

Long-Term Cardiovascular Effects of Insulin Sensitizer Troglitazone on Non-Diabetic Individuals With Insulin Resistance: Double Blind, Prospective Randomized Study

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Abstract

Objectives. The study was undertaken to assess the long-term cardiovascular effects of troglitazone on non-diabetic individuals with insulin resistance.

Background. It has been suggested that treatment with troglitazone or similar insulin-sensitizing agents may prevent cardiovascular complications in non-diabetic individuals with insulin resistance. However, the long-term cardiovascular effects of these agents on non-diabetic individuals remain to be defined.

Methods. A total of 137 African-American offspring of type 2 diabetic parents, with normal glucose tolerance and insulin resistance, were randomly divided to receive troglitazone 200 mg/day ($n = 40$), or placebo ($n = 97$) for 24 months. Brachial artery blood pressure (sphygmomanometry); aortic pulse wave velocity (carotid to femoral artery, Doppler); left ventricular diameters and mass (echocardiography); ascending and abdominal aortic distensibility (echocardiography, blood pressure); and metabolic and lipid profile were assessed at baseline, 12, and 24 months after randomization (12, 24 respectively).

Results. The pulse wave velocity increased significantly in the troglitazone group compared to placebo group ($p < 0.05$). Changes from baseline in the troglitazone group were significant ($_{12} = 1.09 \pm 0.36$ m/sec, $_{24} = 2.08 \pm 0.45$ m/sec, ANOVA $p < 0.001$) while pulse wave velocity remained unchanged in the placebo group. This increase in pulse wave velocity is consistent with a decrease in the elastic properties of the aorta.

Conclusions. Long-term administration of troglitazone to non-diabetic African-Americans with insulin resistance was associated with a decrease in the elastic properties of the aorta. Long-term therapy with troglitazone or similar agents for the prevention of cardiovascular complications in non-diabetic individuals with insulin resistance has to be critically evaluated.

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Key Words

■ Aorta (pulse wave velocity) ■ Insulin (resistance, troglitazone) ■ Prevention
■ Diabetes mellitus ■ Complications

INTRODUCTION

It is well known that insulin resistance and hyperinsulinemia may precede for years the devel-

opment of glucose intolerance and type 2 diabetes mellitus (DM)¹. Normal glucose tolerant offspring of patients with type 2 DM have reduced insulin sensitivity and increased plasma insulin levels^{2,3}.

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Such subjects demonstrate an increased risk for developing type 2 DM in the future⁴). These abnormalities may be particularly marked among different ethnic groups^{5,6}).

It has been suggested that improvement of insulin sensitivity in high-risk individuals by lifestyle and dietary modification⁷ or by treatment with insulin-sensitizing pharmacological agents, may delay the development of type 2 DM and the related cardiovascular complications⁸). Oral antidiabetic troglitazone improves glucose control and insulin sensitivity in patients with type 2 DM^{9,10}). However, the long-term cardiovascular effects of troglitazone and similar agents in non-diabetic individuals with insulin resistance remain to be defined.

In this prospective, randomized, double-blind study, the long-term effects of troglitazone on multiple cardiovascular parameters in non-diabetic African-Americans with insulin resistance and a family history of type 2 DM have been studied.

SUBJECTS AND METHODS

Study population

The study population was comprised of 137 non-diabetic African-American offspring of at least one parent with type 2 DM, with an age range from 22 to 55 years (mean age 41 ± 7 years). The diagnosis of type 2 DM in parents was defined using the National Diabetes Data Group criteria¹¹). All subjects had fasting plasma glucose < 115 mg/dl, plasma glucose 2 hr after administration of 75 g oral glucose load < 140 mg/dl and decreased peripheral action of insulin as defined by insulin sensitivity index (S_I). Individuals with a history of excessive alcohol use, liver, kidney, or heart diseases, as well as pregnant or current breastfeeding women were excluded prior to entry into the study. Subjects on pharmacological agents known to affect cardiovascular system, glucose metabolism, or insulin levels were also excluded.

The study protocol was approved by the Human Subjects Research Review Committee of The Ohio State University. Written informed consent was obtained from all individuals prior to enrollment into the study.

Cardiovascular studies

After the initial physical examination, brachial artery pressure was measured by sphygmomanometry with subjects in the supine position. Pulse pressure was obtained by subtracting the diastolic from

the systolic blood pressure.

