Diabetic Nephropathy

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Diabetic Nephropathy (2005)

- Diabetic nephropathy: 942
- Diabetic nephropathy (English): 793
- Diabetic nephropathy (English, Human): 605
- Diabetic nephropathy (English, Human, Randomized controlled trial): 42

Diabetic Nephropathy (2005)

- RAS inhibitor: 15
- Transplantation: 8
- Hemodialysis: 3
- Spironolactone, PPAR-γ agonist, Statins, Pentoxifylline: 2
- Ruboxistaurin, Fenofibrate, Vitamin/Mineral supplementation, Diltiazem: 1
- Others: 4

Kidney International Vol 68 (2005), pp. 2829–2836

Beneficial impact of spironolactone in diabetic nephropathy

KATRINE JORDAN SCHJOEDT, KASPER ROSSING, TINA RAGNHOLM JUHL, FRANS BOOMSMA, PETER ROSSING, LISE TARNOW, and HANS-HENRIK PARVING

Steno Diabetes Center, Gentofte, Denmark; Erasmus MC, Rotterdam, The Netherlands, and Faculty of Health Science, University of Aarhus, Aarhus, Denmark

- Steno Diabetes Center
- 22 Caucasian type I diabetic patients
- Persistent macroalbuminuria despite antihypertensive treatment including RAS blockade
- Randomized, double-masked, placebo-controlled, and crossover trial
- Spironolactone 25 mg vs. Placebo 1 T/D for 2 months
- 1° endpoint: Albuminuria
- 2° endpoints: 24-hour BP and GFR

Table 2. Effect of adding spironolactone 25 mg to conventional antihypertensive medication, including an ACEI or ARB in recommended doses, on kidney function, blood pressure, and laboratory variables in 20 type 1 diabetic patients with diabetic nephropathy

	Placebo	Spironolactone 25 mg	Mean difference (95% CI)	*P* value
● Albuminuria *mg/24 hour*	831 (624 to 1106)	384 (441 to 829)	−30% (−41 to −17)	<0.001
Systolic blood pressure *mm Hg*				
Office	136 (3)	131 (4)	−6 (−14 to 2)	0.157
◆ 24-hour	144 (3)	136 (4)	−8 (−17 to 1)	0.082
Day (7–23)	150 (3)	139 (4)	−10 (−19 to −2)	0.017
Night (23–7)	131 (5)	130 (7)	−1 (−14 to 12)	0.874
Diastolic blood pressure *mm Hg*				
Office	72 (2)	71 (2)	−1 (−5 to 2)	0.445
◆ 24-hour	72 (2)	69 (2)	−3 (−7 to 0.2)	0.067
Day (7–23)	76 (2)	71 (2)	−5 (−8 to −1)	0.010
Night (23–7)	65 (2)	64 (2)	0 (−5 to 5)	0.909
Glomerular filtration rate *mL/min per 1.73 m²*	85 (6)	92 (6)	−3.4 (−8.9 to 0.1)	0.059
● Fractional albumin clearance (V_{alb}) (× 10^{-5})*	197 (122 to 317)	129 (78 to 210)	−35% (−46 to −20)	<0.001
Urinary sodium excretion *mmol/24 hour*	198 (13)	203 (13)	14 (−15 to 44)	0.306
Urinary K/Na ratio	0.45 (0.05)	0.43 (0.03)	−0.04 (−0.1 to 0.02)	0.192
Plasma renin activity *ng/AI/mL/h*†	15 (10 to 21)	21 (13 to 33)	86% (−8 to 107)	0.110
Plasma aldosterone *pg/mL*†	44 (31 to 62)	68 (50 to 92)	54% (18 to 101)	0.001
Plasma creatinine *μmol/L*	115 (9)	120 (11)	5 (−1 to 11)	0.095
Plasma potassium *mmol/L*	4.0 (0.1)	4.2 (0.1)	0.13 (−0.04 to 0.3)	0.134
Plasma sodium *mmol/L*	139 (1)	139 (1)	−1 (−3 to 1)	0.343
Hemoglobin *mmol/L*	7.9 (0.2)	7.7 (0.2)	−0.18 (−0.4 to 0.3)	0.097
Hemoglobin A_{1c} %	8.4 (0.2)	8.6 (0.2)	0.2 (−0.01 to 0.4)	0.056
Plasma cholesterol *mmol/L*	4.6 (0.2)	4.6 (0.2)	0.01 (−0.2 to 0.2)	0.936
Plasma low-density lipoprotein *mmol/L*	2.4 (0.1)	2.3 (0.2)	−0.1 (−0.6 to 0.4)	0.121
Plasma high-density lipoprotein *mmol/L*	1.7 (0.2)	1.6 (0.1)	−0.1 (−0.24 to 0.03)	0.660

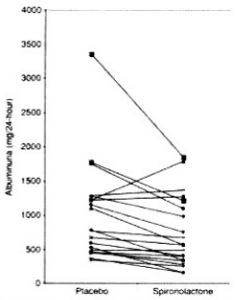


Fig. 1. Individual responses to spironolactone 25 mg once daily for two months added to recommended antihypertensive treatment in 20 type 1 diabetic patients with diabetic nephropathy. Overall reduction was 30%, $P < 0.001$.

Pathophysiology/Complications — *Diabetes Care 28:2728, 2005*

ORIGINAL ARTICLE

Effect of Pitavastatin on Urinary Liver-Type Fatty Acid–Binding Protein Levels in Patients With Early Diabetic Nephropathy

- Japan multicenter study
- 58 Japanese type II diabetic patients
  - A: No nephropathy
  - B: Microalbuminuria (Trial)
  - C: Microalbuminuria, normal renal function
  - D: Renal failure
- 20 healthy age-matched subjects (E)
- Randomized, double-blind, placebo-controlled trial
- Pitavastatin 1 mg/day vs. Placebo for 12 months
- 1° endpoints: Urinary L-FABP and UAE

Table 3—*Urinary L-FABP levels*

Group	L-FABP (μg/g creatinine)
A	6.2 ± 4.6
B	19.6 ± 13.5
C	26.8 ± 20.4
D	52.4 ± 46.8
E	5.8 ± 4.0

Data are means ± SD. A vs. B, $P < 0.05$; A vs. C, $P < 0.01$; A vs. D, $P < 0.001$; A vs. E not significant; B vs. C, $P < 0.05$; B vs. D, $P < 0.01$; B vs. E, $P < 0.05$; C vs. D, $P < 0.01$; C vs. E, $P < 0.01$; D vs. E, $P < 0.001$.

