Diabetologia (2011) 54:2978–2986
DOI 10.1007/s00125-011-2325-z

ARTICLE

Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study

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Received: 3 May 2011 / Accepted: 1 September 2011 / Published online: 13 October 2011
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Abstract
Aims/hypothesis The renal and cardiovascular protective effects of angiotensin receptor blocker (ARB) remain controversial in type 2 diabetic patients treated with a contemporary regimen including an angiotensin converting enzyme inhibitor (ACEI).
Methods We examined the effects of olmesartan, an ARB, on primary composite outcome of doubling of serum creatinine, endstage renal disease and death in type 2 diabetic patients with overt nephropathy. Secondary outcome included composite cardiovascular outcomes, changes in renal function and proteinuria. Randomisation and allocation to trial group were carried out by a central computer system. Participants, caregivers, the people carrying out examinations and people assessing the outcomes were blinded to group assignment.
Results Five hundred and seventy-seven (377 Japanese, 200 Chinese) patients treated with antihypertensive therapy (73.5% [n=424] received concomitant ACEI), were given either once-daily olmesartan (10–40 mg) (n=288) or placebo (n=289) over 3.2±0.6 years (mean±SD). In the olmesartan group, 116 developed the primary outcome (41.1%) compared with 129 (45.4%) in the placebo group (HR 0.97, 95% CI 0.75, 1.24; p=0.791). Olmesartan significantly decreased blood pressure, proteinuria and rate of change of reciprocal serum creatinine. Cardiovascular

E. Imai and J. C. N. Chan contributed equally to this study.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-011-2325-z) contains peer-reviewed but unedited supplementary material, including a list of the ORIENT study investigators, which is available to authorised users.

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death was higher in the olmesartan group than the placebo group (ten vs three cases), whereas major adverse cardiovascular events (cardiovascular death plus non-fatal stroke and myocardial infarction) and all-cause death were similar between the two groups (major adverse cardiovascular events 18 vs 21 cases, all-cause deaths; 19 vs 20 cases). Hyperkalaemia was more frequent in the olmesartan group than the placebo group (9.2% vs 5.3%).
Conclusions/interpretation Olmesartan was well tolerated but did not improve renal outcome on top of ACEI.

Trial registration: ClinicalTrials.gov NCT00141453
Funding: The ORIENT study was supported by a research grant from Daiichi Sankyo.

Keywords Angiotensin receptor blocker · Diabetic nephropathy · Macroproteinuria · Type 2 diabetes

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin II receptor blocker
CVD	Cardiovascular disease
ESRD	Endstage renal disease
HF	Heart failure
IDMC	Independent data monitoring committee
IDNT	Irbesartan Type II Diabetic Nephropathy Trial
MI	Myocardial infarction
ORIENT	Olmesartan Reducing Incidence of End stage renal disease in diabetic Nephropathy Trial
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
SCr	Serum creatinine
TIA	Transient ischaemic attack
UACR	Urinary albumin/creatinine ratio

Introduction

In this global epidemic of diabetes, 60% of affected people come from Asia. Approximately 10% of adults in Japan [1] and Hong Kong [2] have diabetes. Diabetic complications cause premature death and disabilities with reduced productivity and high healthcare costs [3]. Type 2 diabetes is the leading cause of endstage renal disease (ESRD) worldwide [4]. Annually, 15,000 Japanese develop ESRD due to diabetes [5]. In Hong Kong with 6.7 million southern Chinese, 4,268 patients received renal replacement therapy in 1999, that is 627 patients per million [6]. Glycaemic [7] and BP [8] control have been shown to reduce proteinuria and slow decline of renal function. In two landmark studies of type 2 diabetic nephropathy (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [9] and Irbesartan Type II Diabetic Nephropathy Trial (IDNT) [10]), treatment with angiotensin II receptor blockers (ARB) reduced proteinuria, slowed decline of renal function and reduced incidence of ESRD. In the RENAAL subgroup analysis including 17% of its participants of Asian ethnicity, ARB reduced risk of renal outcomes by 35% in Asians [11] and 45% in Japanese [12] compared with 16% in the whole cohort. Despite the high risk of East Asians for diabetic kidney disease, they often tolerate angiotensin-converting enzyme inhibitors (ACEI) poorly due to cough [13]. Furthermore, there are ongoing concerns regarding the risk–benefit ratio of dual therapy with ARB and ACEI in high-risk patients [14].

