scenario

あなたは病院・診療所薬剤師 P です。
60 歳の男性 A さんは体重 74kg、身長 175cm、高血圧、脂質異常症、糖尿病で内服加療中です。

前月の処方内容:
1 日 2 回朝夕食後:
　グリベンクラミド錠 5mg、メトホルミン錠 500mg、オルメサルタン錠 10mg、ニフェジピン CR 錠 40mg
1 日 1 回ねる前:
　アトロバスタチン錠 5mg、ドキサゾシン錠 1mg
1 日 1 回朝食後:
　ピオグリタゾン錠 15mg、アテノロール錠 25mg

今月の検査値:
BP 140-150/85-90 mmHg、HbA1C 6.5-7.4 %（NGSP 基準値 4.6-6.2% ）、LDL 95-105 mg/dl、
eGFR 73-79ml/min、血清 Cr 0.7-0.8mg/dl（基準値 0.31～1.10mg/dL）、
微量アルブミンのクレアチニン補正値 15-25mg/gCr（基準値 10.0 以下 mg/g･Cr）

A さんはここ数回、家庭血圧も高めに推移しています。
今月の処方から、オルメサルタン錠が 20mg に増量されていました。

P　「今日から夜のオルメサルタン錠が追加になっていますね？ 朝の血圧が高かったんでしょうか？」
A さん「そうなんだ～ 朝の血圧が高くてね･･･。」
P　「オルメサルタン錠が夕食後に追加されていますので、朝の血圧のモニタリングをお願いしますね。」

あなたはお薬の説明が終わってから、ふと、以前から正常アルブミン尿高値だったな･･･と思い出しました。
自分のお薬の説明の内容が、血圧に関してだけでよかったのかが気になりました。
そこで、オルメサルタンの海外臨床試験で、2 型糖尿病患者の糖尿病腎症の早期予防を評価した試験が、
話題になったのを思いだし、ROADMAP 試験を読んでみることにしました。

Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes.
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; ROADMAP Trial Investigators.
N Engl J Med. 2011 Mar 10;364(10):907-17.
PMID: 21388309

治療 Goal（治療目標）
① 生存率の向上
② 脳心血管イベント発症予防
③ 糖尿病性腎症発症予防
　厳格な血糖コントロール（目標 HbA1c 6.9% 未満）
　ACEI や ARB を中心とした降圧療法により，130／80mmHg 未満に管理
④ 予後に影響のある危険因子（HL、HU、smoking、食事、運動不足）を最小限にする
⑤ QOL の向上

■ Scenario の PICOT（Time は観察期間など）

P:
60 歳の男性 A さんは体重 74kg、身長 175cm、高血圧、脂質異常症、糖尿病で内服加療中

血圧高め、正常高値アルブミン尿（15～30mg/gCr）

E:
Non dipper HT の治療
オルメサルタンの増量

C:
オルメサルタンの維持

O:
・ 糖尿病腎症の発症は防げるか？
・ 慢性腎不全や腎透析を防げるか？
・ 心イベントの発症率は低下するか？

T: 15-20 年くらい

E: 肝代謝型 DPP4 阻害剤の追加

C: SU 剤の追加

O:
・ 糖尿病腎症の発症は防げるか？
・ 慢性腎不全や腎透析を防げるか？
・ 心イベントの発症率は低下するか？

T: 15-20 年くらい

■ 論文の PECOT

P: 18～75 歳 2 型 DM、BP 基準なし（正常値含む）

Inclusion criteria:
□ presence of type 2 diabetes
(FBG ≥7.0 mmol/l and HbA1c ≥6.5%,
or treatment for diabetes);
□ normoalbuminuria
(UACR [mg/g]:≦35 for females,≦25 for males);
□ At least one additional cardiovascular risk factor including
-Lipid disorder defined as TCh >5.2 mmol/l
or treatment for HL,
- HDL-cholesterol <1.1 mmol/L,
- Triglycerides >1.70 mmol/L;
- Hypertension defined as
SBP ≥130 mmHg and/or DBP≥80 mmHg
or antihypertensive medication;
- Obesity BMI ≥28 kg/m2)
- High waist circumference
(>88 cm for females, >102 cm for males);
- Smoking more than five cigarettes per day.