Table 5—*UAE, urinary L-FABP levels, and total cholesterol before and after treatment in diabetic patients with microalbuminuria (group B)*

	Before treatment	6 months	12 months
UAE (μg/min)			
Pitavastatin	110 ± 74	88 ± 60*†	58 ± 32†§
Nonpitavastatin	104 ± 68	110 ± 72	118 ± 74
L-FABP (μg/g creatinine)			
Pitavastatin	18.6 ± 12.5	12.2 ± 8.8*†	8.8 ± 6.4†§
Nonpitavastatin	20.6 ± 14.5	22.0 ± 16.0	24.0 ± 18.0
Total cholesterol (mg/dl)			
Pitavastatin	180 ± 28	172 ± 24	170 ± 26
Nonpitavastatin	185 ± 34	180 ± 28	184 ± 30

Data are means ± SD. Versus before treatment: *$P < 0.05$ and †$P < 0.01$. Versus nonpitavastatin treatment: ‡$P < 0.05$ and §$P < 0.01$.

Emerging Treatments and Technologies
ORIGINAL ARTICLE
Diabetes Care 28:2686, 2005

The Effect of Ruboxistaurin on Nephropathy in Type 2 Diabetes

- American multicenter study
- 123 type II diabetic patients with albuminuria and stage 2 renal failure
- On treatment with an ACEi, ARB, or both for at least 6 months
- Randomized, double-blind, placebo-controlled trial
- Ruboxistaurin (PKC-β inhibitor) 32 mg/D
  vs. Placebo for 12 months
- 1° endpoint: Reduction in ACR

Table 3—*Change from baseline in urinary ACR and eGFR, blood pressure, and A1C at follow-up visits*

Treatment	n	1 month	3 months	6 months	12 months
Urinary ACR change (%)*					
Placebo	62	−16 ± 7†	−9 ± 8	−9 ± 10	−9 ± 11
RBX	59	−24 ± 7†	−28 ± 6†	−29 ± 8†	−24 ± 9†
Urinary ACR change (mg/g)‡					
Placebo	62	17 (424)	−37 (413)†	21 (661)	26 (896)†
RBX	59	−60 (363)†§	−139 (417)†§	−136 (598)	−121 (481)
eGFR change (ml/min per 1.73 m²)					
Placebo	62	—	—	−2.7 ± 1.8	−4.8 ± 1.8†
RBX	57	—	—	−0.2 ± 1.9	−2.5 ± 1.9
Systolic blood pressure (mmHg)					
Placebo	62	135 ± 16	135 ± 15	136 ± 16	138 ± 19
RBX	59	135 ± 15	136 ± 15	134 ± 16	134 ± 18
Diastolic blood pressure (mmHg)					
Placebo	62	77 ± 12	76 ± 8	76 ± 10	76 ± 10
RBX	59	74 ± 10	74 ± 9	73 ± 11	74 ± 10
A1C (%)					
Placebo	62	—	—	7.7 ± 1.1	7.7 ± 1.2
RBX	56	—	—	8.0 ± 1.3	7.9 ± 1.3

Data are means ± SD unless otherwise indicated. *ACR change from baseline (%) was calculated from log-transformed values using the ANCOVA model with least-square means (prespecified primary outcome). †Change from baseline, $P < 0.05$. ‡ACR change from baseline (mg/g) without log transformation reported as median (interquartile range for the middle two quartiles). §Difference between groups, $P < 0.05$. RBX, 32 mg/day ruboxistaurin.

Pathophysiology/Complications
ORIGINAL ARTICLE
Diabetes Care 28:2458, 2005

Comparison of the Effects of Vitamins and/or Mineral Supplementation on Glomerular and Tubular Dysfunction in Type 2 Diabetes

- Iran study
- 76 Iranian type II diabetic patients
- Diabetes for at least 1 year without macroalbuminuria (ACR > 300 mg/g) and HiBP(> 160/100 mmHg)
- Randomized, double-blind, placebo-controlled trial
- Treatment for 3 months
  - M: 200 mg Mg + 30 mg Zn
  - V: 200 mg vitamin C + 100 IU vitamin E
  - MV: M + V
  - P: Placebo
- 1° endpoint: UAE and *N*-acetyl-β-p-glucosaminidase activity

Table 3—*Levels of glycemic and nephropathy indices before and after 3 months of vitamin and mineral supplementation in type 2 diabetic patients*

	Group P	Group M	Group V	Group MV
n	19	16	18	17
Fasting serum glucose (mmol/l)				
Before	9.02 ± 2.81	9.31 ± 2.81	10.99 ± 2.64	9.76 ± 2.25†
After	9.02 ± 2.99	9.56 ± 2.53	9.95 ± 2.31	9.01 ± 2.53
Fructosamine (μmol/l)				
Before	430 ± 136	453 ± 140	491 ± 123	433 ± 71
After	446 ± 121	483 ± 125	472 ± 90	423 ± 79
HbA1 (%)				
Before	9.23 ± 2.05	10.56 ± 2.70	11.23 ± 3.36	9.29 ± 1.86
After	10.04 ± 1.98	10.94 ± 2.25	11.01 ± 2.39	9.39 ± 2.18
Microalbuminuria (mg/g creatinine) (95% CI)				
Before	30.7 (9.7–52.7)	30.4 (12.5–48.4)	35.6 (6.2–64.9)	29.3 (−3.2 to 61.9)
After	42.8 (11.6–73.8)*	39.0 (13.9–34.1)	22.1 (3.2–39.0)	10.8 (4.2–17.3)
NAG (units/g Cr) (95% CI)				
Before	13.7 (8.1–19.3)	14.3 (12.6–23.8)	16.9 (13.1–20.7)	16.0 (11.1–20.9)
After	15.6 (10.3–21.0)	25.3 (13.4–37.3)	19 (11.0–26.9)	17.2 (10.2–24.2)
Urine protein (g/g creatinine)				
Before	1.38 ± 1.04	2.32 ± 0.96	2.06 ± 1.20	2.61 ± 1.05
After	2.25 ± 1.03	2.09 ± 0.74	2.31 ± 0.79	2.21 ± 0.72

Data are means ± SD, unless otherwise indicated. †Statistically significant difference (*) between before and after taking period of five months. *$P = 0.033$, †$P = 0.034$, ‡$P = 0.005$.

