

## IRMA 2(080603)

IDNT の続き。

### ●PECO

P: hypertensive patients with type 2 diabetes and microalbuminuria

E: irbesartan, at a dose of either 150 mg daily or 300 mg daily

C: placebo

O: The primary outcome was the time to the onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens, with a urinary albumin excretion rate that was greater than 200  $\mu$ g per minute and at least 30 percent higher than the base-line level.

つまり、微量アルブミン尿を伴う2型糖尿病患者の高血圧に対して、irbesartanを投与するとプラセボと比較して糖尿病性腎症の発症が抑制できるかどうかを調べた研究であることが分かる。

血圧のターゲットは135/85で、ACE阻害薬以外の利尿剤、 $\beta$ ブロッカー、CCB(ジヒドロピリジン系以外)、アルファブロッカーが適宜使用されているようだ。

### Procedures, Measurements, and Outcome

The target blood pressure three months after randomization was less than 135/85 mm Hg for all three groups. Additional antihypertensive drugs used by patients included diuretics, beta-blockers, calcium-channel blockers (except dihydropyridines), and alpha-blockers; ACE inhibitors were not allowed.

### ●妥当か

抄録中に randomized, double-blind とあり、Statistical Analysis に intention-to-treat principle とある。試験期間は2年間。大きな問題はなさそうだが・・・ベースラインの特徴を眺めると、ちょっと気になる項目がある。Known duration of diabetes と Retinopathy の項目である。プラセボの Known duration of diabetes が  $10.4 \pm 8.6$  年であるのに対し、irbesartan 300mg の群は  $9.2 \pm 6.9$  年である。Retinopathy の頻度を見ても差が際立っていると思う・・・。特にレーザー治療はプラセボで14.1%、irbesartan 300mg の群は8.9%である。インスリン治療に関しても、プラセボ群は36.8%なのに対して、irbesartan 300mg の群では29.4%である。どちらかといえばプラセボで不利な割付になってしまっているかもしれない。結果に関しては少々割り引いて評価してもいいのかもしれない。

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)
<b>Demographic characteristics</b>			
Age — yr	58.3±8.7	58.4±8	57.3±7.9
Male sex — no. (%)	138 (68.7)	129 (66.2)	137 (70.6)
Race — no. (%)			
White	197 (98.0)	190 (97.4)	187 (96.4)
Nonwhite	4 (2.0)	5 (2.6)	7 (3.6)
<b>Clinical characteristics</b>			
Body-mass index†	30.3±4.4	29.9±3.8	30.0±4.3
Known duration of diabetes — yr	10.4±8.6	9.5±6.9	9.2±6.9
Retinopathy — no. (%)‡			
None	110 (55.3)	105 (55.0)	122 (64.2)
Simplex	50 (25.1)	59 (30.9)	37 (19.5)
Maculopathy	4 (2.0)	8 (4.2)	5 (2.6)
Proliferative	7 (3.5)	7 (3.7)	9 (4.7)
Laser treatment	28 (14.1)	12 (6.3)	17 (8.9)
Smoking — no. (%)			
Never	96 (47.8)	81 (41.5)	80 (41.2)
Formerly	69 (34.3)	72 (36.9)	82 (42.3)
Currently	36 (17.9)	42 (21.5)	32 (16.5)
<b>Medical history</b>			
Known cardiovascular disorders — no. (%)§	47 (23.4)	59 (30.3)	51 (26.3)
Myocardial infarction — no. (%)	3 (1.5)	9 (4.6)	6 (3.1)
Coronary artery disease — no. (%)¶	6 (3.0)	10 (5.1)	11 (5.7)
Peripheral arterial disease — no. (%)	8 (4.0)	13 (6.7)	10 (5.2)
Venous insufficiencies — no. (%)	5 (2.5)	6 (3.1)	4 (2.1)
Stroke or transient ischemic attack — no. (%)	7 (3.5)	6 (3.1)	5 (2.6)
<b>Laboratory variables</b>			
Glycosylated hemoglobin — %	7.1±1.6	7.3±1.7	7.1±1.7
Blood pressure — mm Hg			
Systolic	153±15	153±14	153±14
Diastolic	90±9	90±9	91±10
Urinary albumin excretion — µg/min	54.8±2.5	58.3±2.7	53.4±2.2
Serum creatinine — mg/dl**			
Male patients	1.1±0.1	1.1±0.2	1.1±0.2
Female patients	0.9±0.1	0.9±0.1	1.0±0.2
Creatinine clearance — ml/min/1.73 m <sup>2</sup> of body-surface area	109±2	110±2	108±2
Triglycerides — mg/dl††	168.5±105.6	184.1±110.2	187.3±117.7
Cholesterol — mg/dl‡‡			
Total	223.2±42.1	227.4±54.2	222.2±46.9
Low-density lipoprotein	143.0±36.9	142.4±46.4	134.6±36.6
High-density lipoprotein	44.9±11.9	43.0±10.6	42.8±12.1