Exclusion criteria:
□ Creatinine clearance <30 mL/min.
□ Renal–vascular disease
□Recent cardiovascular event in the last 6 months
□ Severe hypertension
(SBP >200 mmHg and/or DBP >110 mmHg)
□ Treatment with ARB or ACE inhibitors
within 6 month prior to screening

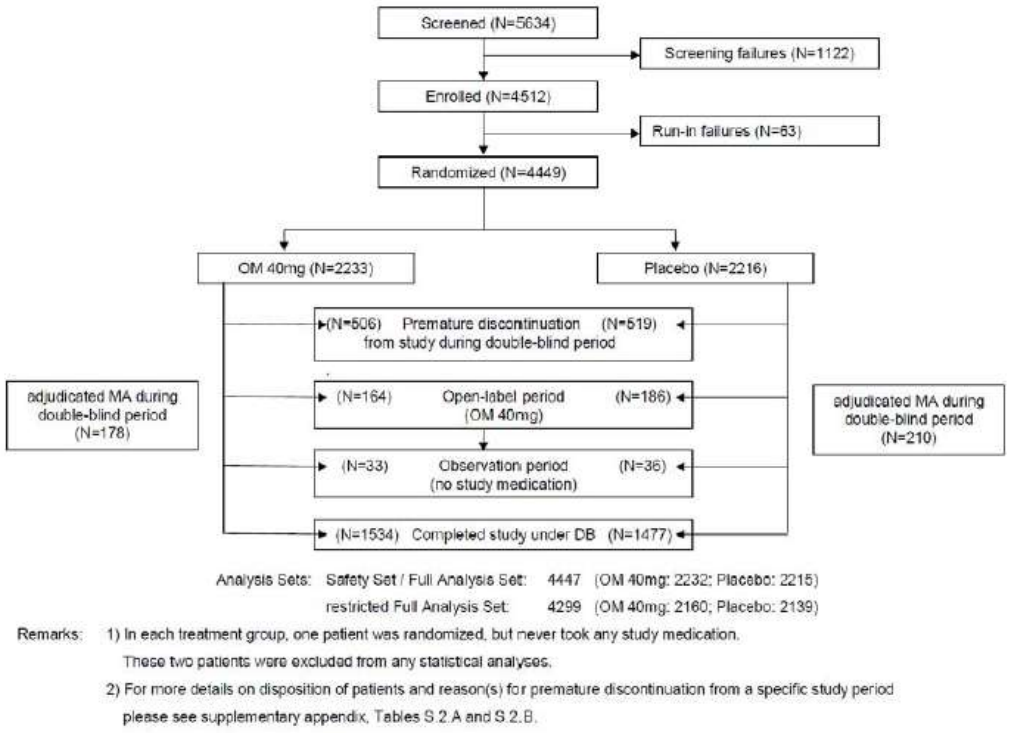
E: olmesartan 40mg/日群（2,232 例）
C: プラセボ群（2,215 例）。
※二重盲検試験期間に，＜130/80mmHg 達成のための ACE 阻害薬，ARB 以外の降圧薬使用は両群可
※試験終了時に，24h 自由行動下血圧測定を 568 例（olmesartan 群 270 例 vs プラセボ群 298 例）で実施。

O: primary endpoints：Microalbuminuria
Secondary endpoints：
Renal Function
Composite of cardiovascular complications or
death from cardiovascular causes
Composite of death from any cause
Death from cardiovascular causes
Death not related to cardiovascular causes
Death from unknown cause
Composite of death from cardiovascular causes
Sudden cardiac death
Death due to fatal myocardial infarction
Evidence of recent MI on autopsy
Death due to congestive heart failure
Death during or after PTCA or CABG
Death due to fatal stroke
Composite of cardiovascular complications,
excluding newonset
atrial fibrillation and transient ischemic attack
Composite of new-onset atrial fibrillation or TIA
Composite of all cardiovascular complications

T: 3.2 年

■ この試験の結果は信頼できるか～内的妥当性（デザイン）の吟味

Figure S.1: Overview of disposition of patients



デザイン　　：無作為割付け，プラセボ対照，二重盲検，
不完全だが intention-to-treat 解析 (実際は-2 人。ノンコンプライアンスのため)
A total of 4447 of the 4449 patients who underwent randomization were included in the ITT

ランダム化手法 ：？ デザイン文献にも記載なし
Ｍａｓｋｉｎｇ　：患者と医師はマスキング．
統計学的解析は，独立
追跡方法　　：protocol P24 に訪問時期と評価項目のリストの詳細があり
セッティング　：多施設（欧州 19 か国 262 施設）
追跡期間　　：追跡期間は 3.2 年（中央値）
登録期間　　：2004 年 10 月～2006 年 5 月
追跡中の両群の治療について（追加された治療）・・・EC 欄に
その他の評価　：
試験計画　　：有意差あり→ 症例数は十分
計算された症例数：4400 人
治療効果の大きさ：yearly average incidence rates of microalbuminuria of 2% in the placebo group yielding in 90.39% of event-free patients after a median time of five years of treatment
RRR 30%
α level：5%（両側）
検出力：90%
protocol P47 参照