Table 5—*Levels of serum lipids, lipoproteins, and MDA before and after 3 months of vitamin and mineral supplementation in type 2 diabetic patients*

	Group P	Group M	Group V	Group MV
n	18	16	18	17
Cholesterol (mmol/l)				
Before	4.56 ± 0.99	4.69 ± 0.85	4.87 ± 0.66	5.26 ± 0.86
After	4.66 ± 0.71	4.74 ± 0.85	4.82 ± 0.93	5.26 ± 0.96
Triglycerides (mmol/l)				
Before	1.83 ± 1.24	1.89 ± 0.95	2.44 ± 1.52	2.21 ± 0.93
After	1.74 ± 0.75	2.17 ± 1.23	2.15 ± 0.68	2.26 ± 1.19
HDL cholesterol (mmol/l)				
Before	1.01 ± 0.31	1.04 ± 0.41	0.93 ± 0.18	1.05 ± 0.25*
After	0.91 ± 0.19	1.00 ± 0.29	1.09 ± 0.40	1.31 ± 0.50
LDL cholesterol (mmol/l)*				
Before	2.80 ± 0.81	2.77 ± 0.63	3.16 ± 0.66	3.31 ± 0.88
After	2.95 ± 0.63	2.72 ± 0.62	3.13 ± 1.11	3.21 ± 0.80
ApoA1 (mg/dl)				
Before	143 ± 22	142 ± 27	145 ± 25	156 ± 24†
After	143 ± 24	146 ± 23	146 ± 20	170 ± 34
ApoB (mg/dl)				
Before	128 ± 24	137 ± 36	135 ± 30	155 ± 24
After	140 ± 30	143 ± 38	135 ± 26	157 ± 22
MDA (μmol/ml)				
Before	1.32 ± 0.37	1.34 ± 0.44‡	1.43 ± 0.60	1.43 ± 0.61§
After	1.56 ± 0.51	1.31 ± 0.39	1.44 ± 0.66	1.51 ± 0.48
Lipid-standardized MDA (μmol/mg lipid)				
Before	0.43 ± 0.17	0.42 ± 0.20‖	0.41 ± 0.24	0.39 ± 0.21¶
After	0.50 ± 0.18	0.38 ± 0.16	0.41 ± 0.27	0.35 ± 0.13

*Statistically significant differences between before and after using general linear models: †$P = 0.018$, ‡$P = 0.034$, §$P = 0.009$, ‖$P = 0.026$, ¶$P = 0.018$

Table 6—*Levels of systolic, diastolic, and mean blood pressure before and after 3 months of vitamin and mineral supplementation in type 2 diabetic patients*

	Group P	Group M	Group V	Group MV
n	18	16	18	17
Systolic blood pressure (mmHg)				
Before	127 ± 16	122 ± 15	125 ± 15	130 ± 19*
After	128 ± 18	119 ± 12	122 ± 16	122 ± 16
Diastolic blood pressure (mmHg)				
Before	82 ± 9	78 ± 12	81 ± 9	83 ± 11†
After	84 ± 11	78 ± 10	79 ± 12	77 ± 9
Mean arterial pressure (mmHg)				
Before	97 ± 9	93 ± 13	95 ± 10	99 ± 13‡
After	98 ± 12	92 ± 10	93 ± 12	92 ± 9

Data are means ± SD. Statistically significant differences between before and after using general linear models. *$P = 0.008$, †$P = 0.017$, ‡$P = 0.009$.

Clinical Care/Education/Nutrition
ORIGINAL ARTICLE

Diabetes Care 28:2458, 2005

Beneficial Effects of Adding Spironolactone to Recommended Antihypertensive Treatment in Diabetic Nephropathy

A randomized, double-masked, cross-over study

- Steno Diabetes Center
- 21 Caucasian type II diabetic patients
- Persistent macroalbuminuria despite maximal recommended dose of ACEi and/or ARB
- Randomized, double-masked, placebo-controlled, and crossover trial
- Spironolactone 25 mg vs. Placebo 1 T/D for 8 weeks
- 1° endpoint: Albuminuria
- 2° endpoints: 24-hour BP, fractional clearance of albumin and GFR

Review

Table 3—*Effects of adding spironolactone (25 mg once daily) to conventional antihypertensive medication, including an ACE inhibitor and/or an ARB in maximally recommended doses in 20 type 2 diabetic patients with nephropathy*