Objectives

In this randomised, placebo-controlled, multicentre clinical trial named ORIENT (Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial), we examined the renoprotective benefits of olmesartan medoxomil, an ARB, using the composite endpoint of time to the first occurrence of doubling of serum creatinine (SCr), ESRD and death, mostly in the presence of ACEI therapy. The safety of olmesartan and its effect on renal function, proteinuria and cardiovascular outcome was also evaluated.

Methods

Participants The study design was in line with the CONSORT statement [15] and conducted in good clinical practice by experts in nephrology and endocrinology. The study design has previously been described [16]. We enrolled type 2 diabetic patients from Japan and Hong Kong with the following inclusion criteria: (1) age between 30 and 70 years; (2) urinary albumin/creatinine ratio (UACR) >33.9 mg/mmol (>300 mg/g) in the first morning urine sample; (3) serum creatinine (SCr) concentration of 88.40–221.00 μmol/l (1.0–2.5 mg/dl) in women and 106.08–221.00 μmol/l (1.2–2.5 mg/dl) in men. Major exclusion criteria included: (1) type 1 diabetes; (2) history of myocardial infarction (MI) or coronary artery bypass grafting (CABG) within 3 months prior to consent; (3) percutaneous coronary intervention, carotid artery or peripheral artery revascularisation within 6 months; (4) stroke or transient ischaemic attack (TIA) within 1 year; (5) unstable angina pectoris or heart failure (HF) of New York Heart Association functional class III or IV; (6) rapidly progressive renal disease within 3 months prior to consent; (7) severe orthostatic hypotension; and (8) serum potassium level ≤3.5 mmol/l or ≥5.5 mmol/l.

Study design, governance and implementation The trial commenced in 2003 and was approved by the institutional ethics committee concerned. All patients provided written informed consent. In Hong Kong, all patients were treated with ACEI. In 2006 when losartan was approved for use in type 2 diabetic nephropathy with hypertension by the Japanese Ministry of Health, Labor and Welfare, we re-obtained a written informed consent from each patient in Japan to continue to participate in the study. The study was governed by a steering committee, an independent data monitoring committee (IDMC) and an endpoint adjudication committee, all consisting of academics and clinicians independent of the sponsor. The steering committee provided guidance for the overall study design, conduct of the trial, data management and analysis. The endpoint adjudication committee evaluated and classified the primary and secondary outcomes under blinded conditions.

The source data included case report forms, hospital records and laboratory data (e.g. biomarkers, electrocardiogram, images of computerised tomography [CT] scans and MRI). For each specialty (cardiology, neurology and nephrology), two or three experts independently classified all clinical endpoints.

An IDMC comprising a nephrologist, a diabetologist and a statistician, independently monitored the trial for safety and ethical issues with access to assigned codes as indicated. The IDMC was able to discontinue the entire study if an unusually high number of participants developed unexpected severe adverse events or in the unlikely event that unblinding was indicated for clinical decision making. During the entire study period, none of the treatment codes have been unblinded. Daiichi Sankyo monitored the implementation of the trial, validated all source data and performed the analysis as guided by the steering committee. All members of the steering committee had full access to data and prepared the final manuscript. The protocol was approved by regulatory authorities and the ethics review committee at each participating institution.

Interventions During the initial 6-week screening period, patients were treated with placebo and assessed for inclusion and exclusion criteria. Eligible patients were randomly assigned to receive either 10 mg of olmesartan once-daily or placebo. If the target BP of <130/85 mmHg was not achieved 4 weeks after randomisation or at any time thereafter, the dose of olmesartan was increased to 20 mg daily (or placebo), with further titration to 40 mg (or placebo), if necessary, upon which additional antihypertensive agents could be used. These included diuretics, β blockers, calcium channel blockers and α blockers. Every reasonable attempt was made to up-titrate the test drug to the maximum dose, even if target BP was achieved. Use of potassium-sparing diuretics or ARB was prohibited, and addition of ACEI after enrolment was not allowed. Patients treated with ACEI at baseline must continue with the same dosage throughout the study.

