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

The main outcome of the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study was published in 2011.[1] The ROADMAP study was a randomized, double-blind, prevention study with the primary endpoint "time to first event of microalbuminuria."[1,2] CV and renal events were analyzed as secondary endpoints. In the ROADMAP study 4447 patients with type 2 diabetes with at least 1 CV risk factor and normoalbuminuria were enrolled. The ROADMAP study compared olmesartan medoxomil 40 mg o.d. versus placebo (additional non-RAS anti-hypertensive medication was allowed for patients to reach the blood pressure target of <130/80 mm Hg, consistent with the recommendations at that time).[3] The ROADMAP study documented that during a mean follow-up of 3.2 years after treatment with 40 mg olmesartan significantly reduced the time to onset of microalbuminuria by 23% despite very good blood pressure control in both study groups. This was the scientific rationale for an extended observational follow-up with the aim of investigating whether the ROADMAP OM treatment resulted in potential long-term micro- and macrovascular benefit.

Therefore, after completion of the ROADMAP study, patients were offered to participate in the prespecified observational longitudinal follow-up study (ROADMAP-OFU) to determine whether sustained treatment with the ARB Olmesartan during the ROADMAP study caused long-term sustained beneficial ("legacy") effects. A recent meta-analysis,

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 animal[5,6] and clinical[7–9] 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 (ClincalTrials.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, HbA1$_c$), 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/m^2), 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.

Table 2. Characteristics of ROADMAP-OFU Population and ROADMAP Population That Did Not Participate in the OFU Study

	ROADMAP Patients Not Enrolled in OFU			ROADMAP Patients Enrolled in OFU		
	Placebo (N=1338)	Olmesartan (N=1351)	Total (N=2689)	Placebo (N=877)	Olmesartan (N=881)	Total (N=1758)
Mean age (y) (SD)	57.7 (8.79)	57.6 (9.03)	57.7 (8.91)	57.9 (8.35)	57.8 (8.45)	57.8 (8.40)
Male gender, n (%)	585 (43.7)	608 (45.0)	1193 (44.4)	418 (47.7)	441 (50.1)	859 (48.9)
Mean BMI (SD)	31.0 (4.99)	31.3 (5.00)	31.2 (5.00)	30.6 (4.73)	30.9 (4.79)	30.7 (4.76)
Mean duration of diabetes (months) (SD)	70.9 (73.4)	72.6 (73.05)	71.8 (73.22)	75.6 (71.0)	75.8 (71.2)	75.7 (71.1)
Metabolic syndrome, %	1068 (79.8)	1113 (82.4)	2181 (81.1)	729 (83.1)	721 (81.8)	1450 (82.5)
Anti-diabetic drugs, n (%)	1298 (97.0)	1290 (95.5)	2588 (96.2)	825 (94.1)	839 (95.2)	1664 (94.7)
Anti-hypertensive drugs, n (%)	1003 (75.0)	1018 (75.4)	2021 (75.2)	662 (75.5)	656 (74.5)	1318 (75.0)
Mean SBP (mm Hg) (SD)	135.5 (14.99)	136.4 (15.45)	135.9 (15.23)	136.1 (15.03)	137.2 (15.61)	136.7 (15.33)
Mean DBP (mm Hg) (SD)	80.5 (9.46)	80.7 (9.54)	80.6 (9.5)	80.1 (9.29)	81.0 (9.81)	80.5 (9.56)
Mean HbA1c (%) (SD)	7.7 (1.72)	7.7 (1.72)	7.7 (1.72)	7.6 (1.46)	7.5 (1.43)	7.6 (1.45)
Mean eGFR (mL/min per 1.73 m^2) (SD)	84.7 (17.88)	85.1 (17.15)	84.9 (17.51)	84.7 (16.38)	84.8 (16.8)	84.8 (16.59)
Mean blood glucose (mmol/L) (SD)	9.0 (3.13)	9.0 (3.13)	9.0 (3.13)	9.1 (2.92)	9.1 (2.96)	9.1 (2.94)
Mean total cholesterol (mmol/L) (SD)	5.2 (1.14)	5.2 (1.13)	5.2 (1.13)	5.2 (1.11)	5.1 (1.00)	5.2 (1.06)
Mean HDL (mmol/L) (SD)	1.2 (0.30)	1.2 (0.29)	1.2 (0.30)	1.2 (0.30)	1.2 (0.30)	1.2 (0.30)
Mean LDL (mmol/L) (SD)	3.1 (0.91)	3.0 (0.90)	3.0 (0.90)	3.1 (0.89)	3.0 (0.84)	3.0 (0.86)
Mean triglyceride (mmol/L) (SD)	2.0 (1.23)	2.2 (1.91)	2.1 (1.61)	2.1 (1.34)	2.1 (1.31)	2.1 (1.33)
UACR (mg/g) (SD)	6.0 (6.97)	6.6 (8.34)	6.3 (7.69)	5.7 (6.20)	5.9 (6.24)	5.8 (6.22)
Smoker; >5 cigarettes/day (%)	227 (17.0)	222 (16.4)	449 (16.7)	139 (15.8)	139 (15.8)	278 (15.8)