追跡率・group 脱落・中断理由 ： Table S.2.A 参照
Founding　　：製薬会社からの funding 第 3 相試験

Table S.2.A: Overview of Patient Disposition			
All patients	**Olmesartan**	**Placebo**	**Overall**
Screened			5634
Screening failures			1122
Enrolled			4512
Run-in failures			63
Randomized	2233	2216	4449
Double-blind (DB) period			
Entered double-blind period	**2233 (100.0%)**	**2216 (100.0%)**	**4449 (100.0%)**
Discontinued prematurely from study (DB period)	506 (22.7%)	519 (23.4%)	1025 (23.0%)
Discontinued prematurely due to microalbuminuria from DB period into open-label period	163 (7.3%)	186 (8.4%)	349 (7.8%)
Discontinued prematurely due to microalbuminuria from DB period into observation period	2 (0.1%)	1 (0.0%)	3 (0.1%)
Discontinued prematurely due to MI, stroke or low CLCR from DB period into open-label period	1 (0.0%)	0 (0.0%9	1 (0.0%)
Discontinued prematurely due to MI, stroke or low CLCR from DB period into observation period	27 (1.2%)	31 (1.4%)	58 (1.3%)
Discontinued prematurely due to other reasons (not foreseen in protocol) from DB period into observation period	0 (0.0%)	2 (0.1%)	2 (0.0%)
Completed the study under double-blind study medication	1534 (68.7%)	1477 (66.7%)	3011 (67.7%)
Analysis Data Sets			
Safety Set [1]	2232	2215	4447
Full Analysis Set [1]	2232	2215	4447
Restricted Full Analysis Set [2]	2160	2139	4299

The reasons for premature discontinuation from the various study periods can be found in Table 1.B.

[1] One patient in each treatment group was randomized but never took any study medication. These two patients were excluded from the analysis set and consequently from the statistical analyses.

[2] The restricted Full Analysis Set consists of all patients from the Full Analysis Set excluding all patients having confirmed microalbuminuria at baseline (Visit 1) and/or patients without any evaluable follow-up evaluation of microalbuminuria. The restricted Full Analysis Set will only be used for the confirmatory analysis of the primary efficacy parameter, the exploratory analysis of the incidence rates of microalbuminuria and of the quantitative secondary efficacy parameters related to spot urine collection, but not for any analyses of secondary efficacy parameters except for microvascular morbidity.

Table S.2.B: Reason for Premature Discontinuation from the Double Blind Study Period (As Indicated by Investigator on Termination Form)			
	Olmesartan	**Placebo**	**Overall**
Run-in period			**4512 (100.0%)**
Lost to follow-up			2 (0.0%)
Withdrawal of consent			55 (1.2%)
Myocardial infarction			1 (0.0%)
Stroke			1 (0.0%)
Adverse events			3 (0.1%)
Other reason(s)			9 (0.2%)
Double-blind period	**2233 (100.0%)**	**2216 (100.0%)**	**4449 (100.0%)**
Lost to follow-up	51 (2.3%)	57 (2.6%)	108 (2.4%)
Withdrawal of consent [1]	319 (14.3%)	332 (15.0%)	651 (14.6%)
Death	26 (1.2%)	15 (0.7%)	41 (0.9%)
Development of microalbuminuria	168 (7.5%)	189 (8.5%)	357 (8.0%)
Myocardial infarction	21 (0.9%)	32 (1.4%)	53 (1.2%)
Stroke	10 (0.4%)	7 (0.3%)	17 (0.4%)
Adverse events	85 (3.8%)	89 (4.0%)	174 (3.9%)
Concomitant medication	22 (1.0%)	34 (1.5%)	56 (1.3%)
Decrease in creatinine clearance	5 (0.2%)	2 (0.1%)	7 (0.2%)
Other reason(s)	72 (3.2%)	81 (3.7%)	153 (3.4%)

A patient may have discontinued prematurely from a specific study period due to multiple reasons.

[1] Patients with "Withdrawal of Consent" received similar anti-hypertensive, anti-diabetic and/or lipid lowering medication as the general study population.

■ 結果は何か?

● Baseline は同等か？

平均年齢(olmesartan 群 57.7 歳, プラセボ群 57.8 歳), 男性(47.0%, 45.3%), BMI(31.1kg/m2, 30.9kg/m2), 糖尿病罹病期間(6.2 年, 6.1 年), 喫煙:現喫煙者(18.5%, 18.9%);喫煙歴なし(61.2%, 60.6%), メタボリックシンドローム(82.2%, 81.1%), 既往:冠動脈疾患(25.3%, 24.4%);心筋梗塞(6.0%, 5.4%);脳卒中, 一過性脳虚血発作(2.5%, 2.2%), 糖化ヘモグロビン(両群とも 7.7%), 尿中アルブミン/クレアチニン比(6.3, 5.9), クレアチニン値(0.9mg/dL, 0.9mg/dL), 推算 GFR(85.0mL/分/1.73m2, 84.7mL/分/1.73m2), LDL-C(両群とも 119.8mg/dL), HDL-C(46.4mg/dL, 47.2mg/dL), トリグリセライド(186mg/dL, 177.1mg/dL)。