Study outcomes and definitions All patients visited the clinic at 2, 4, 8 and 12 weeks, and then returned every 12 weeks throughout the study duration. At each visit, BP was measured and clinical samples were collected for measurement of urinary protein/creatinine ratio and serum levels of creatinine and potassium. All randomised patients including those discontinued from the study for any reason other than death were followed up for ascertainment of primary and secondary endpoints until termination of study.

The efficacy measure was the time to the first event of the primary composite outcome of doubling of SCr, ESRD (SCr >442.01 μmol/l [5 mg/dl]), chronic dialysis, transplantation and all-cause death. SCr was measured at a central laboratory in Japan (SRL, Tokyo, Japan). The secondary composite outcome included: (1) a composite endpoint of first occurrence of any of the following events: cardiovascular death, non-fatal stroke except for TIAs, non-fatal MI, hospitalisation for unstable angina, hospitalisation for HF, revascularisation of coronary, carotid or peripheral arteries, lower extremity amputation; (2) change in proteinuria; (3) rate of decline of SCr reciprocal (1/SCr).

Randomisation and blinding After written informed consent was obtained and following the run-in period, eligible patients were randomised into olmesartan group or placebo group by the registration centre in Japan (EPS, Tokyo, Japan) through fax contact. The centre assigned each patient by the dynamic allocation method, depending on whether or not they were using ACEIs, further stratified by UACR and SCr. The proportion of patients included in each category was similar between the olmesartan and placebo groups.

All persons involved in the study were unaware of the drug assignments, except for the person in charge of drug assignment who was not involved in the study. The IDMC examined the data in a blinded fashion, except for serious adverse events for which a causal relationship with the study drug cannot be ruled out.

Sample-size estimation We assumed the primary endpoint in this study, defined as the composite renal event rate, to be 0.583 events/patient during an average 4-year follow-up period in the placebo group. The assumed event rate was calculated based on the results from Japanese patients in the RENAAL Study [11] (event rate, 34/52=0.654 with an average follow-up period of 3.4 years). We assumed a 30% risk reduction with baseline ACEI treatment [17]. Therefore, the event rate of the placebo group with baseline ACEI treatment was estimated to be 0.583 with an average follow-up period of 4 years. On the other hand, the event rate of the olmesartan group with ACEI treatment was assumed to be

0.434, as we hypothesised an additional 35% risk reduction in the olmesartan group compared with the placebo group. Based on these assumptions, 172 patients were needed in each treatment group to detect a statistically significant difference between treatment groups using the logrank test with α=0.05 (two-sided) and $1-\beta$=0.80. Assuming that fewer than 15% of patients would be lost to follow-up, the number of patients was determined to be 200 per group.

Statistical analysis All analyses of the outcomes were conducted under the intention-to-treat principle. The Cox regression model was applied to estimate the HR between treatment groups with 95% CI for the renal and cardiovascular composite event rates [18]. The covariates in the model selected based on review of blinded data were (1) UACR and SCr at baseline and regions (Japan/Hong Kong) for the renal composite event rate, and (2) baseline UACR and age for cardiovascular composite event rate.

After unblinding, approximately twofold more patients assigned to the olmesartan group were found to have history of cardiovascular disease (CVD) than in the placebo group (60 in olmesartan group vs 33 in placebo group, Table 1), which was a strong prognostic factor for cardiovascular outcome. Thus, this variable was included as an additional covariate in the model of composite cardiovascular event rate. We also adjusted for BP differences between the two groups by including the mean arterial pressure during treatment as a time-dependent covariate in the Cox model for composite event rates. The Kaplan–Meier method was used to estimate the cumulative event rate by treatment groups [19].

The linear mixed effect model was used to compare the trend in the percentage change of urinary protein/creatinine ratio and trend in the change in 1/SCr between treatment groups. Consistency of treatment effects in prespecified subgroups was explored by Cox regression model with tests for interaction. Serious adverse events and discontinuation of the study drug due to adverse event were summarised. All statistical tests were two-sided with 0.05 significance level. Statistical analyses were performed using SAS version 8.2.