BMI indicates body mass index; DBP, 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; UACR, urinary albumin creatinine ratio.

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.),

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

	ROADMAP			ROADMAP-OFU		
	Placebo (n=877)	Olmesartan (n=881)	P Value	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)	0.6573	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.

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.
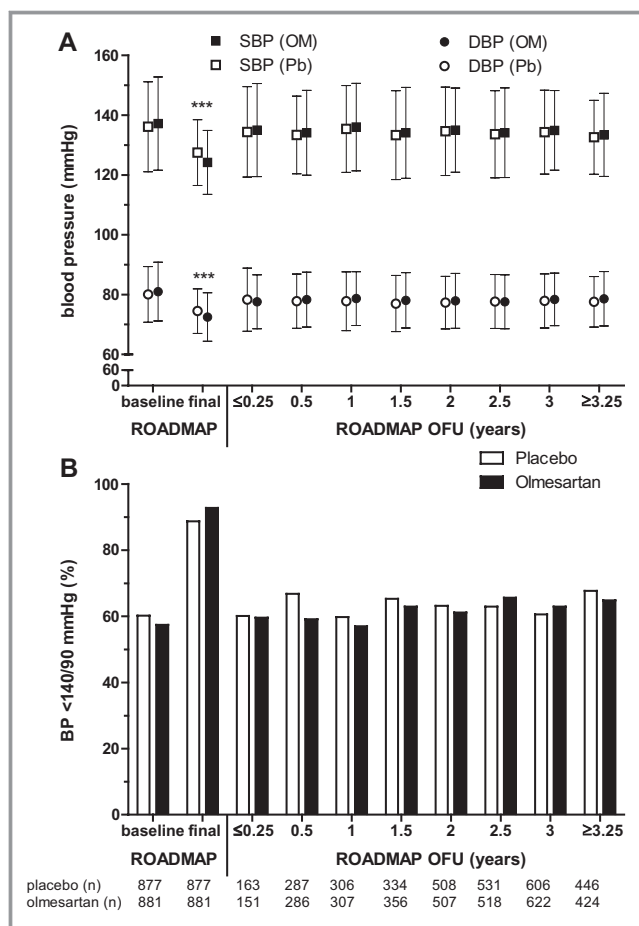
Figure 1. Blood pressure control per former ROADMAP treatment group. A, systolic (SBP) and diastolic (DBP) blood pressure; (B) BP goal <140/90 mm Hg. ***P<0.001. OFU indicates observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.
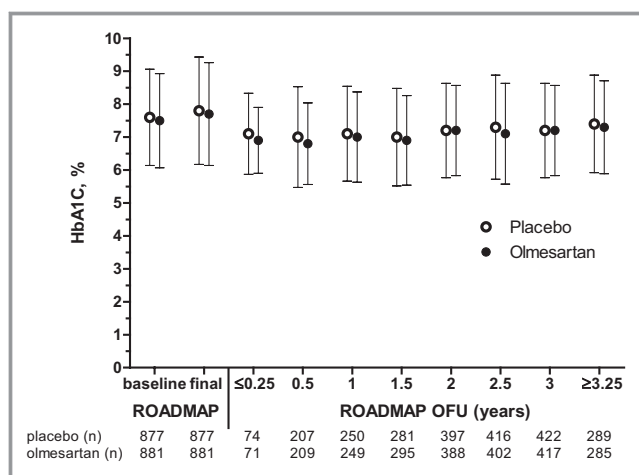
Figure 2. HbA1c control during ROADMAP-OFU. OFU indicates observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

