (9.2)	87 (7.6)	0.1663	332 (34.1)	349 (34.3)	0.9251
Smoker	162 (13.9)	152 (13.3)	0.6743	242 (24.8)	247 (24.3)	0.7955
Metabolic syndromeP[a]P, n (%)	983 (84.4)	987 (86.4)	0.1740	753 (77.3)	786 (77.2)	0.9576
Cardiovascular diseaseP[b]P, n (%)	286 (24.5)	291 (25.5)	0.5792	233 (23.9)	257 (25.2)	0.5006
HbAR$_{1c}$R, %	7.7 ± 1.7	7.8 ± 1.7	0.1579	7.5 ± 1.5	7.4 ± 1.5	0.1371
Mean sitting blood pressure, mm Hg						
Systolic	135.4 ± 15.9	136.3 ± 15.9	0.1742	136.1 ± 14.1	137.1 ± 14.8	0.1231
Diastolic	80.3 ± 9.5	80.5 ± 9.5	0.6132	80.4 ± 9.3	81.0 ± 9.7	0.1593
Urine albumin, mg/L	5.2 ± 3.8	6.5 ± 12.3	**0.0006**	6.6 ± 6.2	6.8 ± 7.3	0.5108
UACRP[c]P, mg/g	5.7 ± 4.2	6.5 ± 5.0	**<0.0001**	5.3 ± 3.8	5.3 ± 3.6	>0.9999
eGFRP[d]P, mL/min/1,73mP^2	82.3 ± 16.2	82.1 ± 16.7	0.7703	87.5 ± 17.8	88.0 ± 16.4	0.5142
eGFR <60 mL/min/1,73 m2, n (%)	84 (7.2)	96 (8.4)	0.2825	32 (3.3)	35 (3.4)	0.9014
Total cholesterol, mmol/l	5.4 ± 1.1	5.4 ± 1.1	>0.9999	5.0 ± 1.1	5.0 ± 1.1	>0.9999
LDL-cholesterol, mmol/l	3.2 ± 0.9	3.2 ± 0.9	>0.9999	3.0 ± 0.8	3.0 ± 0.9	>0.9999
HDL-cholesterol, mmol/l	1.3 ± 0.3	1.3 ± 0.3	>0.9999	1.1 ± 0.3	1.1 ± 0.3	>0.9999
Triglycerides, mmol/l	2.0 ± 1.1	2.1 ± 1.5	0.0676	2.1 ± 1.3	2.2 ± 1.9	0.1724

Note: Values are means ± SD, if not marked otherwise.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; g, gram; HbA1c %: glycated hemoglobin; HDL, high-density lipoprotein; kg, kilogram; L, liter; LDL, low-density lipoprotein; mg, milligram; min, minute; mL, milliliter; mm Hg, millimeter of mercury; mmol, millimole; mP^{2}P, square meter; UACR, urine albumin to creatinine ratio; y, years.

Bold values denote statistically significant values.

[a]PNational Cholesterol Education Program Adult Treatment Panel-III criteria.

[b]PThe identification of these diseases is based on groupings of preferred terms (based on MedDRA, V. 11.0).

[c]PThe baseline UACR is defined as the geometric mean of the last three evaluable UACR measurements at Visit 1 (BL). In case there were not enough adequate measurements available at baseline, the last measurements from the screening period were used.

[d]PThe estimated glomerular filtration rate (eGFR) is calculated according to the abbreviated Modification of Diet in Renal Disease formula.

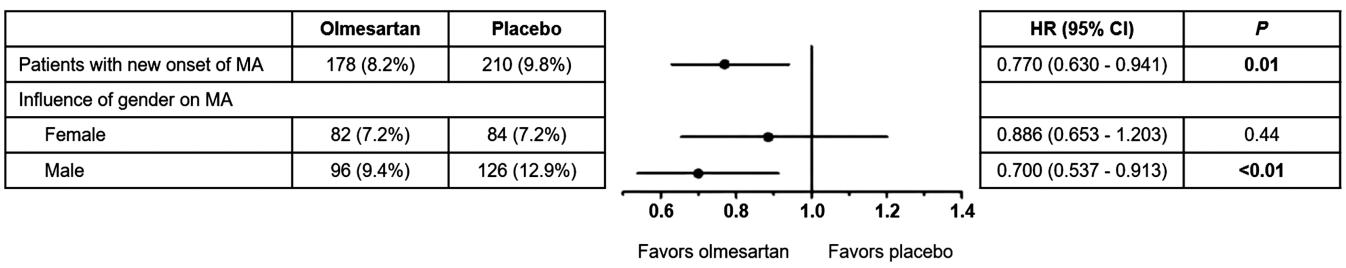

FIGURE 1 Effects on gender in response to treatment with olmesartan. CI, confidence interval; HR, hazard ratio; MA, microalbinuria

the lower one. This should be considered in the interpretation of the results.

Gender independently contributes to albuminuria progression and plain albuminuria alone is probably superior to UACR. Using UAE instead of UACR could help to overcome the confounding effect of gender but this has to be tested in prospective studies.

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CONFLICT OF INTEREST

The authors of the manuscript have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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