Results

Patients From May 2003 to July 2005, 857 type 2 diabetic patients were screened at 74 centres in Japan and three centres in Hong Kong with a final enrolment of 577 patients (377 Japanese and 200 Chinese) (Electronic supplementary material [ESM] Fig. 1). Eligible patients were randomised to receive either olmesartan or placebo using a central allocation system based in Japan. We stopped the study early in February 2008 according to the recommendation of the IDMC, which indicated that the primary renal events had reached the expected rate. Eleven patients were excluded from the final analysis due to protocol violation from the viewpoint of good clinical practice. Amongst the analysed patients (n=566), 282 received olmesartan and 284 received placebo in addition to conventional antihypertensive therapy. Of these, 414 (73.1%) patients treated with ACEI continued with the same dosage throughout the study period, which lasted 3.2 (0.6)years (mean [SD]). Both groups had similar clinical profiles except for a higher percentage of CVD in the olmesartan group (Table 1).

BP At baseline, 93.8% of patients were receiving antihypertensive treatment (Table 1). In the olmesartan group, BP fell from 141.7/77.8 mmHg at baseline to 137.5/75.1 mmHg at week 12 and to 131.8/72.2 mmHg at week 144. In the placebo group, BP fell from 140.8/77.2 mmHg to 140.3/76.6 mmHg at week 12 and to 136.6/73.6 mmHg at week 144 (ESM Fig. 2). Time-averaged differences of systolic and diastolic BP between the olmesartan and placebo groups were 2.8 (1.0) mmHg and 1.6 (0.6) mmHg, respectively ($p<$ 0.01). The daily dose of olmesartan ranged from 10 to 40 mg, with 49.1%, 60.3% and 63.4% of patients receiving 40 mg at weeks 12, 48 and 144, respectively.

Primary outcome The primary composite outcome occurred in 116 patients in the olmesartan group (41.1%) and 129 patients in the placebo group (45.4%) (Fig. 1). The HR for primary renal composite outcome in the olmesartan group was 0.97 (0.75, 1.24; p=0.791) with HR 1.02 (0.79, 1.32; p=0.852) after adjustment for BP (Table 2). The neutral effect of treatment was consistent across all prespecified subgroups.

Secondary outcome The composite secondary cardiovascular outcome occurred in 40 olmesartan-treated patients (14.2%) and 53 placebo-treated patients (18.7%) with HR 0.73 (0.48, 1.09; p=0.126) (Fig. 2). In a post hoc analysis, HR was decreased to 0.64 (0.43, 0.98; p=0.039) after adjusting for unbalanced distribution of history of CVD at baseline (Table 3). HR was changed little after adjusting for BP (0.66 [0.43, 1.00; p=0.049]). The HR in cardiovascular outcome was consistent in patients treated with or without ACEI.

In the placebo group with a baseline value of proteinuria of 231.9 mg/mmol Cr, median percentage changes from baseline were +12.6% at week 12, +6.9% at week 48 and −3.1% at week 144. In the olmesartan group with a baseline value of proteinuria of 247.7 mg/mmol Cr, the corresponding figures were −19.5% at week 12, −20.0% at week 48 and −24.9% at week 144 (Fig. 3, p=0.005). The trend in the change in 1/SCr was different between the treatment and placebo groups ($p<$0.001). The median yearly rate of change of 1/SCr was −0.933 (interquartile

Table 1 Baseline characteristics of type 2 diabetic patients with overt proteinuria and renal insufficiency treated with antihypertensive drugs including angiotensin converting enzyme inhibitor randomised to receive either olmesartan or placebo treatment for a mean period of 3.2 years