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±17.5 to 79.7±21.3 mL/min at year 3 in the former placebo group and increased from 78.1±18.0 to 79.9±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 (CHD) 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

Table 4. Detection of MA With Albumin Dipstick Tests During the ROADMAP-OFU by Former ROADMAP Treatment Group

	Placebo	Olmesartan	Odds Ratio (95%-CI)	P Value
(A) *Number of patients*	(n=436)	(n=426)		
Counting rule 1: result "likely" taken as positive				
Approach 1: most serious results	119 (27.3)	108 (25.4)	0.905 (0.668; 1.225)	0.5177
Approach 2: most frequent results	98 (22.5)	85 (20.0)	0.860 (0.620; 1.192)	0.3652
	(n=431)	(n=417)		
Approach 1: most serious results	105 (24.4)	91 (21.8)	0.867 (0.629; 1.193)	0.3807
Approach 2: most frequent results	87 (20.2)	74 (17.7)	0.853 (0.605; 1.203)	0.3654
(B) *Number of patients (without MA during ROADMAP study)*	(n=395)	(n=400)		
Counting rule 1: result "likely" taken as positive				
Approach 1: most serious results	94 (23.8)	91 (22.8)	0.943 (0.679; 1.310)	0.7268
Approach 2: most frequent results	76 (19.2)	71 (17.8)	0.906 (0.633; 1.296)	0.5884
Counting rule 2: result "likely" excluded				
	(n=390)	(n=391)		
Approach 1: most serious results	81 (20.8)	74 (18.9)	0.891 (0.626; 1.266)	0.5185
Approach 2: most frequent results	65 (16.7)	60 (15.3)	0.906 (0.618; 1.329)	0.6146

(A) All patients; (B) Excluding patients who had developed microalbuminuria during the ROADMAP study. MA indicates microalbuminuria; OFU, observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

