The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) Observational Follow-Up Study: Benefits of RAS Blockade With Olmesartan Treatment Are Sustained After Study Discontinuation

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Background—The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study showed that 40 mg Olmesartan medoxomil (OM) versus placebo delayed microalbuminuria onset in patients with type 2 diabetes and normoalbuminuria.

Methods and Results—One thousand seven hundred and fifty-eight ROADMAP patients (placebo arm: 877; OM arm: 881) participated in the observational follow up (OFU) with an average of 3.3 years. They received standard medical care and micro- and macrovascular events were documented. During observational follow-up 62.9% and 60.1% in the former OM and placebo group, respectively, received treatment with a RAS blocking agent. During the OFU period the systolic blood pressure (SBP) increased to mean values of 135 mm Hg in both groups. Patients who had developed microalbuminuria during ROADMAP had a higher incidence of cardio- and cerebrovascular events (OR 1.77, CI 1.03 to 3.03, \(P=0.039\)) during the OFU period compared with patients in whom this was not the case. Diabetic retinopathy was significantly reduced in the former OM group (8 [0.9%] versus 23 [2.6%], OR: 0.34, CI 0.15 to 0.78, \(P=0.011\)) and the rate of microalbuminuria was numerically reduced. Congestive heart failure requiring hospitalization (3 [0.3%] versus 12 [1.4%], OR: 0.23, CI 0.06 to 0.85, \(P=0.027\)) was reduced and there was a trend of reduced cardio-/cerebrovascular events (OM versus Pb: 73 [8.3%] versus 86 [9.8%] patients). Seven (0.8%) deaths (including 2 CV events) were reported in former placebo patients versus 3 (0.3%) (non-CV events) in former OM patients.

Conclusions—Development of microalbuminuria is a valid marker for future CV events. RAS blockade with Olmesartan might cause sustained reduction (legacy effect) of micro- and macrovascular events. (J Am Heart Assoc. 2014;3:e000810 doi: 10.1161/JAHA.114.000810)

Key Words: albuminuria • angiotensin receptor blocker • diabetic nephropathy • proteinuria
including 18 studies, demonstrated that blood pressure-lowering treatment will have a sustained benefit on mortality after study termination.4 Furthermore, the authors demonstrated that such a benefit was independent of the drug administered (ACE inhibitors, diuretics, or beta-blockers). However, the interpretation of this meta-analysis is limited by the fact that in the majority of the cited studies, patients with acute myocardial infarction or systolic heart failure were included. Additionally, in most of the studies the study medication was compared with placebo and large blood pressure differences were reported during the active treatment phase.4 Therefore it is unclear if the meta-analysis data are applicable to patients with hypertension with or without diabetes and no major acute cardiovascular disease as well as patients with well-controlled blood pressure. Furthermore, it is currently unclear if the RAS blockade has a legacy effect beyond other blood pressure-lowering drugs. There is some evidence from animal5,6 and clinical7–9 studies, but presently these data are still limited.10 Therefore, the ROADMAP population (hypertensive, diabetic patients with good blood control and active blood pressure treatment in both study arms) was well suited to answer these open questions.

In the OFU, former ROADMAP patients received standard medical care and treatment. Selected endpoints, including the occurrence of microalbuminuria, blood pressure control, cardiovascular and renal events, were investigated over an extended period of time. Due to the observational character of the OFU study only medical examinations and treatment according to the standard of medical care were documented. The results of this OFU study are presented here.

Methods

Study Design

The ROADMAP OFU was a prespecified, multicenter, longitudinal observational, follow-up of patients who formerly participated in the ROADMAP study (ClinicalTrials.gov ID no.: NCT00185159).1,2 After they had completed the final ROADMAP visit the patients received standard medical care and were treated at the discretion of the primary physician. Due to the nature of a noninterventional study, the patient treatments varied accordingly and the visits to the physicians were not performed in a standardized way but at variable time points according to local medical standard and patient needs.

During the OFU study, data were captured at 2 data collection points corresponding to a reporting date on which all available data were collected from routine visits at the study center and from the primary physician. Collection point 1: After a mean duration of 2.3 years (range: 1.4 to 5.1 years) after the last ROADMAP visit. Collection point 2: After a mean duration of 3.3 years (range: 2.1 to 6.7 years) after the last ROADMAP visit. For a better assessment of the time course of vital signs and laboratory parameters obtained in the study centers, or by the primary physician, we used the following classification scheme: <0.25 years: 1 day to <3 months; 0.5 years: 3 to <9 months; 1.0 years: 9 to <15 months; 1.5 years: 15 to <21 months; 2.0 years: 21 to <27 months; 2.5 years: 27 to <33 months; 3.0 years: 33 to <39 months; >3.25 years: ≥39 months.