All subjects underwent echocardiography using a Hewlett-Packard Model 77020 A device. Echocardiograms were performed with subjects in the supine position. Parasternal long axis, apical four-chamber and apical two-chamber views were obtained. An electrocardiogram was recorded simultaneously with the echocardiogram. Recordings were performed in SVHS format videotape with a Panasonic Model AG 7300 video recorder at a rate of 30 frames per second.

1) Pulse wave velocity

For the measurements of aortic pulse wave velocity (PWV), the Doppler flow velocities from the carotid and femoral arteries were recorded simultaneously with the electrocardiogram. The time from the beginning of the QRS complex to the upstroke of the carotid artery Doppler flow velocity and the time from the beginning of the QRS complex to the upstroke of the left femoral artery Doppler flow velocity were measured. PWV was calculated as the ratio of the time required for the pulsed wave Doppler velocity to travel from the carotid to the femoral artery, over the distance between the carotid and femoral arteries¹²).

2) Left ventricular mass

Left ventricular diameters were measured according to the recommendations of the American Society of Echocardiography¹³) at end-diastole and end-systole, using freeze-frames from the two-dimensional directed M-mode echocardiogram. Systolic and diastolic thickness of the left ventricular posterior wall and the interventricular septum were measured at the same time in the cardiac cycle as the measurements of the left ventricular diameters.

Left ventricular mass was calculated using the formula: Left ventricular mass (g) = $\{ [\text{left ventricular diastolic diameter} + \text{left ventricular posterior wall diastolic thickness} + \text{interventricular septum diastolic thickness}]^3 - (\text{left ventricular diastolic diameter})^3 \} \times 1.05 \} - 13.6$, where 1.05 is the specific gravity of the myocardial tissue. Left ventricular mass calculated this way overestimates the ventricular mass as measured by autopsy by 13.6 g¹⁴); consequently this amount should be subtracted from the calculated value. Left ventricular mass was corrected for body surface area (g/m²).

3) Aortic distensibility

Systolic and diastolic diameters of the ascending aorta were measured approximately 3 cm above the

aortic valve, in the two-dimensional guided M-Mode echocardiographic tracings from the parasternal long-axis view. Systolic aortic diameter was measured at the maximal anterior motion of the aortic root, while diastolic aortic diameter was measured before the opening of the aortic valve, at the peak of the QRS complex in the simultaneously recorded electrocardiogram. The averaged value of 5 beats was used for analysis. Abdominal aortic diameter was measured in systole and diastole by echocardiography. Systolic aortic diameter was measured at the maximal anterior motion of the aorta, and diastolic aortic diameter was measured 100 msec before the beginning of the anterior motion of the aorta. Aortic distensibility was calculated using the formula¹²⁾:

$$\text{Aortic distensibility} (\text{cm}^2 \cdot \text{dynes}^{-1} \cdot 10^{-6}) = 2 \times (\text{systolic aortic diameter}) - (\text{diastolic aortic diameter}) \times (\text{diastolic aortic diameter}) \times (\text{pulse pressure})$$

Metabolic studies

With subjects in the supine position, two intravenous needles were inserted into the forearm veins and kept patent with 0.9% normal saline infusion. One intravenous line was used to draw samples and the other for glucose and exogenous insulin administration.

Plasma glucose concentrations were measured by the glucose oxidase method, using a glucose auto-analyzer (Beckman). Insulin and C-peptide levels were determined by a standard double-antibody radioimmunoassay technique, at the Core Laboratories of The Ohio State University Hospitals. The sensitivity of the insulin assay was 2.5 $\mu\text{U}/\text{ml}$. The intra- and interassay coefficients of variation of insulin assay were 6% and 10%, respectively. The lower limit for C-peptide assay was 0.47 ng/ml and the intra- and interassay coefficients of variation were 7% and 13% respectively.

1) Oral glucose tolerance test

Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for 3 days before the study. Following a 10 to 12 hr overnight fast, all subjects ingested a 75 g oral glucose load (Koladex Baltimore) in a total volume of 250 ml over a two-minute period. Blood samples for serum glucose, insulin, and C-peptide were obtained at baseline, and at 30, 60, 90, and 120 min after glucose administration. Glucose tolerance status was defined using the National Diabetes Data

Group criteria¹¹⁾.