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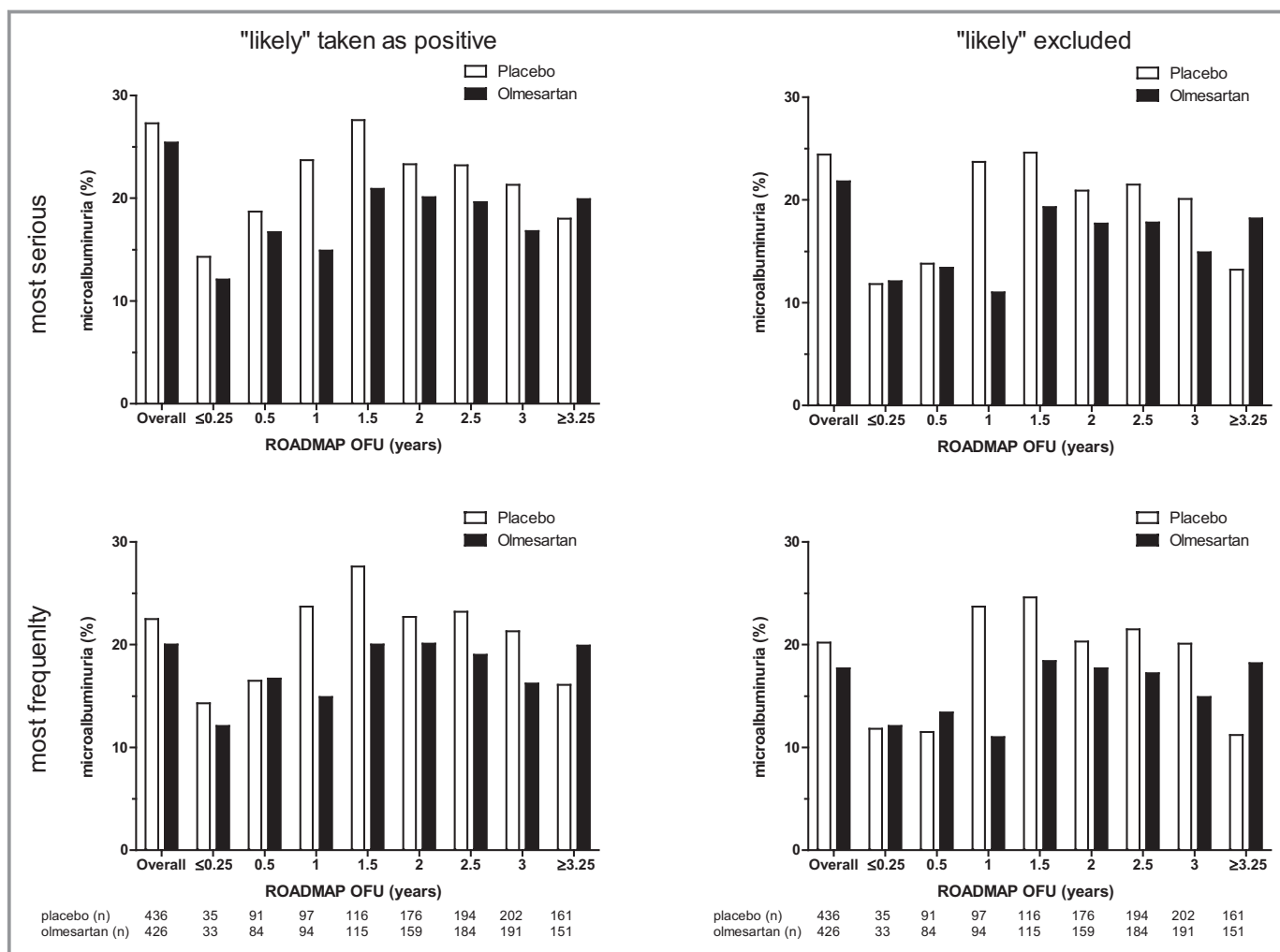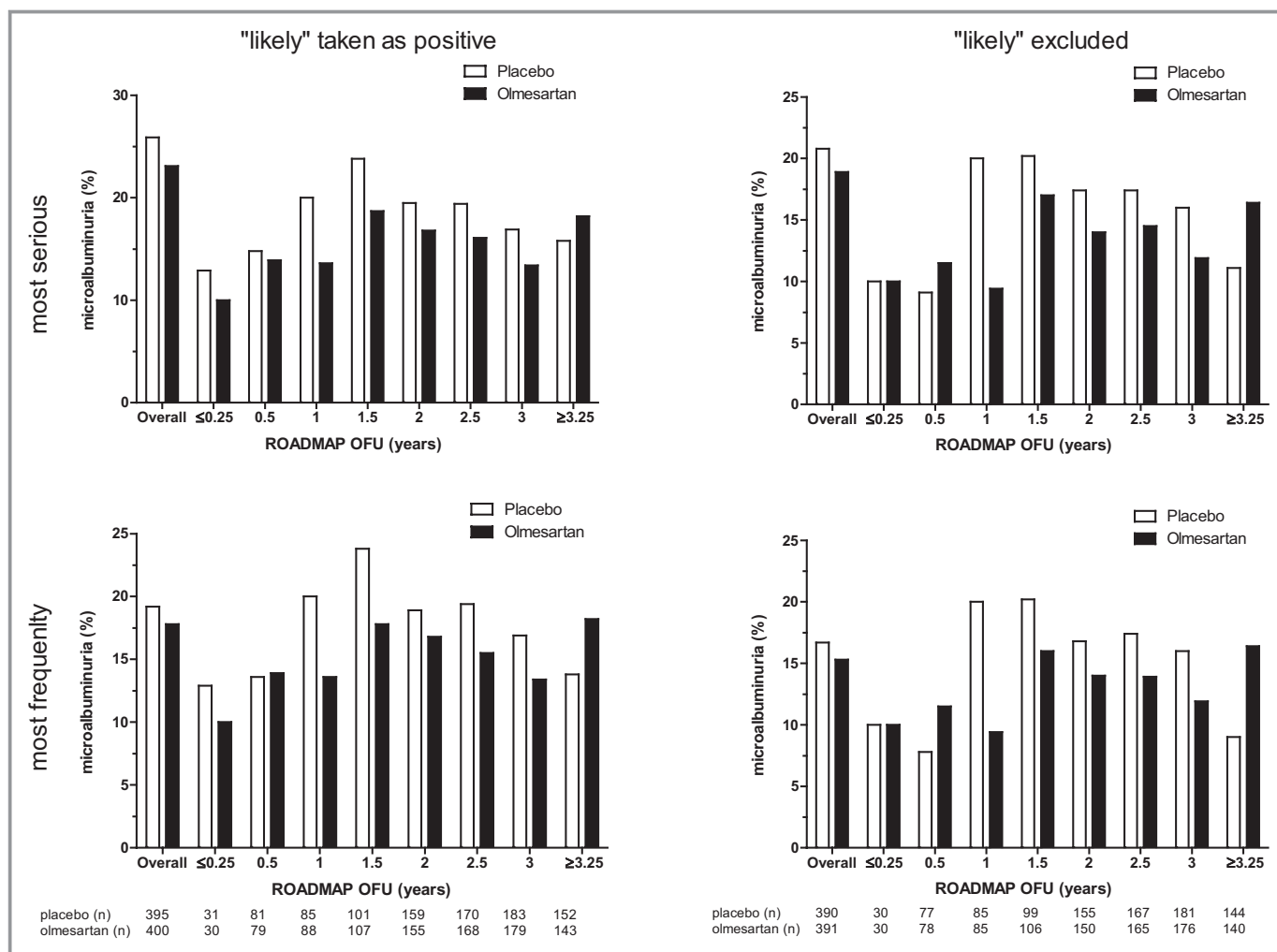
Figure 3. Presence of microalbuminuria during the ROADMAP-OFU trial by former ROADMAP treatment groups. Four different counting rules were applied to identify patients with microalbuminuria. *P<0.05. OFU indicates observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