	Conventional antihypertensive treatment			
	+ Placebo	+ Spironolactone (25 mg once daily)	Mean difference (95% CI)	*P* value
Albuminuria (mg/24 h)	1,366 (653–4,208)	1,067 (429–2,338)	−376 (−41 to −25)	<0.001
24-h albuminuria (μg/min)	1,301 (644–2,005)	741 (455–1,209)	−438 (−27 to −56)	<0.001
GFR (ml/min per 1.73 m²)	74 ± 6	73 ± 4	−3 (−6 to 0.3)	0.08
Fractional albumin clearance (R_{alb}) ($\times 10^{-5}$)	301 (116–791)	298 (156–836)	−40% (−53 to −24)	<0.001
Systolic blood pressure (mmHg)				
Other	142 ± 4	132 ± 4	−10 (−16 to −5)	0.001
24 h	136 ± 3	132 ± 3	−4 (−10 to −2)	0.003
Day (7:00 a.m. to 11:00 p.m.)	141 ± 3	134 ± 3	−7 (−11 to −3)	0.001
Night (11:00 p.m. to 7:00 a.m.)	129 ± 4	124 ± 5	−5 (−13 to 2)	0.17
Diastolic blood pressure (mmHg)				
Other	76 ± 1	71 ± 2	−5 (−9 to −1)	<0.01
24 h	72 ± 1	67 ± 1	−4 (−6 to −2)	<0.001
Day (7:00 a.m. to 11:00 p.m.)	74 ± 1	69 ± 1	−4 (−7 to −2)	<0.001
Night (11:00 p.m. to 7:00 a.m.)	65 ± 2	63 ± 2	−2 (−5 to 1)	0.18
Plasma creatinine (μmol/l)	121 ± 7	132 ± 10	11 (3–19)	<0.01
Weight (kg)	100.3 ± 3	100.2 ± 3	−1.4 (−2.5 to −0.2)	0.02
Urinary sodium excretion (mmol/l)	217 (163–266)	205 (138–293)	7% (−2 to 15)	0.09
Urinary K-to-Na ratio	0.96 ± 0.04	0.42 ± 0.03	0.01 (−0.06 to 0.03)	0.39
Plasma albumin (g/l)	37.5 ± 0.6	37.9 ± 0.5	0.4 (−0.4 to 1.1)	0.27
Plasma renin activity (ng angiotensin I ml⁻¹ h)	6.3 (3–12)	16 (8–23)	263% (150–360)	<0.001
Plasma aldosterone (pg/ml)	99 (27–413)	87 (36–143)	22% (−18–128)	<0.001
Plasma potassium (mmol/l)	4.0 ± 0.1	4.3 ± 0.1	0.3 (0.1–0.4)	<0.01
Plasma sodium (mmol/l)	140 ± 0.5	139 ± 0.6	−1.4 (−2.4 to −0.4)	<0.01
Hemoglobin (mmol/l)	8.0 ± 0.3	7.9 ± 0.2	−0.04 (−0.2 to 0.1)	0.66
ANF (%)	7.8 ± 0.4	8.1 ± 0.3	0.3 (−0.06–0.7)	0.23
Plasma cholesterol (mmol/l)	4.1 ± 0.3	4.2 ± 0.1	0.1 (−0.2 to 0.4)	0.64
Plasma LDL (mmol/l)	1.9 ± 0.1	2.0 ± 0.2	0.1 (−0.05 to 0.2)	0.44
Plasma HDL (mmol/l)	1.14 ± 0.06	1.15 ± 0.07	0% (−0.03 to 2.06)	0.82

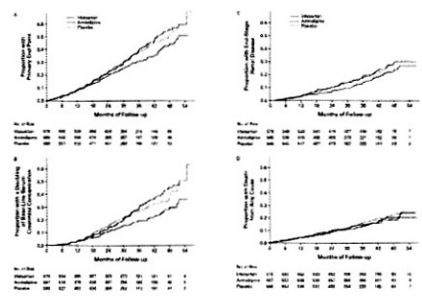
Data during treatment with placebo and 25 mg spironolactone once daily are means ± SE of geometric mean (interquartile range). Changes from placebo to 25 mg spironolactone are expressed as mean difference (placebo − spironolactone) with 95% CI.

Clinical Science Articles *J Am Soc Nephrol 16:3027, 2005*

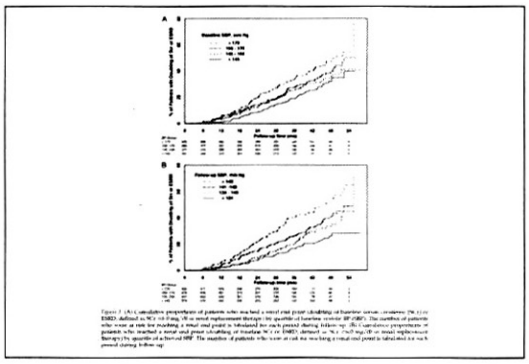
Independent and Additive Impact of Blood Pressure Control and Angiotensin II Receptor Blockade on Renal Outcomes in the Irbesartan Diabetic Nephropathy Trial: Clinical Implications and Limitations

Marc A. Pohl,* Samuel Blumenthal,† Daniel J. Cordonnier,‡ Fernando De Alvaro,§ Giacomo DeFerrari,‖ Gilbert Eisner,¶ Enric Esmatjes,** Richard E. Gilbert,†† Lawrence G. Hunsicker,‡‡ Jose B. Lopes de Faria,§§ Ruggero Mangili,‖‖ Jack Moore, Jr.,¶¶ Efrain Reisin,*** Eberhard Ritz,††† Guntram Schernthaner,‡‡‡ Samuel Spitalewitz,§§§ Hilary Tindall,‖‖‖ Roger A. Rodby,¶¶¶ and Edmund J. Lewis,*** for the Collaborative Study Group***

- Irbesartan in Diabetic Nephropathy Trial (IDNT)
- 1,590 type II diabetic patients
- Accompanied with hypertension, macroalbuminuria, and mild to moderate renal failure (< 3.0 mg/dL)
- Randomized, double-blind, placebo-controlled trial
- Irbesartan 300 mg vs. Amlodipine 10 mg vs. Placebo
- 1° outcome: Time to a composite end point of doubling of the baseline serum creatinine, ESRD, or all-cause mortality



Cumulative Proportion of Patients with the Primary Outcome



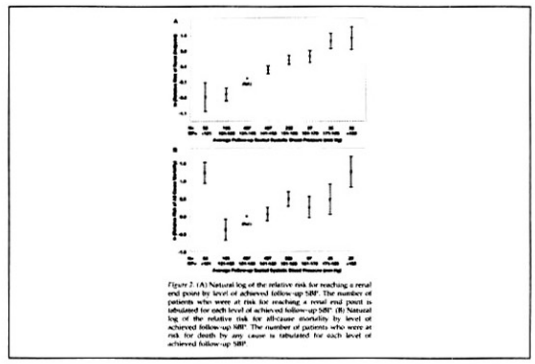


Table 2. Renal risk reduction (doubling of SCr or ESRD) by level of achieved seated SBP and assigned treatment