Characteristics	Olmesartan (n=282)	Placebo (n=284)
Age (years)	59.1±8.1	59.2±8.1
Japanese/Chinese, *n*	182:100	184:100
Male sex, *n* (%)	199 (70.6)	192 (67.6)
Smoker, *n* (%)	72 (25.5)	72 (25.4)
Weight (kg)	66.7±13.6	66.1±12.0
Body mass index (kg/m^2)	25.3±4.2	25.3±3.8
Systolic blood pressure (mmHg)	141.7±17.0	140.8±18.0
Diastolic blood pressure (mmHg)	77.8±10.4	77.2±10.6
UACR (mg/mmol)	192.3 (87.1–339.4)	191.2 (98.4–352.9)
Urinary protein/creatinine ratio (mg/mmol)	247.7 (112.0–437.8)	231.9 (124.4–429.9)
Serum creatinine (μmol/l)	143.21±28.29	143.21±30.94
Serum potassium (mmol/l)	4.61±0.43	4.61±0.41
HbA_{1c}		
%	7.11±1.20	7.05±1.24
mmol/mol	57.1±12.5	56.4±12.9
Total cholesterol (mmol/l)	5.41±1.38	5.36±1.18
Blood haemoglobin (g/l)	124±20	121±19
Uric acid (mmol/l)	434.24±95.18	428.29±89.23
Medical history, *n* (%)		
Diabetic retinopathy	228 (80.9)	233 (82.0)
Diabetic neuropathy	144 (51.1)	154 (54.2)
Cardiovascular disease	60 (21.3)	33 (11.6)
MI	11 (3.9)	5 (1.8)
Coronary revascularisation	24 (8.5)	8 (2.8)
HF	12 (4.3)	9 (3.2)
Peripheral arterial disease	33 (11.7)	19 (6.7)
Stroke or TIA	41 (14.5)	42 (14.8)
Severe orthostatic hypotension	3 (1.1)	5 (1.8)
Medications, *n* (%)		
Insulin	139 (49.3)	153 (53.9)
Oral glucose-lowering drugs	165 (58.5)	175 (61.6)
Lipid regulating drugs	155 (55.0)	149 (52.5)
Erythropoietin	10 (3.5)	6 (2.1)
Aspirin	58 (20.6)	55 (19.4)
Antihypertensive agents	262 (92.9)	269 (94.7)
Diuretics	108 (38.3)	99 (34.9)
Calcium channel blockers	186 (66.0)	198 (69.7)
ACEI	205 (72.7)	209 (73.6)
α Blockers	41 (14.5)	41 (14.4)
β Blockers	54 (19.1)	42 (14.8)
Others	37 (13.1)	38 (13.4)

Data are means±SD, *n* (%) or median (interquartile range)

range (IQR) −1.934 to −0.419) l mmol^{-1} year^{-1} in the olmesartan and −1.164 (IQR −1.976 to −0.575) l mmol^{-1} year^{-1} in the placebo group (Fig. 4). We further categorised patients by their median 1/SCr slope. In patients with accelerated rate of decline of renal function who had 1/SCr slope greater than the median, the slope in olmesartan-treated patients overlapped with the placebo (Fig. 4). More than 90% of renal outcomes occurred in patients with steep slope of 1/SCr who had higher BP and heavier proteinuria at baseline than those with less accelerated rate of decline of 1/SCr.

Safety Serious adverse events occurred in 146 olmesartan-treated patients (51.8%) and 169 placebo-treated patients

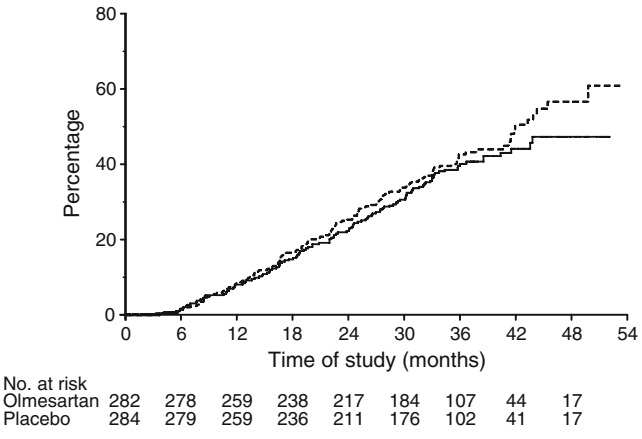

Fig. 1 Kaplan–Meier analysis of the time to primary composite renal endpoint in type 2 diabetic patients with overt proteinuria and renal insufficiency. Solid line, olmesartan; dashed line, placebo