thus confirming that microalbuminuria is a powerful predictor of CVD events.[15] 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 1263 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.[16] 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.

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

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.

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 regression[9,19] of diabetic retinopathy. The ROADMAP OFU study is consistent with this finding and
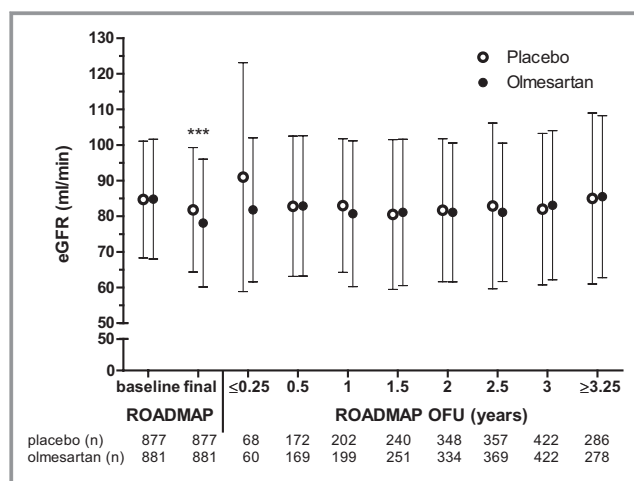
Figure 5. eGFR per former ROADMAP treatment group. ***P<0.001. eGFR indicates estimated glomerular filtration rate; OFU, observational follow up; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.
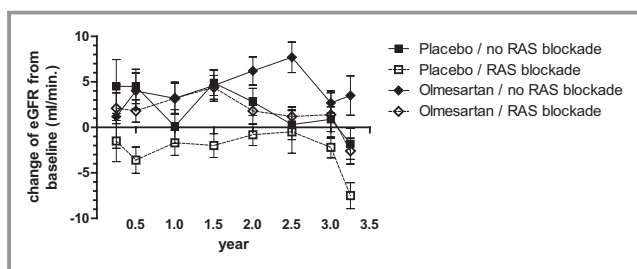
Figure 6. Change in eGFR (mean±SEM) per former ROADMAP treatment group and RAS blockade during OFU period. eGFR indicates estimated glomerular filtration rate; OFU, observational follow up; RAS, renin-angiotensin-system; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention.