Due to the noninterventional character of the OFU study the amount of patient data (blood pressure, GFR, and albuminuria measurements) available per time interval was variable and could be between 0 and several measurements per patient. In case there was more than 1 value of a vital sign or laboratory parameter within a given time interval, the mean of all values of the respective parameter was analyzed. The last ROADMAP assessment was set as the OFU baseline for this purpose.

Study Population

One hundred and forty centers from 18 countries out of the original 262 ROADMAP centers from 19 countries participated actively in the ROADMAP-OFU trial. Other centers did not participate for different reasons. Out of 2198 eligible patients (placebo group 1104; olmesartan group: 1094) a total of 1758 patients (placebo group: [79.4%]; olmesartan group: [80.6%]) participated in the OFU. The ROADMAP-OFU study was reported and approved by the applicable ethics committees or competent authorities for each participating site according to the national requirements.

Objectives

It was the objective of the ROADMAP OFU study to collect and evaluate selected items corresponding to the former primary and secondary events in the ROADMAP study (eg, microalbuminuria, cardiovascular as well as cerebrovascular morbidity and mortality, total mortality, renal disease, diabetic retinopathy) as well as vital signs. Due to the observational character of the OFU only medical examinations and treatment according to standard medical care were documented. Therefore, in contrast to the ROADMAP study, microalbuminuria was detected according to different local standards and was not centrally assessed. CV and renal events reported by the investigators were not adjudicated by an independent endpoint-monitoring committee. Additionally, vital signs (blood pressure, pulse rate, weight, body mass index, and waist circumference), laboratory parameters (creatinine eGFR, HbA1c), and information on the use of antihypertensive and antidiabetic drugs were collected.
Analysis and Statistics

Logistic regression was performed to assess single and combined cardiovascular and cerebrovascular endpoints. The effect of treatment strategy and of occurrence of microalbuminuria during the ROADMAP study was analyzed. The values were adjusted for differences in UACR, eGFR, SBP, DBP, and HbA1c at baseline (final ROADMAP visit). Analyses of the time to onset of microalbuminuria and time to onset of cardiovascular events were performed using a Cox proportional hazard regression model; baseline UACR (final visit in ROADMAP main study) was logarithmically transformed (base 10) as a covariate. All statistical analyses were performed using SAS System for Windows V.9.1.3 (SAS Institute) with values expressed as mean±SD if not otherwise indicated. Any P value should be interpreted as purely exploratory. The graphics were prepared with Prism 5 (GraphPad Software).

Two different counting rules were used to assess the presence of microalbuminuria. For this purpose 2 different combinations were tested. Counting rule 1: If the result was documented to be likely in urine albumin dipstick this value was counted as positive (Approach 1) or was excluded (Approach 2). Counting rule 2: If during a certain time period more than 1 albumin measurement was obtained and the results varied, we used the highest value (Approach 1) or the most frequent result (Approach 2). Therefore, 4 different criteria combinations for the diagnosis of microalbuminuria were possible. UACR values above 30 mg/g were counted as positive (ie, as microalbuminuria).

Results

In this analysis, patients were assigned to the following cohorts according to their previous study medication in the ROADMAP study. Eight hundred and seventy-seven patients had been in the former placebo (Pb) group and 881 had been in the former olmesartan (OM) group. The mean follow-up in both groups during the OFU was 3.3±0.6 years. The patient populations in the 2 OFU groups were comparable (Table 1) and representative for the entire ROADMAP cohort (this is depicted in Table 2 with regard to demographics, vital signs, and laboratory parameters). Seventy-eight (8.9%) of the former patients on placebo and 54 (6.1%) of the former patients on olmesartan