	SBP (mmHg)				Row Totals
	<134	134 to 140	141 to 149	>149	
No. of patients	379	357	428	426	1590
No. of events (%)	63 (17)	91 (32.7)	125 (29.2)	164 (38.5)	435 (27)
RR					
irbesartan versus amlodipine + placebo	16/151 versus 45/228	27/128 versus 54/229	26/122 versus 97/306	42/136 versus 122/290	115/537 versus 318/1053
irbesartan (%) versus amlodipine + placebo (%)	12 versus 20	21 versus 24	23 versus 32	31 versus 42	21 versus 30
irbesartan versus amlodipine + placebo	0.55 (P = 0.034)	0.92 (P = 0.71)	0.66 (P = 0.05)	0.70 (P = 0.05)	0.67 (P = 0.0002)

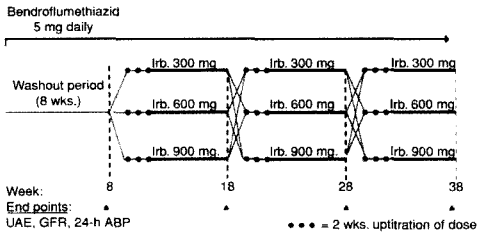
Kidney International, Vol. 68 (2005), pp. 1190–1198

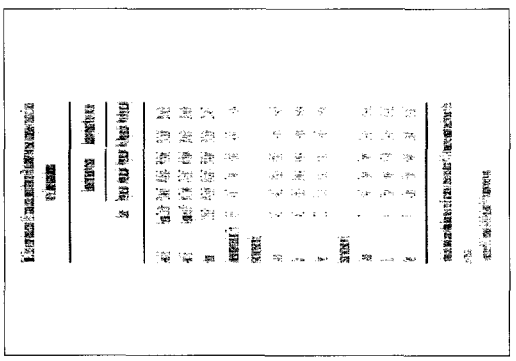
Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria

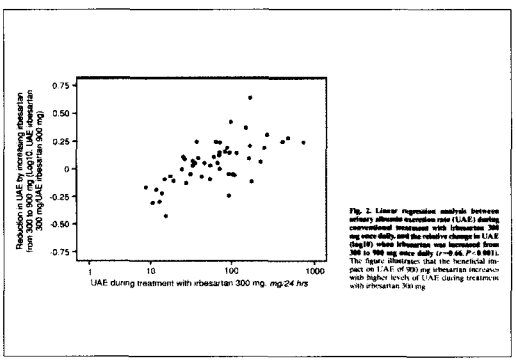
KASPER ROSSING, KATRINE J. SCHJOEDT, BERTI R. JENSEN, FRANS BOOMSMA, and HANS-HENRIK PARVING

Steno Diabetes Center, Gentofte, Denmark; Erasmus MC, Rotterdam, The Netherlands; and Faculty of Health Science, University of Aarhus, Aarhus, Denmark

- Steno Diabetes Center
- 52 Caucasian type II diabetic patients
- Accompanied with HiBP and microalbuminuria
- Randomized, double-masked, crossover trial
- 8-week washout period of all previous medications
- 2-week dose titration period + Tx period
- Irbesartan 300 mg vs. 600 mg vs. 900 mg
- 1° endpoint: UAE
- 2° endpoints: 4-hour UAE, fractional clearance of albumin, 24-hour BP, and GFR







Diabetes 54:2206, 2005

Rosiglitazone Improves Glomerular Hyperfiltration, Renal Endothelial Dysfunction, and Microalbuminuria of Incipient Diabetic Nephropathy in Patients

Frank Pistrosch,[1] Kay Herbrig,[1] Beate Kindel,[2] Jens Passauer,[1] Sabine Fischer,[2] and Peter Gross[1]

- University Hospital "Carl Gustav Carus", Germany
- 19 type II diabetic patients
  - 9 without microalbuminuria (Group 1)
  - 10 with microalbuminuria (Group 2)
- Randomized, double-blind, placebo-controlled, and crossover trial
- Group 1: Rosiglitazone vs. Nateglinide for 12 weeks
- Group 2: Rosiglitazone vs. Placebo for 12 weeks
- Measurements: RPF, GFR, insulin sensitivity index, UAE, and plasma renin activity

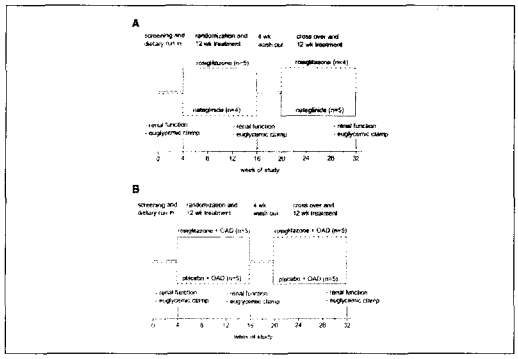


TABLE 2
Clinical characteristics of type 2 diabetic patients with and without microalbuminuria after rosiglitazone or an alternative treatment

	Without microalbuminuria		With microalbuminuria	
	Nateglinide	Rosiglitazone	Placebo + previous oral antidiabetic drug	Rosiglitazone + previous oral antidiabetic drug
A1C (%)	6.4 ± 0.3	6.2 ± 0.3	6.8 ± 0.2	6.6 ± 0.2
Fasting plasma glucose (mmol/l)	6.9 ± 0.6	6.2 ± 0.4	7.9 ± 0.7	7.0 ± 0.7
Insulin sensitivity index (M_{ISI}) (mg · kg^{-1} · min^{-1})	2.4 ± 0.4	3.7 ± 0.3*	2.0 ± 0.4	2.9 ± 0.3*
Systolic blood pressure (mmHg)	127.9 ± 4.0	123.0 ± 2.7	140.4 ± 3.7	137.4 ± 3.1
Diastolic blood pressure (mmHg)	77.8 ± 3.4	76.1 ± 4.0	84.6 ± 3.4	79.7 ± 2.4
MAP (mmHg)	94.8 ± 3.2	92.6 ± 3.3	103.0 ± 3.4	99.8 ± 3.1
Urinary albumin excretion (mg/24 h)	5.6 ± 1.4	6.6 ± 1.9	118.5 ± 31.1	30.4 ± 12.3*
Urinary protein excretion (mg/24 h)	106.3 ± 21.9	97.5 ± 20.1	816.57 ± 56.4	106.5 ± 24.0*
Urinary sodium excretion (mmol/24 h)	203.8 ± 19.3	204.7 ± 19.0	200.6 ± 19.1	202.4 ± 17.8
Urinary urea excretion (mmol/24 h)	441.9 ± 46.0	455.1 ± 25.6	438.5 ± 27.8	432.3 ± 29.1
Plasma renin (pg/ml)	20.8 ± 7.3	23.4 ± 8.3	45.6 ± 15.4	47.0 ± 15.1
C-reactive protein (mg/l)	2.4 ± 1.1	1.5 ± 0.8	2.4 ± 0.3	1.8 ± 0.9
Creatinin (µmol/l)	82.4 ± 5.5	84.7 ± 6.7	85.3 ± 5.0	85.7 ± 4.9

Data are means ± SE. *$P < 0.01$ vs. nateglinide or placebo.