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 reno-protective.

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

	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)		
Congestive heart failure	1 (0.1)	0 (0.0)	n.a.	n.a.
Fatal stroke	1 (0.1)	0 (0.0)		
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.

Table 6. Occurrence of Cardio- and Cerebrovascular as Well as Other Events During the Longitudinal Follow-Up in the 2 ROADMAP Treatment Groups

	Placebo (n=877)	Olmesartan (n=881)	Odds Ratio (95%-CI)	P Value
Cardio-/cerebrovascular morbidity and mortality, n (%)	86 (9.8)	73 (8.3)	0.845 (0.604; 1.182)	0.325
Cardio-/cerebrovascular morbidity, n (%)	86 (9.8)	73 (8.3)	0.845 (0.604; 1.182)	0.325
Cardiovascular morbidity, n (%)	71 (8.1)	60 (6.8)	0.829 (0.574; 1.196)	0.316
Acute coronary syndrome	23 (2.6)	24 (2.7)	1.025 (0.566; 1.854)	0.936
Coronary revascularisation	22 (2.5)	20 (2.3)	0.895 (0.476; 1.683)	0.731
Silent myocardial infarction	2 (0.2)	2 (0.2)	0.772 (0.101; 5.903)	0.803
Congestive heart failure*	12 (1.4)	3 (0.3)	0.231 (0.063; 0.846)	0.027
New onset of atrial fibrillation	24 (2.7)	17 (1.9)	0.675 (0.355; 1.281)	0.229
Peripheral vascular disease*	6 (0.7)	10 (1.1)	1.840 (0.645; 5.249)	0.254
Cerebrovascular morbidity, n (%)	22 (2.5)	14 (1.6)	0.668 (0.334; 1.336)	0.254
Non fatal stroke	18 (2.1)	7 (0.8)	0.436 (0.178; 1.067)	0.069
Transient ischemic attack	5 (0.6)	7 (0.8)	1.244 (0.377; 4.105)	0.720
Cardio-/cerebrovascular mortality†, n (%)	2 (0.2)	0 (0.0)		
Congestive heart failure	1 (0.1)	0 (0.0)	n.a.	n.a.
Fatal stroke	1 (0.1)	0 (0.0)		
Non-CV related mortality, n (%)	5 (0.6)	3 (0.3)	0.476 (0.108; 2.109)	0.329
Not CV related death	3 (0.3)	2 (0.2)	0.554 (0.087; 3.515)	0.531
Death of unknown cause	2 (0.2)	1 (0.1)	0.369 (0.030; 4.567)	0.437
Total mortality, n (%)	7 (0.8)	3 (0.3)	0.374 (0.093; 1.505)	0.166
Other endpoints, n (%)				
End stage renal disease	1 (0.1)	1 (0.1)	1.245 (0.060; 26.006)	0.888
New onset diabetic retinopathy	23 (2.6)	8 (0.9)	0.342 (0.149; 0.782)	0.011

CV indicates cardio-/cerebrovascular events; 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.

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Disclosures

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References

1. Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011;364:907–917.

2. Haller H, Viberti GC, Mimran A, Remuzzi G, Rabelink AJ, Ritz E, Rump LC, Ruilope LM, Katayama S, Ito S, Izzo JL Jr, Januszewicz A. Preventing microalbuminuria in patients with diabetes: rationale and design of the randomised olmesartan and diabetes microalbuminuria prevention (ROADMAP) study. *J Hypertens*. 2006;24:403–408.

3. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.

4. Kostis WJ, Thijs L, Richart T, Kostis JB, Staessen JA. Persistence of mortality reduction after the end of randomized therapy in clinical trials of blood pressure-lowering medications. *Hypertension*. 2010;56:1060–1068.

5. Nagai Y, Yao L, Kobori H, Miyata K, Ozawa Y, Miyatake A, Yukimura T, Shokoji T, Kimura S, Kiyomoto H, Kohno M, Abe Y, Nishiyama A. Temporary angiotensin II blockade at the prediabetic stage attenuates the development of renal injury in type 2 diabetic rats. *J Am Soc Nephrol*. 2005;16:703–711.

6. Nakaya H, Sasamura H, Hayashi M, Saruta T. Temporary treatment of prepubescent rats with angiotensin inhibitors suppresses the development of hypertensive nephrosclerosis. *J Am Soc Nephrol*. 2001;12:659–666.

7. Cherney DZ, Zinman B, Kennedy CR, Moineddin R, Lai V, Yang S, Miller JA, Prokopec SD, Boutros PC, Scholey JW, Reich HN. Long-term hemodynamic and molecular effects persist after discontinued renin-angiotensin system blockade in patients with type 1 diabetes mellitus. *Kidney Int*. 2013;84:1246–1253. epub date 2013/2006/2014.

8. Bosch J, Lonn E, Pogue J, Arnold JM, Dagenais GR, Yusuf S. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the hope study extension. *Circulation*. 2005;112:1339–1346.

9. Ruggenenti P, Iliev I, Filipponi M, Tadini S, Perna A, Ganeva M, Ene-Iordache B, Cravedi P, Trevisan R, Bossi A, Remuzzi G. Effect of trandolapril on regression of retinopathy in hypertensive patients with type 2 diabetes: a prespecified analysis of the benedict trial. *J Ophthalmol*. 2010;2010:106384.

10. Chatzikyrkou C, Menne J. Legacy effects of RAS blockade in diabetes mellitus. *Nat Rev Nephrol*. 2013;9:566–568.

11. Tonelli M, Muntner P, Lloyd A, Manns BJ, James MT, Klarenbach S, Quinn RR, Wiebe N, Hemmelgarn BR. Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease: a cohort study. *Ann Intern Med*. 2011;154:12–21.

12. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, Levey AS, de Jong PE, El-Nahas M, Eckardt KU, Kasiske BL, Ninomiya T, Chalmers J, Macmahon S, Tonelli M, Hemmelgarn B, Sacks F, Curhan G, Collins AJ, Li S, Chen SC, Hawaii Cohort KP, Lee BJ, Ishani A, Neaton J, Svendsen K, Mann JF, Yusuf S, Teo KK, Gao P, Nelson RG, Knowler WC, Bilo HJ, Joosten H, Kleefstra N, Groenier KH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular

mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79:1341–1352.

13. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, Tonelli M. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet*. 2010;376:2096–2103.

14. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423–429.

15. Perkovic V, Verdon C, Ninomiya T, Barzi F, Cass A, Patel A, Jardine M, Gallagher M, Turnbull F, Chalmers J, Craig J, Huxley R. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med*. 2008;5:e207.

16. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke*. 2010;41:2625–2631.

17. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, Bilous R, Sjolie AK. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. *Lancet*. 2008;372:1394–1402.

18. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, Drummond K, Donnelly S, Goodyer P, Gubler MC, Klein R. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009;361:40–51.

19. Sjolie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, Bilous R, Chaturvedi N. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. *Lancet*. 2008;372:1385–1393.

20. Ruggenenti P, Porrini E, Motterlini N, Perna A, Ilieva AP, Iliev IP, Dodesini AR, Trevisan R, Bossi A, Sampietro G, Capitoni E, Gaspari F, Rubis N, Ene-Iordache B, Remuzzi G. Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with type 2 diabetes. *J Am Soc Nephrol*. 2012;23:1717–1724.