Table 1. Characteristics of the ROADMAP-OFU Patient Population at OFU Baseline (=Final ROADMAP Visit)

|                                      | ROADMAP-OFU Baseline/Final ROADMAP Visit |
|--------------------------------------|------------------------------------------|
|                                      | Placebo (n=877)                           | Olmesartan (n=881)                              | P Value |
| Male gender, n (%)                   | 418 (47.7)                               | 441 (50.1)                                    | 0.3153  |
| Age, y                               | 61.3 (8.4)                               | 61.2 (8.5)                                    | 0.8234  |
| Roadmap duration (y), mean (SD)      | 3.3 (0.6)                                | 3.4 (0.6)                                     | 0.6908  |
| Body mass index (kg/m²), mean (SD)   | 30.7 (4.9)                               | 31.0 (4.8)                                    | 0.1776  |
| Duration of diabetes (y), mean (SD)  | 9.7 (5.9)                                | 9.7 (6.0)                                     | 0.9185  |
| Blood glucose (mmol/L), mean (SD)    | 9.6 (3.4)                                | 9.3 (3.2)                                     | 0.0779  |
| HbA1c (%), mean (SD)                 | 7.8 (1.6)                                | 7.7 (1.6)                                     | 0.0896  |
| Average number of antihypertensive drugs*, (SD) during ROADMAP | 2.3 (1.5) | 2.1 (1.5) | 0.0005  |
| SBP (mm Hg), mean (SD)               | 127.5 (11.0)                             | 124.2 (10.7)                                  | <0.0001 |
| DBP (mm Hg), mean (SD)               | 74.5 (7.5)                               | 72.5 (8.1)                                    | <0.0001 |
| eGFR (mL/min), mean (SD)             | 81.8 (17.5)                              | 78.1 (18.0)                                   | <0.0001 |
| Total cholesterol (mmol/L), mean (SD)| 5.1 (1.2)                                | 5.1 (1.4)                                     | 0.4813  |
| HDL (mmol/L), mean (SD)              | 1.3 (0.4)                                | 1.3 (0.4)                                     | 0.1265  |
| LDL (mmol/L), mean (SD)              | 2.9 (1.0)                                | 2.9 (1.0)                                     | 0.8846  |
| Triglyceride (mmol/L), mean (SD)     | 2.1 (1.6)                                | 2.2 (2.9)                                     | 0.1433  |

At baseline of ROADMAP main study

|                                      |                                            |
| Smoker, n (%)                        | 139 (15.8)                                | 139 (15.8)                                   | 0.9670  |
| History of coronary heart disease, n (%) | 183 (20.9)                               | 198 (22.5)                                   | 0.4133  |

DBP indicates diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OFU, observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SBP, systolic blood pressure.

*With exception of olmesartan.
who participated in the OFU had developed microalbuminuria already during the preceding ROADMAP study. Both numbers are slightly lower than the numbers in the entire ROADMAP cohort (9.8% and 8.2%, respectively).

### Blood Pressure Control

During the OFU period, 88.3% of the patients received antihypertensive drugs with comparable distributions in both groups (Table 3). In addition, a similar use of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEI) or calcium channel blockers was reported. More patients from the former placebo group, however, received a beta-blocker or a diuretic (Table 3). The percentage of patients who received an antihypertensive medication and especially a beta-blocker, a calcium-channel blocker, or a diuretic was lower during the OFU period than the main study (Table 3). This was also true for RAS blockade in the former olmesartan group.

As a consequence of the lower intake of antihypertensive medications the blood pressure increased after termination of the ROADMAP study (Figure 1A). It was comparable between the 2 groups (former placebo versus former olmesartan) during long-term follow-up (Figure 1A). The increase was more pronounced in those who had received OM; they generally had better blood pressure control during the double-blind ROADMAP period, although 60% had subsequently received an ACEI or ARB during the OFU period (Table 3). At the end of the ROADMAP study the systolic blood pressure was 127.5±11.0 mm Hg in the placebo group and 124.2±10.7 mm Hg in the olmesartan group (P<0.001). At year 3 of the ROADMAP-OFU study the systolic blood pressure was 134.3±14.0 mm Hg and 134.9±13.3 mm Hg (P=n.s.), respectively, in the 2 groups. The diastolic blood pressure values increased from 74.5±7.5 mm Hg and 72.5±8.1 mm Hg (P=0.001), respectively, to 77.9±9.0 mm Hg and 78.4±8.8 mm Hg (P=n.s.), respectively.

After the ROADMAP study the number of patients reaching the target blood pressure of <140/90 mm Hg decreased from >90% to ≈60% and this was seen even within the first 3 months of the OFU. Blood pressure control was comparable in both OFU groups (Figure 1B).