TABLE 3
Effects of i-NMMA on renal function and hemodynamic parameters (expressed as percentage change of each parameter)

		Without microalbuminuria		With microalbuminuria	
	Control subjects	Nateglinide	Rosiglitazone	Placebo + oral antidiabetic drug	Rosiglitazone + oral antidiabetic drug
GFR	2.8 ± 5.9	−1.7 ± 5.4	2.1 ± 4.1	−3.6 ± 3.4	−2.1 ± 3.1
RPF	10.9 ± 2.5*	1.1 ± 3.1†	13.1 ± 4.3*	2.8 ± 6.6	9.6 ± 3.1*
Filtration fraction	17.4 ± 4.2*	1.1 ± 2.5†	16.5 ± 5.0*	0.8 ± 3.1†	11.9 ± 3.8*
MAP	9.0 ± 4.7*	3.6 ± 2.8†	7.6 ± 1.6*	4.8 ± 1.9†	6.5 ± 2.1*
Renal vascular resistance	21.0 ± 4.3*	16.6 ± 3.0*	26.9 ± 5.7*	14.7 ± 3.1*	20.4 ± 3.2*

Data are means ± SE. *Indicates a significant change ($P < 0.05$) of the hemodynamic parameter after i-NMMA administration compared with the corresponding baseline parameter. †$P = 0.02$ vs. rosiglitazone.

TABLE 4
Renal hemodynamic function of type 2 diabetic patients with and without microalbuminuria after rosiglitazone or an alternative treatment

	Without microalbuminuria		With microalbuminuria	
	Nateglinide	Rosiglitazone	Placebo + previous oral antidiabetic drug	Rosiglitazone + previous oral antidiabetic drug
GFR (ml/min)	118.7 ± 7.2	103.2 ± 4.0*	121.1 ± 9.8	119.6 ± 8.7†
RPF (ml/min)	550.3 ± 39.6	553.9 ± 32.0	568.4 ± 40.9	567.5 ± 37.2
Filtration fraction (%)	22.0 ± 1.4	19.9 ± 1.1*	23.2 ± 1.7	20.5 ± 1.6†
Renal vascular resistance (mmHg · min^{-1} · l^{-1})	116.3 ± 8.4	165.9 ± 7.3	108.8 ± 7.6	106.1 ± 9.4

Data are means ± SE. *$P < 0.05$ vs. nateglinide or placebo.

Kidney International, Vol. 66 (2004), pp. 164–170

Impact of diabetic nephropathy and angiotensin II receptor blockade on urinary polypeptide patterns

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Steno Diabetes Center, Gentofte, Denmark; Mosaiques Diagnostics and Therapeutics AG, Hannover, Germany; Hannover Medical School, Hannover, Germany; and Faculty of Health Sciences, Aarhus University, Aarhus, Denmark

- Steno Diabetes Center
- 78 type 2 diabetic patients
  - 20 with normoalbuminuria and no retinopathy
  - 20 with normoalbuminuria and retinopathy
  - 20 with microalbuminuria and retinopathy
  - 18 with macroalbuminuria and retinopathy
- Randomized, double-blind, crossover trial
- Placebo vs. Candesartan cilexetil 8, 16, and 32 mg
- Four treatment periods each lasting 2 months
- Measurement: Urinary polypeptide patterns

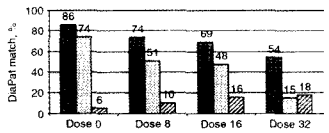

Fig. 6. Polypeptide pattern recognition for monitoring of therapeutic effects. The list of 113 diabetic renal damage marker polypeptides was applied to the samples undergoing candesartan treatment. A pattern recognition algorithm (DiaPat) was used to specify the analogy between the sample pattern and the marker list (first bar). Since the marker list is composed of positive (present/increased in diabetic renal damage samples) and negative (absent/decreased in diabetic renal damage samples) markers, both types are displayed in percent in the second bars and the third bars. As a result of the treatment, the detection of "diabetic renal damage positive markers" decreases in the samples of this patient from 74% to 15%, while the detection of "diabetic renal damage negative markers" increases from 6% to 18%. The overall calculated factor for diabetic renal damage decreases from 86% without treatment, to 74% at dose level 8, 69% at dose level 16, and down to 54% at dose level 32.

Horm Metab Res 37(Suppl. 1):4, 2005

Dual Blockade of the Renin-angiotensin-aldosterone System in Diabetic Nephropathy: The Role of Aldosterone

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K. Rossing[1]
F. Boomsma[2]
H. H. Parving[1,3]

- Steno Diabetes Center
- 51 type I diabetic patients with macroalbuminuria
- Randomized, double-masked, crossover trial
- Dual RAAS blockade vs. Monotherapy with an ACEi
- ARB (Irbesartan 300 mg or Valsartan 80 mg)
- ACEi (Captopril 100 mg or Enalapril 20 mg or Benazepril 20 mg or Enalapril 40 mg)
- Each treatment period lasting 8 weeks
- Measurements: 24-hour BP, UAE, GFR, aldosterone, ACE/ID genotyping

Table 1 Effects of dual blockade of the renin-angiotensin system compared to ACEI monotherapy in 51 type 1 diabetic patients with diabetic nephropathy

	Monotherapy with an ACEI	*Dual RAAS blockade*	*Mean difference (95% CI)*	*Value of p*
Albuminuria (mg/24-hour)*	**558 (392,794)**	**349 (233,524)**	**−37% (−47, −26)**	**<0.0001**
GFR (ml/min/1.73 m²)	67 (4)	64 (4)	−4 (−6, −1)	0.0064
24-hour systolic BP (mmHg)	**137 (2)**	**129 (2)**	**−7 (−11, −3)**	**0.0007**
24-hour diastolic BP (mmHg)	76 (1)	71 (1)	−5 (−7, −3)	<0.0001
Plasma potassium (mmol/l)	**4.1 (0.1)**	**4.4 (0.1)**	**0.3 (0.2, 0.40)**	**<0.0001**
Plasma aldosterone (pg/ml)*	59 (45,78)	43 (32,56)	−28% (−42, −11)	0.004

GFR, glomerular filtration rate; BP, blood pressure. Data are expressed as means (SEM), or * geometric mean (95% CI).