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Olmesartan (N=2232)	Placebo (N=2215)	Total (N=4447)	P Value
Male sex — no. (%)	1049 (47.0)	1003 (45.3)	2052 (46.1)	0.25†
Age				
Mean — yr	57.7±8.8	57.8±8.6	57.7±8.7	0.74‡
≥65 yr — no. (%)	564 (25.3)	554 (25.0)	1118 (25.1)	0.84†
Body-mass index§	31.1±4.9	30.9±4.9	31.0±4.9	0.05‡
Diabetes				
Duration — yr	6.2±6.0	6.1±6.0	6.1±6.0	0.60‡
Prior treatment — no. (%)	2072 (92.8)	2069 (93.4)	4141 (93.1)	0.45†
Smoking status — no. (%)				0.91†
Never smoked	1367 (61.2)	1343 (60.6)	2710 (60.9)	
Former smoker	452 (20.3)	453 (20.5)	905 (20.4)	
Current smoker	413 (18.5)	419 (18.9)	832 (18.7)	
Metabolic syndrome — no. (%)¶	1834 (82.2)	1797 (81.1)	3631 (81.7)	0.37†
Cardiovascular history — no. (%)				
Coronary heart disease	564 (25.3)	540 (24.4)	1104 (24.8)	0.49†
Myocardial infarction	134 (6.0)	119 (5.4)	253 (5.7)	0.36†
Stroke or TIA	55 (2.5)	49 (2.2)	104 (2.3)	0.58†
Peripheral vascular disease	17 (0.8)	8 (0.4)	25 (0.6)	0.07†
Glucose — mmol/liter	9.0±3.1	9.0±3.1	9.0±3.1	1.00‡
Glycated hemoglobin — %	7.7±1.6	7.7±1.6	7.7±1.6	0.89‡
Blood pressure while seated — mm Hg				
Systolic	137±16	136±15	136±15	0.02‡
Diastolic	81±10	80±9	81±10	0.11‡

Table 1. (Continued.)

Characteristic	Olmesartan (N=2232)	Placebo (N=2215)	Total (N=4447)	P Value
Urinary albumin-to-creatinine ratio‖				
Geometric mean	6.3±7.6	5.9±6.7	6.1±7.2	0.06‡
Median	4	3	4	
Interquartile range	2–7	2–7	2–7	
Serum creatinine — μmol/liter	77.4±15.2	77.5±17.1	77.5±16.2	0.96‡
Estimated GFR**				
Mean — ml/min/1.73 m^2	85.0±17.0	84.7±17.3	84.9±17.2	0.60‡
<60 ml/min/1.73 m^2 — no. (%)	138 (6.2)	120 (5.4)	258 (5.8)	0.28†
Cholesterol — mmol/liter				
Total	5.2±1.1	5.2±1.1	5.2±1.1	0.76‡
LDL	3.1±0.9	3.1±0.9	3.1±0.9	0.31‡
HDL	1.20±0.30	1.22±0.30	1.21±0.30	0.02‡
Triglycerides — mmol/liter	2.1±1.7	2.0±1.3	2.1±1.5	0.02‡

* Plus–minus values are means ±SD. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert the values for triglycerides to milligrams per deciliter, divide by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and TIA transient ischemic attack.

† Exploratory comparisons were performed with the use of a chi-square test.

‡ Exploratory comparisons were performed with the use of Student's t-test.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

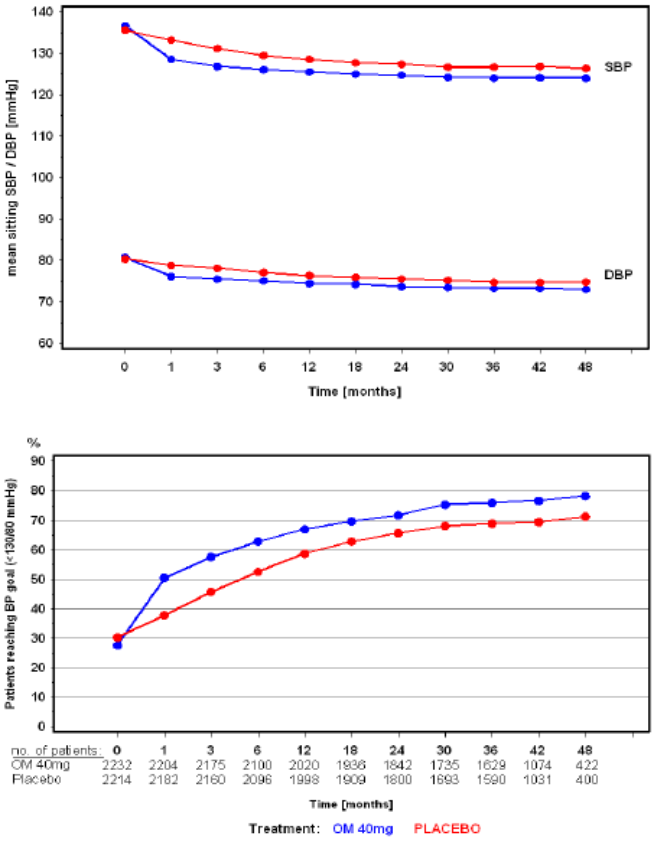
¶ The metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