### Other Treatment Modalities

The use of antidiabetic drugs was comparable between the 2 OFU groups (Table 3). HbA1c levels were also similar (Figure 2), ie, at year 3 7.3±1.4% and 7.3±1.4% (P=n.s.),...
respectively. Use of lipid-lowering drugs (Table 3) and LDL concentrations were comparable between the 2 groups, ie, 2.9 ± 1.0 mmol/L and 2.9 ± 1.0 mmol/L (P = n.s.), respectively, at baseline and year 3.

### Microvascular Events

In 862 (49.0%) OFU patients (436 [49.7%] of the former placebo group and 426 [48.4%] of the former olmesartan group) albumin excretion was measured at least once using albumin dipstick. Microalbuminuria was diagnosed in roughly 20% to 25% of patients after the termination of the ROADMAP study. We used 4 different counting rules (Table 4) to account for different assessment approaches to determine the presence of microalbuminuria. Dependent of the rule used, we found a nonsignificant relative risk reduction of 9.5% to 14.7% and an absolute risk reduction of 1.9% to 2.6% in patients formerly on OM (Table 4A). If we exclude patients who had developed microalbuminuria during the ROADMAP main study, we observed a relative risk reduction of 5.7% to 10.9% and an absolute risk reduction of 1.0% to 1.9% (Table 4B). Analysis of the time to occurrence of microalbuminuria did not change the findings reported in Table 4. No significant difference between the OM and placebo group was observed, when patients with the dipstick classification of likely were included (HR: 0.932, CI: 0.718 to 1.209, P = 0.59) or excluded (HR: 0.890, CI: 0.672 to 1.178, P = 0.41).

Up to year 3 of follow-up the prevalence of microalbuminuria was lower in the former OM group in the total cohort (Figure 3) and in the cohort without patients who had developed microalbuminuria during the main study (Figure 4). Only measurements taken after month 39 revealed no potential benefit.

Additionally at least 1 UACR value was obtained in 231 (former placebo group 113; former OM 118) patients without dipstick results. Adding these patients does not change the overall outcome seen for the reduction of the risk of microalbuminuria based on dipstick testing mentioned above. Of all patients with both dipstick results and UACR measurements, microalbuminuria was found in a total of 134 (24.6%) in the former placebo group and 123 (23.0%) in the former olmesartan group.

The effect of RAS blockade, either with an ACE inhibitor or an ARB on microalbuminuria during the OFU period was investigated in a not prespecified analysis. In patients without RAS blockade at any time during the OFU, 23 (16.5%) former placebo and 26 (19.4%) former olmesartan patients developed microalbuminuria. In patients who received RAS blockade during the OFU, 71 (27.7%) from the former placebo and 65 (24.6%) from the former olmesartan group developed microalbuminuria. The higher incidence of microalbuminuria seen in patients receiving RAS blockade during the OFU is unexpected, but could be partially explained by the fact, that the RAS blockade was started in 17 and 15 patients only after microalbuminuria was diagnosed. If we would add these patients to the group without RAS blockade the incidence of microalbuminuria would increase to 25.6% in the placebo group and 27.5% in the olmesartan group, and decrease in the patients with RAS blockade to 22.6% in the placebo group and 19.9% in the olmesartan group.

### Table 3. Medications Used During the ROADMAP-OFU Study by Former ROADMAP Treatment Group

|                  | ROADMAP Placebo (n=877) | Olmesartan (n=881) | P Value | ROADMAP-OFU Placebo (n=877) | Olmesartan (n=881) | P Value |
|------------------|-------------------------|--------------------|---------|-----------------------------|--------------------|---------|
| Antihypertensives, n (%) | 791 (90.2) | 881 (100) | <0.0001 | 780 (88.9) | 772 (87.6) | 0.3925 |
| RAS inhibitor | 41 (4.7) | 881 (100) | <0.0001 | 530 (60.4) | 554 (62.9) | 0.2908 |
| ACEi | 34 (3.9) | 22 (2.5) | 0.0995 | 279 (31.8) | 272 (30.9) | 0.6713 |
| ARB | 11 (1.3) | 881 (100) | <0.0001 | 292 (33.3) | 322 (36.5) | 0.1524 |
| Olmesartan | 0 (0.0) | 881 (100) | <0.0001 | 46 (5.2) | 51 (5.8) | 0.6176 |
| Beta blocking agent | 536 (61.1) | 470 (53.3) | 0.0010 | 470 (53.6) | 405 (46.0) | 0.0014 |
| Calcium channel blocker | 585 (66.7) | 532 (60.4) | 0.0059 | 398 (45.4) | 381 (43.2) | 0.3674 |
| Diuretic | 487 (55.5) | 416 (47.2) | 0.0005 | 338 (38.5) | 282 (32.0) | 0.0042 |
| Other antihypertensives* | 166 (18.9) | 119 (13.5) | 0.0020 | 117 (13.3) | 94 (10.7) | 0.0849 |
| Antidiabetic agents | 861 (98.2) | 860 (97.6) | 0.4140 | 833 (95.0) | 830 (94.2) | 0.4742 |
| Lipid lowering agents | 495 (56.4) | 488 (55.4) | 0.8573 | 573 (65.3) | 570 (64.7) | 0.7794 |