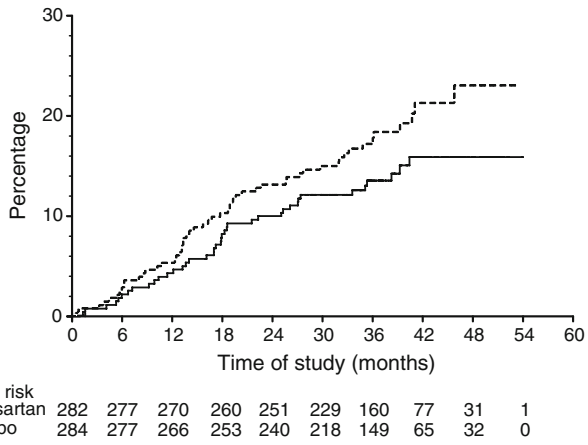

Fig. 2 Kaplan–Meier analysis of the time to secondary composite cardiovascular endpoint in type 2 diabetic patients with overt proteinuria and renal insufficiency. Solid line, olmesartan; dashed line, placebo

(59.5%). In total, 73 (25.9%) olmesartan-treated patients and 64 (22.5%) placebo-treated patients were discontinued before study completion due to adverse events (ESM Table 1). Cardiovascular death was higher in the olmesartan group than the placebo group (ten vs three cases), whereas major adverse cardiovascular events (cardiovascular death plus non-fatal stroke and MI) and all-cause death were similar between the two groups (major adverse cardiovascular events 18 vs 21 cases, all-cause deaths; 19 vs 20 cases). Discontinuation rate due to hyperkalaemia was higher in the olmesartan group than the placebo group (26 [9.2%] vs 15 [5.3%]). The respective rates were 11.7% vs 7.2% in the ACEI-treated patients and 2.6% vs 0% in the non-ACEI-treated patients. None of the patients required acute dialysis in the first 6 months of the study, and only one patient (0.4%) in each group was discontinued due to acute renal failure during the study period.

Discussion

In this study, we enrolled Asian patients with clinical profiles comparable to those in RENAAL, with the majority of them receiving ACEI, and treated them intensively with contemporary regimen targeting a BP <130/85 mmHg. This was compared with a mean systolic BP of >140 mmHg during the entire study period of RENAAL. Although the end-of-study BP was similar between the olmesartan and placebo groups, there was a difference of 2.8 mmHg in systolic BP and 1.6 mmHg in diastolic BP during the treatment period, in favour of olmesartan. After 3.2 years, treatment with olmesartan reduced proteinuria and slowed decline of renal function after adjustment for BP differences. However, HR of composite renal outcome was 1.02 after adjustment for BP, suggesting that olmesartan did not provide additional beneficial effect on renal outcome. Although olmesartan did not reduce cardiovascular outcome adjusted by prespecified SCr and UACR, it reduced risk of cardiovascular outcomes by 34% independent of ACEI treatment after further adjustment for BP and imbalanced distribution of history of CVD at baseline between the two groups in a post hoc analysis.

Renal effects of olmesartan The participants of ORIENT had near optimal BP, serum cholesterol and glycaemic control compared with those enrolled in RENAAL [9].

Table 2 HR of primary composite renal outcome in type 2 diabetic patients with overt proteinuria and renal insufficiency treated with olmesartan or matching placebo during a 3.2 year study period

Outcome	*n* (%)		Olmesartan vs placebo
	Olmesartan	Placebo	HR (95% CI) (covariates: SCr, ACR and region)
All patients group (olmesartan *n*=282, placebo *n*=284)			
Renal composite outcome	116 (41.1)	129 (45.4)	0.97 (0.75, 1.24)[†]
Doubling of SCr	106 (37.6)	120 (42.3)	0.94 (0.73, 1.23)
ESRD	74 (26.2)	78 (27.5)	1.08 (0.78, 1.49)
Death from any cause	19 (6.7)	20 (7.0)	0.99 (0.53, 1.86)

[†] $p=0.791$

Table 3 HR of secondary composite cardiovascular outcomes in type 2 diabetic patients with overt proteinuria and renal insufficiency treated with olmesartan or matching placebo during a 3.2 year study period