‖ Albumin was measured in milligrams, and creatinine in grams. The baseline urinary albumin-to-creatinine ratio was defined as the geometric mean of the last three measurements that could be evaluated at the time of visit 1 (baseline). If insufficient measurements were available at baseline, the last measurements from the screening period were used.

** The estimated glomerular filtration rate (GFR) was calculated with the use of the abbreviated Modification of Diet in Renal Disease formula.

●有効性のまとめ
[血圧]
olmesartan 群：ベースライン時；137/81mmHg→追跡期間中；125.7/74.3mmHg
プラセボ群 136/80mmHg→ 128.7/76.2mmHg。
48 か月後に＜130/80mmHg にコントロールされていたものは，それぞれ約 80%，71%。
外来時血圧は olmesartan 群のほうが 3.3/1.3mmHg 低かった。
24 時間自由行動下血圧も同群が 3.5/1.2mmHg 低かった。

Figure S.2: Mean sitting systolic and diastolic blood pressure [mmHg] (upper part) and rate of patients reaching blood pressure goal (lower part)



［一次エンドポイント］

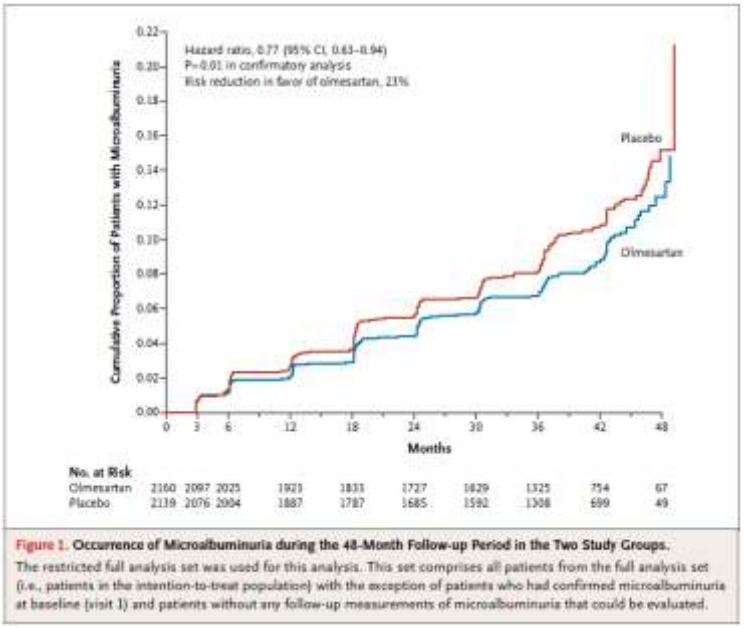
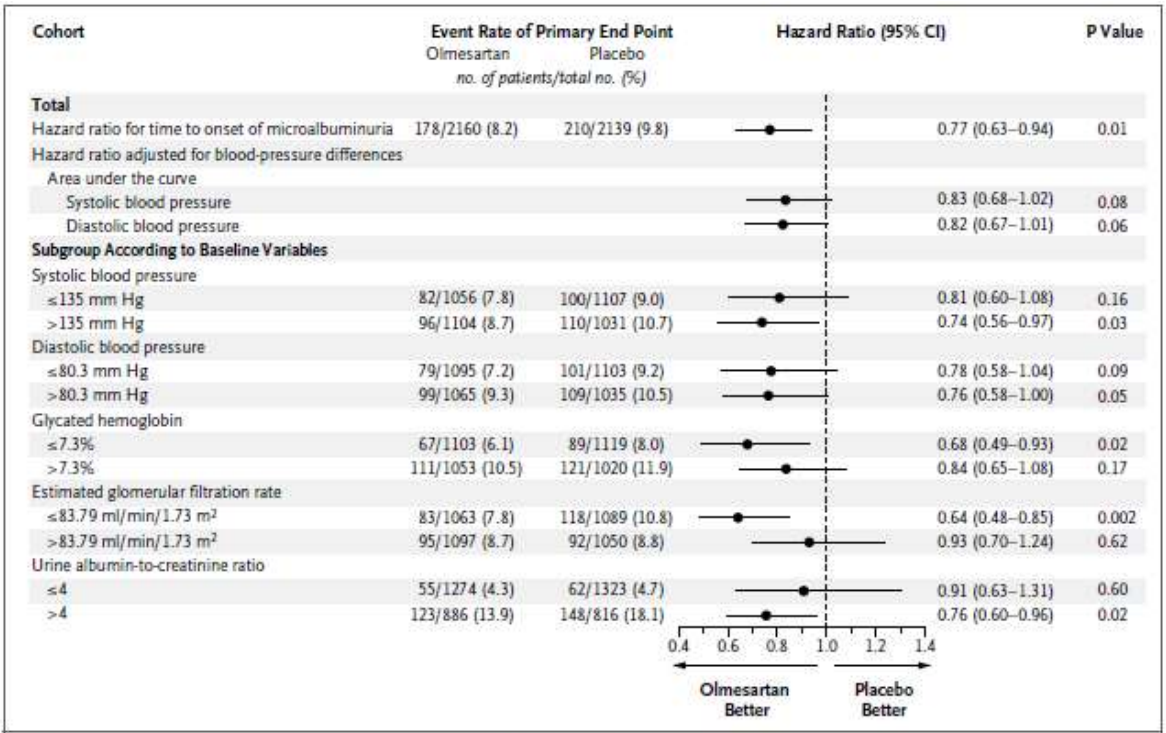