ACEi indicates angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; OFU, observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

*Other anti-HTN medications = ATC code C02.
New onset of diabetic retinopathy was diagnosed during the OFU in 23 patients (2.6%) of the former placebo group and in 8 patients (0.9%) of the former olmesartan group ($P=0.011$; Table 6).

**Renal Function**

After termination of the ROADMAP study the mean eGFR declined during the OFU from $81.8 \pm 17.5$ to $79.7 \pm 21.3$ mL/min at year 3 in the former placebo group and increased from $78.1 \pm 18.0$ to $79.9 \pm 22.1$ mL/min at year 3 in the former olmesartan group. At the start of the OFU study, ie, at the time of last ROADMAP assessment, the eGFR had been significantly different (Table 1, Figure 5); this difference disappeared during observational follow-up (Figure 5). In both former ROADMAP groups, 1 patient developed end-stage renal disease; doubling of serum creatinine was seen in 6 patients (ie, 0.8% of patients who had been on Olmesartan in the preceding trial) and 7 patients (0.9% of the patients on placebo). Likewise for microalbuminuria the effect of RAS blockade, either with an ACE inhibitor or an ARB on eGFR during the OFU period was investigated in a not-prespecified analysis. In patients from the placebo group who were started on RAS blockade in the OFU we observed a drop in the eGFR, whereas patients who had been on olmesartan formerly and did not receive an RAS blockade in the OFU, we observed the largest increase in eGFR compared with the other groups (Figure 6).

**Cardiovascular Events: Microalbuminuria as a Risk Factor**

One hundred thirty-two patients who had developed microalbuminuria during the ROADMAP study had an $1.8$-fold higher risk to develop cardio-/cerebrovascular complications during the OFU compared to the 1626 patients who had not developed microalbuminuria (15.9% versus 8.5%; $P=0.04$; Table 5). Analysis of the time to occurrence of the cardiovascular event resulted in comparable values (HR: 2.067, CI: 1.305 to 3.274, $P=0.002$). Such increase was observed not only with respect to overall combined events, but also with respect to almost all individual outcome parameters. Congestive heart failure requiring hospitalization (CHF) and transient ischemic attacks (TIA) were statistically significantly more common in the group of OFU patients, who had previously developed microalbuminuria during the ROADMAP study (Table 5).

**Cardiovascular Events: Effect of Former Treatment**

The combined cardio-/cerebrovascular overall event rate was slightly higher in patients who had been on placebo in the...
preceding main study, ie, 86 events (9.8%) compared to 73 events (8.3%) in the former olmesartan group (Table 6). This was not significantly different and accounting for the time to occurrence of the cardiovascular event did not alter this finding (HR: 0.846, CI: 0.619 to 1.156, \(P=0.29\)). Congestive heart failure (12 versus 3; \(P=0.027\)) was more common in the former placebo group and nonfatal strokes (18 versus 7; \(P=0.069\)) showed a trend towards more events. The rates of acute coronary syndrome or coronary revascularization were comparable.

In total 10 fatal events were reported during the ROADMAP OFU (Table 6); 7 deaths occurred in the former placebo and 3 in the former olmesartan group. Out of the 7 fatal events in the former placebo group 2 were of cardiovascular origin (ie, CHD and fatal stroke) and in 2 other events the cause was unknown. In the former olmesartan arm no fatal event was of cardiovascular origin.

**Discussion**

In this observational follow-up study we confirm previous data that the occurrence of microalbuminuria is a good predictor of cardiovascular morbidity. Additionally, our data suggest that a sustained clinical benefit might be seen after treatment with an RAS blocking agent for several years, ie, in the ROADMAP study 40 mg olmesartan for 3.2 years. In an exploratory statistical approach we observed reduction of macrovascular events (significant for stroke and congestive heart failure) as well as a reduction of microvascular events (significant for occurrence of diabetic retinopathy) for patients formerly on OM, with the onset of microalbuminuria also reduced. This benefit in the former olmesartan group was documented for up to 3 years after stopping study medication, even though the use of RAS blocking agents was comparable between both groups during the follow-up.