2) Insulin sensitivity index (S_I) using the frequently sampled intravenous glucose tolerance test

The insulin-modified frequently sampled intravenous glucose tolerance test was performed in each subject. Four blood samples were obtained at - 20, - 15, - 10, and 0 min for basal plasma concentrations of glucose, C-peptide and insulin. The average of the four measurements was taken as the baseline value. Thereafter, 0.3 g/kg glucose (50 ml of 50% dextrose water) was infused over a one-minute period. Nineteen min after the completion of glucose administration ($t = 20 \text{ min}$), 0.05 U/kg insulin (Humulin, Lilly) dissolved in 30 ml of 0.9% normal saline, was given intravenously over 60 sec. Blood samples were obtained at frequent intervals from 2 to 180 min after insulin administration, for plasma glucose, C-peptide, and insulin concentrations. All the samples were centrifuged at 4 $^{\circ}\text{C}$ and the sera were frozen and stored at - 20 $^{\circ}\text{C}$ until assay. S_I was calculated using the minimal model software program (MINIMOD) described by Bergman *et al*¹⁵⁾.

Study protocol

After initial evaluation, all subjects were randomly assigned to receive either one tablet of troglitazone 200 mg ($n = 40$), or placebo ($n = 97$) once daily for 24 months. The study was completed before troglitazone was withdrawn from the U.S. market due to liver toxicity.

Systolic and diastolic blood pressure, PWV, ascending and abdominal aortic distensibility and left ventricular mass index were measured at baseline, 12, and 24 months after randomization.

Fasting plasma glucose, C-peptide and insulin, oral glucose tolerance test, S_I ; total cholesterol, high-density lipoprotein cholesterol and triglycerides were measured at baseline, 12, and 24 months after randomization. Low-density lipoprotein cholesterol was evaluated using the Friedwald method¹⁶⁾. Body weight and height were measured every 3 months with subjects wearing an examination gown without shoes. Body surface area was calculated using the formula: Body surface area (m^2) = squared root (body weight in kg \times height in cm / 3,600)¹⁷⁾.

Statistical analyses

Baseline measurements are presented as mean \pm

Table 1 Baseline characteristics of the study population

	Troglitazone group (n = 40)	Placebo group (n = 97)	p value
Age (yr)	40.0 ± 7.5	41.0 ± 7.0	NS
Gender (male/female)	8/32	22/75	NS
Body surface area (m ²)	1.9 ± 0.2	2.0 ± 0.2	NS
Systolic blood pressure (mmHg)	120.6 ± 15.2	126.0 ± 13.9	NS
Diastolic blood pressure (mmHg)	80.5 ± 10.1	82.4 ± 10.4	NS
Left ventricular mass index (g/m ²)	55.0 ± 12.1	62.5 ± 14.6	< 0.05
Ascending aortic distensibility (cm ² · dynes ⁻¹ · 10 ⁻⁶)	3.7 ± 1.7	3.2 ± 1.7	NS
Abdominal aortic distensibility (cm ² · dynes ⁻¹ · 10 ⁻⁶)	4.4 ± 1.7	4.0 ± 1.6	NS
Pulse wave velocity (m/sec)	8.88 ± 1.58	9.61 ± 2.42	NS
Total cholesterol (mg/dl)	183.0 ± 40.2	179.5 ± 33.1	NS
HDL cholesterol (mg/dl)	47.4 ± 13.3	49.5 ± 13.2	NS
LDL cholesterol (mg/dl)	116.8 ± 38.4	106.8 ± 38.2	NS
Total cholesterol/HDL ratio (mg/dl)	4.0 ± 1.4	3.8 ± 1.1	NS
Triglycerides (mg/dl)	100.5 ± 62.0	114.2 ± 154.4	NS
Fasting glucose (mg/dl)	79.6 ± 10.4	82.2 ± 22.6	NS
Glucose at 120 min OGTT (mg/dl)	99.3 ± 29.8	104.2 ± 36.5	NS
Fasting insulin (μU/ml)	12.8 ± 9.7	15.7 ± 13.4	NS
Insulin sensitivity index (min ⁻¹ · μU ⁻¹ · ml ⁻¹)	3.1 ± 2.4	2.7 ± 1.8	NS
Fasting serum C-peptide (ng/ml)	2.9 ± 1.3	2.9 ± 1.6	NS

Continuous values are mean ± SD.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test.

one standard deviation unless otherwise indicated. Changes from baseline to 12 months and to 24 months are presented as mean ± standard error. Differences between the two groups during the follow-up period were analyzed using analysis of variances (ANOVA). Changes within each group were also analyzed by ANOVA. Probability (*p* value) < 0.05 was considered statistically significant. Statistical analyses were performed using SAS JMPIN software.