\*Differences between groups were not statistically significant. Plus-minus values are means ±SD, unless otherwise indicated.

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

‡Data were missing for two patients in the placebo group, four in the 150-mg group, and four in the 300-mg group.

§Data include patients with arrhythmia, pericarditis, valvular disease, and previous heart failure, in addition to the disorders listed.

¶Data are for patients with angina but no myocardial infarction.

||Values are geometric means ±SE.

\*\*To convert values to micromoles per liter, multiply by 88.4.

††To convert values to millimoles per liter, multiply by 0.113.

‡‡To convert values to millimoles per liter, multiply by 0.259.

(参考文献 1 より引用)

**TABLE 2. SIMULTANEOUS TREATMENTS IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA AT THE BEGINNING AND THE END OF THE STUDY.\***

TREATMENT	BEGINNING OF STUDY			END OF STUDY		
	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)	PLACEBO GROUP (N=201)	150-mg IRBESARTAN GROUP (N=195)	300-mg IRBESARTAN GROUP (N=194)
	number (percent)					
Glucose lowering						
Diet alone	27 (13.4)	32 (16.4)	22 (11.3)	21 (10.4)	21 (10.8)	24 (12.4)
Oral hypoglycemic agent	100 (49.8)	104 (53.3)	115 (59.3)	92 (45.8)	101 (51.8)	106 (54.6)
Insulin and oral hypoglycemic agent	28 (13.9)	27 (13.8)	24 (12.4)	35 (17.4)	37 (19.0)	32 (16.5)
Insulin alone	46 (22.9)	32 (16.4)	33 (17.0)	53 (26.4)	36 (18.5)	32 (16.5)
Antihypertensive agents†						
Any	—	—	—	113 (56.2)	88 (45.1)	84 (43.3)
Diuretics	—	—	—	51 (25.4)	42 (21.5)	37 (19.1)
Beta-blockers	—	—	—	38 (18.9)	27 (13.8)	26 (13.4)
Calcium-channel blockers (nondihydropyridine)	—	—	—	55 (27.4)	35 (17.9)	45 (23.2)
Others	—	—	—	30 (14.9)	22 (11.3)	34 (17.5)
Lipid-lowering agents						
Any	36 (17.9)	37 (19.0)	31 (16.0)	52 (25.9)	52 (26.7)	47 (24.2)
Statin alone	21 (10.4)	23 (11.8)	16 (8.2)	38 (18.9)	37 (19.0)	29 (14.9)
Fibrate alone	14 (7.0)	12 (6.2)	13 (6.7)	12 (6.0)	11 (5.6)	14 (7.2)
Statin and fibrate	1 (0.5)	2 (1.0)	2 (1.0)	2 (1.0)	4 (2.1)	4 (2.1)
Aspirin (≤325 mg daily)	19 (9.5)	31 (15.9)	26 (13.4)	29 (14.4)	42 (21.5)	32 (16.5)

\*Differences between groups were not statistically significant, except in the use of antihypertensive agents, for which P=0.03 for the comparison between the placebo group and the 150-mg group and P=0.01 for the comparison between the placebo group and the 300-mg group.