Figure 1. **Occurrence of Microalbuminuria during the 48-Month Follow-up Period in the Two Study Groups.**
The restricted full analysis set was used for this analysis. This set comprises all patients from the full analysis set (i.e., patients in the intention-to-treat population) with the exception of patients who had confirmed microalbuminuria at baseline (visit 1) and patients without any follow-up measurements of microalbuminuria that could be evaluated.

・ olmesartan 群 178 例/2160 例（8.2%） vs プラセボ群 210 例/2139 例（9.8%）。
微量アルブミン尿初発までの時間（中央値）は 722 日 vs 576 日
olmesartan 群で有意に 23%延長した（HR0.77；95.1%CI0.63～0.94，p＝0.01）。
患者背景（BMI，SBP，HDL-C，Tg）で調整後の HR：0.75；95.1%CI 0.62～0.92（p＝0.006）。



Cohort	Event Rate of Primary End Point: Olmesartan (no. of patients/total no. (%))	Event Rate of Primary End Point: Placebo (no. of patients/total no. (%))	Hazard Ratio (95% CI)	P Value
Total				
Hazard ratio for time to onset of microalbuminuria	178/2160 (8.2)	210/2139 (9.8)	0.77 (0.63–0.94)	0.01
Hazard ratio adjusted for blood-pressure differences				
Area under the curve				
Systolic blood pressure			0.83 (0.68–1.02)	0.08
Diastolic blood pressure			0.82 (0.67–1.01)	0.06
Subgroup According to Baseline Variables				
Systolic blood pressure				
≤135 mm Hg	82/1056 (7.8)	100/1107 (9.0)	0.81 (0.60–1.08)	0.16
>135 mm Hg	96/1104 (8.7)	110/1031 (10.7)	0.74 (0.56–0.97)	0.03
Diastolic blood pressure				
≤80.3 mm Hg	79/1095 (7.2)	101/1103 (9.2)	0.78 (0.58–1.04)	0.09
>80.3 mm Hg	99/1065 (9.3)	109/1035 (10.5)	0.76 (0.58–1.00)	0.05
Glycated hemoglobin				
≤7.3%	67/1103 (6.1)	89/1119 (8.0)	0.68 (0.49–0.93)	0.02
>7.3%	111/1053 (10.5)	121/1020 (11.9)	0.84 (0.65–1.08)	0.17
Estimated glomerular filtration rate				
≤83.79 ml/min/1.73 m²	83/1063 (7.8)	118/1089 (10.8)	0.64 (0.48–0.85)	0.002
>83.79 ml/min/1.73 m²	95/1097 (8.7)	92/1050 (8.8)	0.93 (0.70–1.24)	0.62
Urine albumin-to-creatinine ratio				
≤4	55/1274 (4.3)	62/1323 (4.7)	0.91 (0.63–1.31)	0.60
>4	123/886 (13.9)	148/816 (18.1)	0.76 (0.60–0.96)	0.02