RESULTS

The baseline clinical characteristics of the study population are presented in **Table 1**.

Troglitazone was well tolerated by all subjects; none of the subjects demonstrated any severe side effects or persistent elevation on liver enzymes.

Cardiovascular parameters

Compared to placebo, PWV increased significantly in the troglitazone group after 24 months (*p* < 0.05; **Fig. 1**). Changes from baseline in the troglitazone group were also significant (12 = 1.09 ± 0.36 m/sec, *p* < 0.01; 24 = 2.08 ±

0.45 m/sec, *p* < 0.001, ANOVA *p* < 0.001); on the contrary, PWV remained unchanged in the placebo group (**Fig. 2, Table 2**). Ascending and abdominal aortic distensibility, and left ventricular mass did not change significantly in either group.

Lipid concentrations

No significant changes in lipid concentrations were observed during the follow-up period in the troglitazone group. Total cholesterol and high-density lipoprotein cholesterol increased significantly in the placebo group (**Table 3**).

Metabolic parameters

No significant changes from baseline in fasting plasma glucose, insulin and C-peptide levels or S₁ were observed in either group during the follow-up period (**Table 3**). At 24 months, abnormal oral glucose tolerance test indicating glucose intolerance was observed in 20% of the subjects treated with troglitazone, and in 18.7% of the subjects in the placebo group (*p* = 0.88).

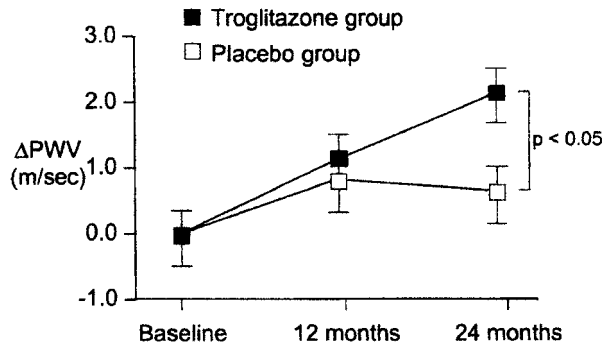


Fig. 1 Changes in pulse wave velocity in troglitazone group compared to placebo group
PWV = changes in pulse wave velocity.

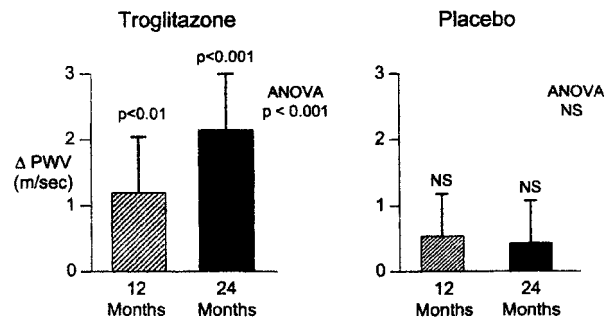


Fig. 2 Changes in pulse wave velocity within each group at 12 and 24 months
Abbreviation as in Fig. 1.

Table 2 Body weight and cardiovascular parameters : Changes from baseline

	Troglitazone group			Placebo group			
	12	24	ANOVA	12	24	ANOVA	ANOVA*
Body weight(kg)	- 2.6 ± 32.0	- 5.7 ± 34.0	NS	1.9 ± 29.0	- 0.03 ± 27.7	NS	NS
Body surface area(m ²)	- 0.02 ± 0.10	- 0.12 ± 0.07	NS	0.02 ± 0.06	- 0.07 ± 0.09	NS	NS
Systolic blood pressure(mmHg)	- 3.5 ± 3.1	- 7.5 ± 3.5	NS	- 4.4 ± 2.6	- 6.5 ± 2.4	< 0.05	NS
Diastolic blood pressure(mmHg)	- 6.2 ± 2.7	- 8.4 ± 2.7	< 0.05	- 5.8 ± 2.0	- 8.7 ± 2.8	< 0.01	NS
Left ventricular mass index(g/m ²)	- 5.9 ± 4.6	0.5 ± 5.1	NS	- 1.0 ± 2.2	- 1.6 ± 3.2	NS	NS
Ascending aortic distensibility (cm ² · dynes ⁻¹ · 10 ⁻⁶)	- 0.12 ± 0.34	- 0.39 ± 0.51	NS	- 0.59 ± 0.40	- 0.06 ± 0.72	NS	NS
Abdominal aortic distensibility (cm ² · dynes ⁻¹ · 10 ⁻⁶)	- 0.17 ± 0.48	- 0.31 ± 0.30	NS	- 0.41 ± 0.29	0.01 ± 0.70	NS	NS
Pulse wave velocity(m/sec)	1.09 ± 0.36	2.08 ± 0.45	< 0.001	0.73 ± 0.37	0.66 ± 0.61	NS	< 0.05

Values are mean ± SE. *Comparison of troglitazone and placebo groups at 24. 12 and 24 = changes from baseline to 12 months and to 24 months.