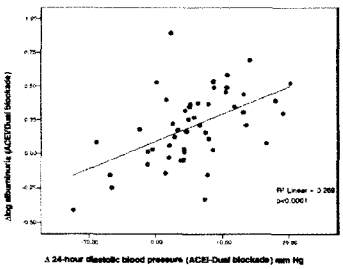

Fig. 1 Linear regression analysis between changes in diastolic blood pressure and changes in albuminuria in type 1 diabetic patients with diabetic nephropathy treated with dual blockade of the renin-angiotensin system.

Table 3 Multivariate linear regression analysis for changes in albuminuria on dual blockade. Changes in plasma aldosterone and variables related to changes in albuminuria in univariate analysis (changes in diastolic blood pressure, changes in GFR, and the ACE/ID genotype) are included in the model

Dependent variable: Changes in albuminuria (%) Independent variables	*Reduction in albuminuria (%)*	*p-value*
Plasma aldosterone (50% reduction)	**10**	**<0.05**
24-hour diastolic blood pressure (1 mmHg reduction)	5	<0.001
Reduction in GFR (per ml/min/1.73 m²)	**1**	**<0.05**
ACE/ID genotype (patients carrying the D-allele)	−39	<0.05

R^2 (adjusted): 0.57, $p < 0.001$, $n = 42$ (due to missing genotypes in 9 patients)

Review

J Am Soc Nephrol 16:2119, 2005

Additive Antiproteinuric Effect of Pentoxifylline in Patients with Type 2 Diabetes under Angiotensin II Receptor Blockade: A Short-Term, Randomized, Controlled Trial

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- Spain study
- 61 type II diabetic patients
- Accompanied with macroalbuminuria despite ARB and diabetic retinopathy but without hypertension
- Randomized trial
- Pentoxifylline (Methylxanthine derivative) 1,200 mg/D vs. No additional treatment for 4 months
- Measurements: UAE, serum and urinary TNF-α

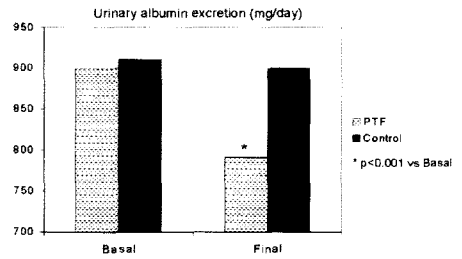

Figure 2. Evolution of urinary albumin excretion in control subjects and patients who received pentoxifylline.

Table 2. Evolution of study parameters in the active and control groups.

	Baseline	Fourth Month	*P*
PTF group (n = 30)			
systolic BP (mmHg)	134 ± 6	135 ± 5	NS
diastolic BP (mmHg)	83 ± 6	84 ± 5	NS
SCr (mg/dl)	0.98 ± 0.20	1.0 ± 0.18	NS
HbA_1 (%)	8.0 ± 0.9	7.9 ± 0.9	NS
BMI (kg/m^2)	30.4 ± 2.1	30.0 ± 2.4	NS
UTNF-α (pg/mg)	16.0 (8.0 to 29.0)	14.2 (3.0 to 26.0)	< 0.01
STNF-α (pg/ml)	6.4 (2.1 to 9.7)	4.6 (0.4 to 9.0)	< 0.01
Control group (n = 31)			
systolic BP (mmHg)	132 ± 6	133 ± 4	NS
diastolic BP (mmHg)	81 ± 7	82 ± 6	NS
SCr (mg/dl)	1.0 ± 0.17	1.03 ± 0.14	NS
HbA_1 (%)	8.0 ± 1.0	8.0 ± 0.9	NS
BMI (kg/m^2)	29.3 ± 1.8	29.3 ± 1.7	NS
UTNF-α (pg/mg)	15.0 (7.0 to 29.0)	14.0 (5.0 to 32.0)	NS
STNF-α (pg/ml)	5.1 (1.4 to 10.0)	5.5 (2.5 to 9.9)	NS

Kidney International, Vol. 67 (2005), pp. 2484–2494

Increased tubular organic ion clearance following chronic ACE inhibition in patients with type 1 diabetes

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Baker Medical Research Institute, Melbourne, Victoria, Australia, Endocrinology Unit and Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Victoria, Australia

- Melbourne Diabetic Nephropathy Study Group
- 33 type I diabetic patients
- Accompanied with microalbuminuria but without hypertension
- Randomized, placebo-controlled trial
- Perindopril vs. Nifedipine vs. Placebo
- Measurements: UAE, Cr clearance, isotopic GFR, N-methylnicotinamide (NMN, endogenous cation) and hippurate (endogenous anion) clearance

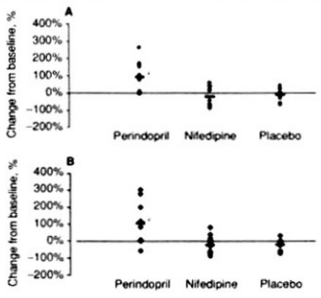

Fig. 1. The effect of 2 years of treatment on treatment on baseline N-methylnicotinamide (NMN) clearance (A) adjusted for isotopic glomerular filtration rate (GFR) (B). * $P < 0.05$ vs. baseline.