**Occurrence of Microalbuminuria Predicts Cardiovascular Complications**

This study showed that patients who had developed microalbuminuria already during the ROADMAP study had a 1.8- to 2.0-fold higher risk of cardio-/cerebrovascular events during the 3.3-year observational follow-up period. This observation is consistent with data collected in large cohort studies involving up to 1.2 million persons uniformly confirming the relationship between albuminuria/proteinuria and cardiovascular outcome.11–13 In a large cohort of individuals receiving routine clinical care and at least 1 outpatient measurement a higher risk of death, myocardial infarction, and progression of kidney disease was observed in patients with microalbuminuria (defined as UACR 30 to 300 mg/g) even without overtly abnormal eGFR, ie, >60 mL/min.14 In a recent meta-analysis patients with microalbuminuria had a 50% higher risk of subsequent coronary heart disease (risk ratio 1.47, 95% CI: 1.30 to 1.66) compared with patients without microalbuminuria.
thus confirming that microalbuminuria is a powerful predictor of CVD events. Another recent meta-analysis assessed the relationship between microalbuminuria and the occurrence of stroke, including 12 studies with a total of 48,596 participants and 1,263 stroke events. The presence of microalbuminuria was associated with greater stroke risk (relative risk 1.92; 95% CI, 1.61 to 2.28; *P* < 0.001) after adjustment for established CV risk factors. Our data are consistent with this observation: we observed a trend towards more episodes of congestive heart failure and transient ischemic attacks in patients who had developed microalbuminuria. Extending the results of the above-mentioned meta-analyses of large cross-sectional populations, our data show in a prospective study, that the new onset of microalbuminuria also predicts cardiovascular events within the next couple of years. To our knowledge this has not been demonstrated in the past.

**Figure 3.** Presence of microalbuminuria during the ROADMAP-OFU trial by former ROADMAP treatment groups. Four different counting rules were applied to identify patients with microalbuminuria. *P* < 0.05. OFU indicates observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

**Effect of Olmesartan on Microvascular Events**

In the ROADMAP study we observed a 23% reduction of the “time to onset of microalbuminuria” and an absolute reduction of 1.6% (ie, from 9.8% to 8.2%). During the observational period ≈20% of patients who were tested for albuminuria were at least on one occasion positive for microalbuminuria. The higher incidence of microalbuminuria may in part be explained by the fact that a single elevated urine albumin level was sufficient for the diagnosis of microalbuminuria in the OFU compared with the more stringent criteria in the ROADMAP study where at least 2 out of 3 measurements had to be positive for the classification as “microalbuminuria”. During the OFU an absolute but nonsignificant difference of 1.9% to 2.6% in favor of olmesartan was still found (depending on the counting rule). Even when patients who had developed microalbuminuria...
during the ROADMAP study were excluded, an absolute reduction of 1.0% to 1.9% in favor of patients in the former OM group was still observed. This benefit was seen up to 3.25 years after closure of the ROADMAP study but no longer subsequently. Thus, at least for a limited time, former treatment with olmesartan seemed to have a small effect on the subsequent development of microalbuminuria. We cannot exclude that the therapy with an ACE or ARB during the OFU might have affected these results, as treatment was not standardized with regards to treatment start and stop as well as regarding to drug type and dosage.

Furthermore, in the follow-up study we observed fewer diabetic retinopathy cases in the olmesartan group. This is in agreement with findings in several studies in recent years, which demonstrated that RAS inhibition with an ACE inhibitor or an ARB can prevent development,17 delay progression,18 and even cause regression9,19 of diabetic retinopathy. The ROADMAP OFU study is consistent with this finding and

Figure 4. Presence of microalbuminuria in patients without microalbuminuria during the ROADMAP trial by former ROADMAP treatment groups. Four different counting rules were applied to identify patients with microalbuminuria. OFU indicates observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

Figure 5. eGFR per former ROADMAP treatment group. ***P<0.001. eGFR indicates estimated glomerular filtration rate; OFU, observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.
shows for the first time that treatment with RAS blockers provides sustained benefit—a legacy effect—on the development of diabetic retinopathy.