†All antihypertensive agents were discontinued during the three-week run-in screening period.

(参考文献 1 より引用)

## ●結果

irbesartan 300mg とプラセボの効果の差を評価してみる。

RRR:  $1-5.2/14.9=65.1\%$

ARR:  $14.9-5.2=9.7\%$

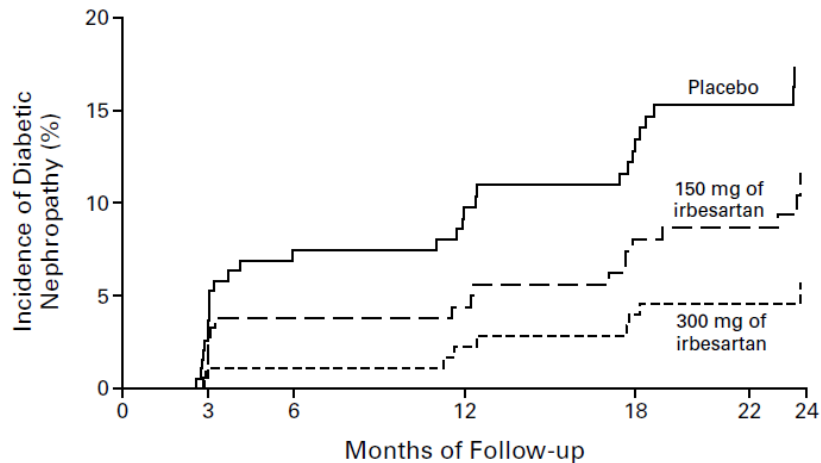
NNT: 10(2年)

Ten of the 194 patients in the 300-mg group (5.2 percent) and 19 of the 195 patients in the 150-mg group (9.7 percent) reached the primary end point, as compared with 30 of the 201 patients in the placebo group (14.9 percent) (hazard ratios, 0.30 [95 percent confidence interval, 0.14 to 0.61; P< 0.001] and 0.61 [95 percent confidence interval, 0.34 to 1.08; P=0.08] for the two

irbesartan groups, respectively).

到達した血圧はプラセボで 143/83mmHg、irbesartan 300mg 群で 141/ 83 mm Hg である。前述のように、ACE 阻害薬以外の利尿剤、βブロッカー、CCB(ジヒドロピリジン系以外)、アルファブロッカーが適宜使用されている。IDNT の考察とも重複するが、140 程度の降圧であればやはり、ARB や ACE 阻害薬でイベントが抑制される傾向にあるかもしれない。

The average blood pressure during the course of the study was 144/83 mm Hg in the placebo group, 143/83 mm Hg in the 150-mg group, and 141/ 83 mm Hg in the 300-mg group (P=0.004 for the comparison of systolic blood pressure between the placebo group and the combined irbesartan groups).



NO. AT RISK							
Placebo	201	201	164	154	139	129	36
150 mg of irbesartan	195	195	167	161	148	142	45
300 mg of irbesartan	194	194	180	172	159	150	49

**Figure 2.** Incidence of Progression to Diabetic Nephropathy during Treatment with 150 mg of Irbesartan Daily, 300 mg of Irbesartan Daily, or Placebo in Hypertensive Patients with Type 2 Diabetes and Persistent Microalbuminuria.

The difference between the placebo group and the 150-mg group was not significant (P=0.08 by the log-rank test), but the difference between the placebo group and the 300-mg group was significant (P<0.001 by the log-rank test).

(参考文献 1 より引用)

## 参考文献

1. Parving HH et al for the irbesartan in patients with type 2 diabetes and microalbuminuria study group. The effect of irbesartan on the development of diabetic nephropathy in patients

with type 2 diabetes. N Engl J Med. 2001; 345: 870–878.