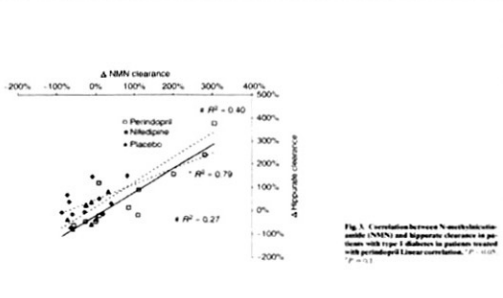

Fig. 3. Correlation between N-methylnicotinamide (NMN) and hippurate clearance in patients with type 1 diabetes in patients treated with perindopril Linear correlation. * $P < 0.05$

Diabet Med 22:410, 2005

Teaching and motivating patients to control their risk factors retards progression of cardiovascular as well as microvascular sequelae of Type 2 diabetes mellitus—a randomized prospective 8 years follow-up study

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- Israel study
- 141 type II diabetic patients
- Accompanied with hypertension and dyslipidemia but without macroalbuminuria
- Standard consultation vs. Patient-participation
  - SC: Attendance at standard consultation visits
  - PP: Additional two 2-hour individual education
- 1° endpoint: Combined cardiovascular event index
- 2° endpoints: eGFR and urinary ACR

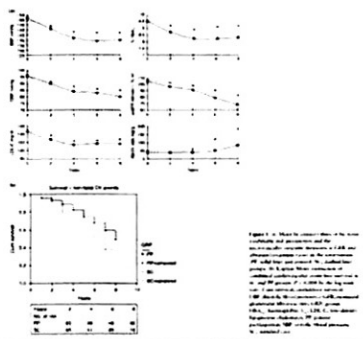

Table 1. Relative risk reduction (95% confidence intervals) of the main cardiovascular parameters in the intervention (PP) vs. the control (SC) groups

Parameter	No. of events SC	PP	RR (95%-CI)	P-value
MI	19	11	0.79 (0.43–1.28)	0.06
Stroke	17	8	0.47 (0.12–0.83)	0.016
CHD + PCI	37	26	0.70 (0.34–0.94)	0.04
Non-fatal CV events	72	47	0.63 (0.41–0.89)	0.012
CV mortality	8	5	0.62 (0.31–1.2)	0.14

CABG, coronary artery bypass graft; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Clinical Practice

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Comparison of the Effect of Pentoxifylline and Captopril on Proteinuria in Patients with Type 2 Diabetes mellitus

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- Iran study
- 39 Iranian type II diabetic patients
- Accompanied with macroalbuminuria
- Randomized, open, crossover trial
- Pentoxifylline 1,200 mg vs. Captopril 75 mg/D for 2 months
- Washout period: 2 weeks
- Measurements: Serum Cr, 24-hour urinary protein excretion, Ccr

Table 2. Comparison of blood pressure, fasting plasma glucose, serum creatinine, creatinine clearance and proteinuria in 39 type 2 diabetic patients before and after treatment with captopril and pentoxifylline

Parameters	Captopril (n = 19) mean (SD)		Differences (95% confidence interval)	Pentoxifylline (n = 20) mean (SD)		Differences (95% confidence interval)
	baseline	after therapy		baseline	after therapy	
Systolic blood pressure, mm Hg	136.8 (15.5)	135.3 (10.9)	1.6 (−4.6 to 7.8)	137.0 (15.0)	135.3 (10.4)	1.8 (−3.7 to 7.2)
Diastolic blood pressure, mm Hg	88.9 (9.4)	86.1 (7.0)	2.8 (0.9 to 4.9)**	89.8 (8.8)	86.3 (6.9)	3.5 (1.6 to 5.4)***
Mean arterial pressure, mm Hg	104.4 (10.7)	101.9 (6.9)	2.4 (−0.3 to 5.1)	105.4 (10.0)	102.2 (6.8)	3.2 (0.8 to 5.5)*
Fasting plasma glucose, mg/dl	164.6 (48.3)	143.5 (29.3)	21.1 (5.5 to 36.6)*	175.2 (49.8)	153.2 (35.9)	22.0 (7.3 to 36.7)**
Serum creatinine, mg/dl	1.08 (0.3)	1.05 (0.2)	0.03 (0.05 to −0.08)	1.1 (0.3)	1.0 (0.3)	0.1 (−0.3 to 0.2)
Creatinine clearance, ml/min	66.9 (18.7)	73.8 (16.6)	−6.9 (−14.0 to 0.3)	65.9 (16.1)	78.8 (21.1)	−12.9 (−20.8 to −5.0)**
Proteinuria, g/24 h	1.3 (0.7)	0.8 (0.7)	0.5 (0.2 to 0.8)**	1.4 (0.7)	1.0 (0.7)	0.4 (0.08 to 0.7)*

* p < 0.05, ** p < 0.01, *** p < 0.001

Journal of Human Hypertension (2005) 19, 139–144

www.nature.com/jhh

ORIGINAL ARTICLE

Rationale and design of a study comparing two fixed-dose combination regimens to reduce albuminuria in patients with type II diabetes and hypertension

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- American multicenter study
- 334 type II diabetic patients
- Accompanied with albuminuria and hypertension
- Randomized, double-blind, parallel-group trial
- Amlodipine besylate + Benazepril HCl vs. Benazepril HCl + Hydrochlorothiazide for 1 year
- 1° objective: Urinary ACR
- 2° objective: Urinary ACR/eGFR, insulin resistance, plasma B-type natriuretic peptide, hs-CRP

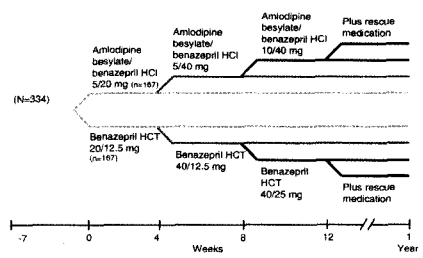

Figure 1 The GUARD study design.

J Am Soc Nephrol 16:3397, 2005

Total Plasma Homocysteine and Arteriosclerotic Outcomes in Type 2 Diabetes with Nephropathy

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Kidney International, Vol. 68 (2005), pp. 774–778

C-reactive protein as a predictor of total arteriosclerotic outcomes in type 2 diabetic nephropathy

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J Am Soc Nephrol 16:S42, 2005

Targeting Albumin Excretion Rate in the Treatment of the Hypertensive Diabetic Patient with Renal Disease

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