**Effect of Olmesartan on Renal Function**

In ROADMAP the eGFR declined by an average of 4 to 5 mL/min, whereas a smaller decline of 0 to 1 mL/min was observed in the placebo group. During the OFU period these changes were completely reversible and, intriguingly, we only observed a decline of the eGFR in patients who were newly started on an RAS blockade in the OFU period, whereas patients who were on olmesartan and discontinued RAS blockade had the largest increase in eGFR compared with the other groups. These data strongly suggest that the observed eGFR decline in the olmesartan group during ROADMAP was due to the well-known RAS blockade-associated intra-renal hemodynamic changes and not due to chronic kidney injury. Taking into account the beneficial effect on albuminuria treatment with olmesartan was renoprotective.

![Figure 6. Change in eGFR (mean±SEM) per former ROADMAP treatment group and RAS blockade during OFU period. eGFR indicates estimated glomerular filtration rate; OFU, observational follow up; RAS, renin-angiotensin-system; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.](image)

**Table 5. Occurrence of Cardio- and Cerebrovascular as Well as Other Events During the Longitudinal Follow-Up in Patients With or Without MA During the ROADMAP Study**

| Event                                                                 | MA No (n=1626) | MA Yes (n=132) | Odds Ratio (95%-CI) | P Value |
|-----------------------------------------------------------------------|----------------|---------------|---------------------|---------|
| Cardio-/cerebrovascular morbidity and mortality, n (%)                | 138 (8.5)      | 21 (15.9)     | 1.766 (1.029; 3.030) | 0.039   |
| Cardio-/cerebrovascular morbidity, n (%)                             | 138 (8.5)      | 21 (15.9)     | 1.766 (1.029; 3.030) | 0.039   |
| Cardiovascular morbidity, n (%)                                       | 114 (7.0)      | 17 (12.9)     | 1.607 (0.887; 2.913) | 0.118   |
| Acute coronary syndrome                                               | 40 (2.5)       | 7 (5.3)       | 1.974 (0.814; 4.784) | 0.132   |
| Coronary revascularisation                                            | 38 (2.3)       | 4 (3.0)       | 0.940 (0.290; 3.046) | 0.918   |
| Silent myocardial infarction                                          | 4 (0.2)        | 0 (0.0)       | n.a.                | n.a.    |
| Congestive heart failure*                                              | 11 (0.7)       | 4 (3.0)       | 3.168 (0.877; 11.451) | 0.079   |
| New onset of atrial fibrillation                                      | 36 (2.2)       | 5 (3.8)       | 1.837 (0.662; 5.096) | 0.243   |
| Peripheral vascular disease*                                          | 14 (0.9)       | 2 (1.5)       | 1.449 (0.285; 7.359) | 0.655   |
| Cerebrovascular morbidity, n (%)                                      | 31 (1.9)       | 5 (3.8)       | 2.070 (0.729; 5.881) | 0.172   |
| Non fatal stroke                                                      | 23 (1.4)       | 2 (1.5)       | 1.389 (0.293; 6.594) | 0.679   |
| Transient ischemic attack                                             | 9 (0.6)        | 3 (2.3)       | 3.389 (0.809; 14.207) | 0.091   |
| Cardio-/cerebrovascular mortality*, n (%)                            | 2 (0.1)        | 0 (0.0)       | n.a.                | n.a.    |
| Congestive heart failure                                              | 1 (0.1)        | 0 (0.0)       | n.a.                | n.a.    |
| Fatal stroke                                                          | 1 (0.1)        | 0 (0.0)       | n.a.                | n.a.    |
| Non-CV related mortality, n (%)                                       | 7 (0.4)        | 1 (0.8)       | 1.098 (0.089; 13.507) | 0.942   |
| Not CV related death                                                  | 5 (0.3)        | 0 (0.0)       | n.a.                | n.a.    |
| Death of unknown cause                                                | 2 (0.1)        | 1 (0.8)       | 4.310 (0.301; 61.702) | 0.282   |
| Total mortality, n (%)                                                | 9 (0.6)        | 1 (0.8)       | 0.838 (0.067; 13.507) | 0.891   |
| Other endpoints, n (%)                                                |                |               |                     |         |
| End stage renal disease                                               | 2 (0.1)        | 0 (0.0)       | n.a.                | n.a.    |
| New onset diabetic retinopathy                                        | 27 (1.7)       | 4 (3.0)       | 1.758 (0.551; 5.605) | 0.340   |

CV indicates cardio-/cerebrovascular events; MA, microalbuminuria; n.a., not applicable; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

*Requiring hospital treatment.