Figure 2. Event Rate of the Primary End Point in the Two Study Groups, According to Subgroups.
The restricted full analysis set was used for this analysis. This set comprises all patients from the full analysis set (i.e., patients in the intention-to-treat population) with the exception of patients who had confirmed microalbuminuria at baseline (visit 1) and patients without any follow-up measurements of microalbuminuria that could be evaluated. All the results are based on adjudicated end points. The primary efficacy end point (the time to the onset of microalbuminuria) was analyzed with the use of a Cox proportional-hazards regression model, with study treatment as the fixed effect and the $\log_{10}$-transformed baseline urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) as the covariate. Owing to a prespecified interim analysis performed by the data and safety monitoring board, the significance level for the final confirmatory analysis was adjusted to 0.049, resulting in a two-sided 95.1% confidence interval. For all other analyses, two-sided 95% confidence intervals are shown. The sensitivity analyses were performed by extending the main model by an additional covariate. The exploratory subgroup analyses were performed with the use of the main model, with the exception of the subgroup analysis of urinary albumin-to-creatinine ratio. In this last analysis, the Cox proportional-hazards regression model with study treatment as the fixed effect was used.

・ オルメサルタン治療に反応しやすい背景因子
SBP ≧ 135 mmHg
HbA1c ≦ 7.3%
eGFR < 83.79 ml/min/1.73 m^2
Urinary albumin-to-creatinine ratio > 4 mg/gCr

[主な二次エンドポイント]
・腎機能
eGFR：
olmesartan 群（ベースライン時 85.0mL/分/1.73m^2→ 80.1mL/分/1.73m^2）
vs
プラセボ群（84.7mL/分/1.73m^2→ 83.7mL/分/1.73m^2）（p＜0.001）。
末期腎不全に至った例なし
Cr 値倍化は両群各およそ 1%

・心血管イベント
心血管合併症＋心血管死の複合エンドポイント
96 例（4.3%） vs 94 例（4.2%）：HR 1.00；0.75～1.33（p＝0.99）。

・全死亡は，26 例（1.2%） vs 15 例（0.7%）：1.70；0.90～3.22（p＝0.10），
　心血管死（15 例[0.7%] vs 3 例[0.1%]）
　非心血管死（8 例 vs 10 例）
　死因不明（3 例 vs 2 例）
・全心血管死のうち，
　心臓突然死（7 例 vs 1 例）
　致死的心筋梗塞（5 例 vs 0 例）
　PTCA あるいは CABG 周術期あるいは手技後の死亡（1 例 vs 0 例）
　致死的脳卒中（2 例 vs 2 例）。
・新規発症心房細動（AF），一過性脳虚血発作（TIA）を除く心血管合併症複合は，63 例（2.8%） vs 71 例（3.2%）：0.87；0.62～1.22（p＝0.42）。
・新規発症 AF，TIA の複合エンドポイントは，19 例（0.9%） vs 28 例（1.3%）：0.67；0.37～1.19（p＝0.17）。
・全心血管合併症：81 例（3.6%） vs 91 例（4.1%）：0.87；0.65～1.18（p＝0.37）。
・心血管死 18 例のうち 12 例が，冠動脈疾患（CAD）既往サブグループ（1,104 例）。
・post hoc 解析によると，olmesartan 群と CAD 既往に相互関連がみられた（olmesartan 群 11 例 vs プラセボ群 1 例：6.9 イベント/1000 人・年 vs 0.7 イベント/1000 人・年，p＝0.02）。

Table 2. Secondary Efficacy End Points during the Double-Blind Treatment Period.*

End Point	Olmesartan (N=2232)	Placebo (N=2215)	Hazard Ratio (95% CI)	P Value
	no. of patients (%)			
Composite of cardiovascular complications or death from cardiovascular causes	96 (4.3)	94 (4.2)	1.00 (0.75–1.33)	0.99
Composite of death from any cause	26 (1.2)	15 (0.7)	1.70 (0.90–3.22)	0.10
Death from cardiovascular causes	15 (0.7)	3 (0.1)		
Death not related to cardiovascular causes	8 (0.4)	10 (0.5)		
Death from unknown cause	3 (0.1)	2 (0.1)		
Composite of death from cardiovascular causes	15 (0.7)	3 (0.1)	4.94 (1.43–17.06)	0.01
Sudden cardiac death	7 (0.3)	1 (<0.1)		
Death due to fatal myocardial infarction	5 (0.2)	0		
Evidence of recent myocardial infarction on autopsy	0	0		
Death due to congestive heart failure	0	0		
Death during or after percutaneous transluminal coronary angioplasty or CABG	1 (<0.1)	0		
Death due to fatal stroke	2 (0.1)	2 (0.1)		
Composite of cardiovascular complications, excluding new-onset atrial fibrillation and transient ischemic attack	63 (2.8)	71 (3.2)	0.87 (0.62–1.22)	0.42
Composite of new-onset atrial fibrillation or transient ischemic attack	19 (0.9)	28 (1.3)	0.67 (0.37–1.19)	0.17
Composite of all cardiovascular complications	81 (3.6)	91 (4.1)	0.87 (0.65–1.18)	0.37

* All results were based on adjudicated end points. The composite secondary efficacy end points were analyzed with the use of a Cox proportional-hazards regression model with study treatment as the fixed effect. For composite end points, the time to the onset of an event was defined as the time from randomization (date of visit 1) to the first occurrence of any component of the composite end point. CABG denotes coronary-artery bypass grafting.