Outcome	*n* (%)		Olmesartan vs placebo	
	Olmesartan	Placebo	HR (95% CI) (covariates: ACR and age)	Adjusted HR (95% CI) (covariates: ACR, age and cardiovascular history)
All patients group (olmesartan *n*=282, placebo *n*=284)				
Cardiovascular composite outcome	40 (14.2)	53 (18.7)	0.73 (0.48, 1.09)†	0.64 (0.43, 0.98)‡
Cardiovascular death	10 (3.5)	3 (1.1)	3.38 (0.93, 12.29)	2.81 (0.76, 10.38)
Non-fatal stroke	8 (2.8)	11 (3.9)	0.73 (0.29, 1.82)	0.73 (0.29, 1.83)
Non-fatal myocardial infarction	3 (1.1)	7 (2.5)	0.43 (0.11, 1.66)	0.45 (0.11, 1.75)
Hospitalisation with unstable angina	5 (1.8)	3 (1.1)	1.67 (0.40, 6.98)	1.37 (0.31, 6.00)
Hospitalisation with heart failure	18 (6.4)	25 (8.8)	0.71 (0.39, 1.30)	0.59 (0.32, 1.10)
Coronary, carotid or peripheral revascularisation	8 (2.8)	21 (7.4)	0.37 (0.16, 0.84)	0.35 (0.15, 0.80)
Amputation	4 (1.4)	0 (0.0)	– (–)	– (–)

† p=0.126, ‡ p=0.039

Baseline HbA_{1c} of patients in ORIENT and RENAAL were 7.1% (57.0 mmol/mol) and 8.5% (69.4 mmol/mol), respectively. Baseline total cholesterol and mean systolic BP were lower by 19.7 mg/dl (0.51 mmol/l) and 12 mmHg in ORIENT compared with RENAAL patients [20]. Despite near optimal management of risk factors and use of ACEI in most patients, treatment with olmesartan further attenuated proteinuria and slowed decline of renal function estimated by 1/SCr compared with placebo. These beneficial renal effects of olmesartan were in agreement with previous findings [21–25]. Despite these favourable renal responses, olmesartan did not reduce the composite renal endpoint in the whole group. On subgroup analysis, the majority of renal endpoint occurred in patients with accelerated decline in renal function in whom treatment with olmesartan was similar to placebo. Taken together, these findings suggest that treatment with olmesartan did not confer additional renoprotection especially in patients with rapidly declining renal function, although its effects in patients with less severe renal impairment require further exploration.

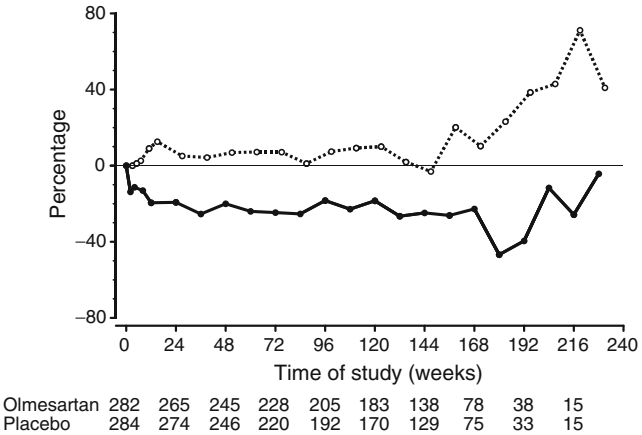

Fig. 3 Changes in proteinuria expressed as percentage change of urinary protein/creatinine ratio from baseline during treatment with olmesartan or placebo in type 2 diabetic patients with overt proteinuria and renal insufficiency. Solid line, black circles, olmesartan; dashed line, white circles, placebo. p=0.005

Cardiovascular effects of olmesartan In the primary analysis, we were unable to confirm the cardiovascular protective effects of olmesartan, which was a predefined secondary endpoint. Although olmesartan-treated patients had numerically fewer MACE (cardiovascular death plus non-fatal stroke and MI) than the placebo group (18 vs 21 cases), our study did not have sufficient power to conclude the effects of olmesartan on cardiovascular outcomes. The amputations that occurred in the olmesartan group were limited to toes.