*No death due to sudden cardiac death, myocardial infarction or during cardiovascular surgery was reported.
Effect of Olmesartan on Cardio-/Cerebrovascular Events

During the observational follow-up period we observed a trend towards less cardio- and cerebrovascular events in the former olmesartan treatment group. Nonfatal stroke and congestive heart failure were significantly reduced even after closure of the randomized controlled trial, although these significances must be seen in the context of the overall low event numbers and the exploratory character of the OFU analysis. These findings are consistent with the results of RAS blockade in the HOPE and the recently published BENEDICT extension trial.8,20 In both trials administration of an ACE inhibitor for several years showed significantly higher benefit compared with placebo even after the randomized treatment had been stopped and although patients had subsequently received comparable RAS blockade. The results of ROADMAP-OFU provide the first evidence that this is also true for an ARB.

During the observational follow-up period with a mean duration of 3.3 years we found lower morbidity and mortality events—although the event rate was overall low—in patients who had been in the olmesartan arm during the ROADMAP study previously.

Limitations of the Study

The OFU study has several limitations. First of all, due to the observational character of this follow-up study, patients received standard medical care at the discretion of the physician: no standardized study activities were allowed and specifically the events were not assessed in a standardized fashion. As a result, we had to rely on the information provided by the treating physicians. Secondly, more than half of the original ROADMAP study population did not participate in the observational follow-up; nevertheless, comparison of the 2 groups in the OFU study (ie, former Olmesartan and...
placebo patients) showed that the groups were well matched and were not significantly different compared with the whole ROADMAP cohort and the patients who were eligible and chose not to enroll (data not shown). Thirdly, the event rate is relatively low; therefore a chance finding cannot be definitely excluded. In addition, we performed many comparisons, which increased the likelihood of a chance finding. However, we do not believe that this is the case, because almost all events analyzed were less frequent in the former olmesartan group. Importantly, this was not attributable to better treatment during the follow-up period because treatment of blood pressure, diabetes, lipid control, etc., was comparable between the groups. Fourthly, presence of albuminuria was tested only in 1093 patients; 62.2% of the total OFU population. Therefore, our finding of a nonsignificant reduction of microalbuminuria might not be true for the complete study population. Last but not least, we cannot rule out that the observed benefit on micro- and macrovascular events was due to the better blood pressure control during the former ROADMAP study. In the ROADMAP average blood pressure was about 3/2 mm Hg lower in the olmesartan than in the placebo group with a blood pressure of 124.2/72.5 versus 127.5/74.5 mm Hg, respectively, at the last assessment. However, all recent studies could not demonstrate an additional benefit of a blood pressure reduction below 130 mm Hg. Therefore, we believe that the majority of the observed effect in the OFU is a blood pressure independent effect of the former RAS inhibition by olmesartan.

In conclusion, the data from the ROADMAP-OFU study suggests that RAS blockade with olmesartan for several years may cause sustained clinical benefit with respect to microvascular (most noteworthy diabetic retinopathy) and macrovascular complications.

Sources of Funding

The funding source (Daiichi-Sankyo Europe) had no direct influence on the design or conduct of the study. Representatives of the sponsor served as nonvoting members of the Steering Committee. The authors had complete control over the formulation and interpretation of the results and the writing of the manuscript. The work of Menne and Chatzikyrkou is supported by the European Union (HEALTH-2011-278249-EU-MASCARA).

Disclosures

Menne has received speaker fees from Alexion, AstraZeneca, Berlin Chemie AG, Boehringer Ingelheim, Daiichi Sankyo, and Novartis. Ritz has received speaker fees, Consultancy and/or Advisory Board fees from Daiichi-Sankyo, Abbott, Boehringer Ingelheim, Kureha, and Hexal. Ruilope has served as speaker/advisor for Daiichi-Sankyo. Christos Chatzikyrkou has no conflict of interest. Viberti has received Advisory Board fees from Daiichi-Sankyo, GSK, Novartis, Pfizer, and Lecture fees from Guidotti and Malesci. Haller has received Speaker fees, Consultancy and Advisory Board fees, etc from Alexion, AstraZeneca, Berlin Chemie AG, Boehringer Ingelheim, CVRx, Daiichi Sankyo, Novartis, Roche. The University Hospital Hannover has received Research funding from Alexion, CVRx, Daiichi-Sankyo, Novartis, Roche.

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