●有害事象

1 件以上の重篤な有害イベント：335 例（15.0%） vs 337 例（15.2%）；p＝0.85，
1 件以上の薬剤関連イベント：255 例（11.4%） vs 166 例（7.5%）；p＜0.001，
頻度の高かったイベントは，
　高血圧（164 例 vs 178 例），頭痛（100 例 vs 153 例；p＜0.001），気管支炎（102 例 vs 104 例），
　めまい（103 例 vs 61 例；p＝0.001）など。低血圧症：58 例 vs 6 例（p＜0.001），高カリウム血症：11 例 vs 8 例。

Table 3. Adverse Events That Occurred during Treatment.

Adverse Event	Olmesartan (N=2232)	Placebo (N=2215)	P Value*
	no. of patients (%)		
At least one serious event	335 (15.0)	337 (15.2)	0.85
At least one drug-related event†	255 (11.4)	166 (7.5)	<0.001
At least one serious drug-related event	4 (0.2)	1 (<0.1)	0.18
Most frequently reported events‡			
Hypertension	164 (7.3)	178 (8.0)	0.39
Headache	100 (4.5)	153 (6.9)	<0.001
Nasopharyngitis	112 (5.0)	94 (4.2)	0.22
Bronchitis	102 (4.6)	104 (4.7)	0.22
Influenza	80 (3.6)	98 (4.4)	0.15
Back pain	96 (4.3)	75 (3.4)	0.11
Dizziness	103 (4.6)	61 (2.8)	0.001
Peripheral edema	60 (2.7)	86 (3.9)	0.03
Events of special interest			
Hypotension	58 (2.6)	6 (0.3)	<0.001
Hyperkalemia	11 (0.5)	8 (0.4)	0.50

* P values were calculated with the use of a chi-square test.
† An event was considered to be drug-related if, according to the investigator's judgment, the event was definitely, probably, or possibly related to the treatment or if information on the relationship of the event to the study treatment was missing.
‡ Events included in this category are those that occurred in at least 3% of the patients in either study group; adverse events that were part of the primary or secondary efficacy end points are not shown.

■ limitation

・First, it is not possible to draw definite conclusions from a short-term prevention study about the way in which changes in microalbuminuria may affect the rates of renal and cardiovascular event rates in the long term. During the study itself, the follow-up period was too short.

・Second, the rate of premature withdrawals in both study groups was high (about 23% in both groups); however, it seems unlikely that withdrawals affected the overall findings of the study, since an exploratory analysis excluding these patients did not affect the primary end point.

・Third, although the differences in blood pressure between the treatment groups may have contributed to the primary outcome,and the benefit was greater in patients with higher baseline blood pressure, adjustment of the analysis for differences in blood pressure during the study did not eliminate the improvement in the primary end point that was seen with olmesartan.

■ 適用について考える

その結果は患者さんに当てはめることができるか？

一応、情報として検討の余地あり。

ただし、他の ARB や ACEI についての情報も精査し、どの程度の微量アルブミン尿や CKD に対して、有効なのかの確認をしてから、患者指導内容を決める。

現場で、どのような事前の説明が必要か？どのスタッフにするべきか？

日本の一般的な医療、歴史的背景と違う点はあるか？

オルメサルタンの通常量は 10~20mg、症例はこの文献の後なので、用量は BP ベースで使用しているよう。

この論文の結果から、何か薬剤師が自施設で取り組めることがないか？

降圧剤使用中の患者さんの治療目標の確認をして、降圧剤の説明をするように心がける。治療目標が不明な場合は、降圧作用以外の作用を指導する前に、患者さんとの対話の中で、医師の指導を確認しておく。

表　糖尿病性腎症に関する合同委員会病期分類

病期	臨床的特徴	
	尿蛋白（微量アルブミン尿）	GFR（CCr）
第1期（腎症前期）	正常	正常ときに高値
第2期（早期腎症）	微量アルブミン尿	正常ときに高値
第3期A（顕性腎症前期）	持続的蛋白尿	ほぼ正常
第3期B（顕性腎症後期）	持続的蛋白尿	低下
第4期（腎不全期）	持続的蛋白尿	著明低下（血清Cr上昇）
第5期（透析療法）	透析療法中	

糖尿病性腎症に関する合同委員会報告．日腎会誌 2002；44(1)：i.