Clinical trials that examined cardiovascular protective effects of ARB alone or in combination with ACEI have

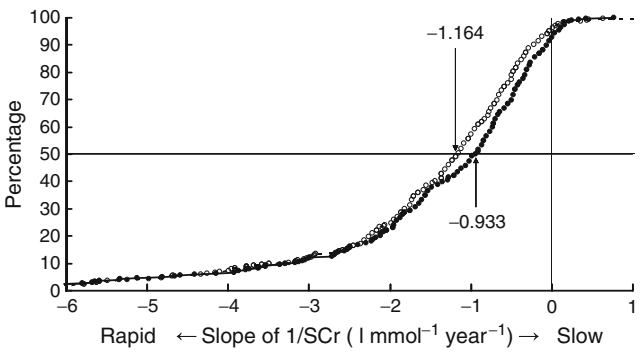

Fig. 4 Cumulative frequency distribution of yearly rate of change of 1/SCr. The two arrows refer to the median values in the placebo or olmesartan groups. Black circles, olmesartan; white circles, placebo

yielded inconsistent results. In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) [26] and the Valsartan in Acute Myocardial Infarction (VALIANT) [27], combination of ACEI and ARB showed neutral effect compared with ACEI alone. In the VAL-HeFT (Valsartan Heart Failure Trial) [28] and the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM)-added [29], a combination of ACEI and ARB was superior to ACEI alone. However, all these studies enrolled only a small number of patients with overt diabetic nephropathy. In RENAAL, which included only type 2 diabetic patients with overt nephropathy [9], losartan alone reduced HF and marginally reduced MI rate. In IDNT [10], irbesartan alone did not confer cardiovascular protection compared with placebo or amlodipine. Taken together, although our results may support possible cardiovascular benefits of combined therapy of ARB and ACEI in type 2 diabetic patients with overt proteinuria and moderate renal insufficiency, larger randomised clinical studies will be needed to confirm these findings.

Safety of olmesartan in patients treated with ACEI Patients in ORIENT had frequent hospitalisations with similar rates between the two groups. Approximately 20% of patients had premature discontinuation due to adverse events with a higher rate of hyperkalaemia in the olmesartan than the placebo group (9.2% vs 5.3%). There were ten cardiovascular deaths (3.5%) in the olmesartan group and three (1.1%) in the placebo group, but none of these adverse events were related to hyperkalaemia. Considering the similar number of all-cause deaths (19 [6.7%] in olmesartan vs 20 [7.0%] in placebo) in both groups, the excess cardiovascular death in the olmesartan group was attributed to the twofold higher rate of past history of CVD in the olmesartan group. The rates of MACE were similar between the two groups, with a tendency of lower cardiovascular outcome rates in the olmesartan group. None of the enrolled patients required acute dialysis in the first 6 months of the study, and only one patient (0.4%) in each group developed acute renal failure during the study period.

Limitations The study has several limitations. First, there was an imbalance of preexisting CVD between the olmesartan and placebo group. The patients with preexisting CVD should be allocated evenly in each group if we primarily analysed cardiovascular outcomes. Despite this imbalance in CVD, it has not affected our analysis on primary renal outcome. Second, cardiovascular outcome was a composite of several events including HF and peripheral arterial disease. Third, the study was underpowered to make a confident statement of safety for cardiovascular mortality as discussed above.

Conclusion

In type 2 diabetic patients with overt nephropathy and renal insufficiency receiving concomitant antihypertensive agents including ACEI, treatment with olmesartan reduced proteinuria and BP but did not further improve renal outcomes. Further study is recommended to confirm the beneficial effect of olmesartan on cardiovascular outcome.

Acknowledgement The ORIENT study was supported by a research grant from Daiichi Sankyo.

Contribution statement EI had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. EI, JCNC, TY, SI, MH, and HM contributed to the study concept and design, and to the interpretation of data, and FK contributed to the analysis of the data. EI, JCNC, TY and FK drafted the manuscript, and SI, MH and HM critically reviewed the manuscript for intellectual content. EI, JCNC, TY, FK, SI, MH and HM gave final approval of the version to be published.

Duality of interest E. Imai, J.C.N. Chan, S. Ito, M. Haneda and H. Makino have received consultancy fees for attending committee meetings. T. Yamasaki and F. Kobayashi are employees of Daiichi Sankyo.

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