Table 3 Lipid and metabolic parameters : Changes from baseline

	Troglitazone group			Placebo group			
	12	24	ANOVA	12	24	ANOVA	ANOVA*
Total cholesterol(mg/dl)	9.4 ± 7.0	5.1 ± 7.3	NS	12.6 ± 6.0	19.8 ± 5.3	< 0.01	NS
HDL cholesterol(mg/dl)	8.5 ± 2.6	4.16 ± 2.8	NS	2.5 ± 3.0	4.6 ± 1.8	< 0.001	NS
LDL cholesterol(mg/dl)	- 0.5 ± 7.2	- 0.6 ± 6.9	NS	15.1 ± 6.4	12.0 ± 5.8	NS	NS
Triglycerides(mg/dl)	7.1 ± 8.6	7.7 ± 11.0	NS	- 25.5 ± 30.0	15.5 ± 21.0	NS	NS
Total cholesterol /HDL ratio(mg/dl)	- 0.4 ± 0.2	- 0.2 ± 0.2	NS	0.4 ± 0.2	0.1 ± 0.2	NS	NS
Fasting serum glucose(mg/dl)	5.6 ± 4.0	0.6 ± 2.9	NS	3.3 ± 3.9	1.9 ± 3.7	NS	NS
Fasting serum insulin(μU/ml)	2.7 ± 1.8	4.1 ± 1.9	NS	1.5 ± 2.2	1.8 ± 2.2	NS	NS
Insulin sensitivity index (min ⁻¹ · μU ⁻¹ · ml ⁻¹)	0.51 ± 0.58	0.58 ± 0.46	NS	0.13 ± 0.23	0.43 ± 0.36	NS	NS
C-peptide(ng/ml)	- 0.3 ± 0.2	- 0.2 ± 0.3	NS	- 0.5 ± 0.2	- 0.4 ± 0.3	NS	NS

Values are mean ± SE. *Comparison of troglitazone and placebo groups at 24. Abbreviations as in Tables 1, 2.

DISCUSSION

The present study demonstrated a significant increase in PWV in insulin-resistant non-diabetic African-Americans treated with troglitazone for 24 months, compared to placebo. PWV is related to the stiffness of the aorta. Thus, long-term administration of an insulin-sensitizing drug to non-diabetic individuals with insulin resistance but normal oral glucose tolerance test may result in a decrease of the elastic properties of the aorta. In this study, the changes in PWV occurred independently from changes in insulin sensitivity, blood pressure or lipid profile, suggesting a possible direct effect of troglitazone on the elastic properties of the aorta. The precise mechanism for this effect remains to be defined. Information about the long-term effects of insulin-sensitizing agents on PWV and aortic stiffness in non-diabetic individuals with insulin resistance is limited to experimental animals and is not available in humans. Moreover, there are no data concerning individuals with insulin resistance and normal glucose tolerance. The present study is the first to show an increase in PWV after long-term treatment with an insulin-sensitizing agent (troglitazone). This is of particular significance, since it is known that carotid-femoral PWV is positively correlated with cardiovascular morbidity and mortality¹⁸⁻²⁰ and it is considered a risk factor for atherosclerosis²¹.

In the troglitazone group, ascending and abdominal aortic distensibility, although decreased slightly, did not change significantly during the follow-up period. However, distensibility reflects elastic properties of the aorta at a specific point, while PWV provides information for the elastic properties of the entire aorta.

A mild reduction in diastolic blood pressure was observed in the troglitazone group. Both systolic and diastolic blood pressures were decreased slightly but significantly in the placebo group. Previous studies have also reported a reduction in systolic and diastolic blood pressure after treatment with troglitazone in patients with type 2 DM²² and in non-diabetic individuals with insulin resistance²³. Other studies have shown a correlation between the degree of blood pressure reduction and the improvement of insulin sensitivity in patients with type 2 DM^{24,25}. In the present study however, the blood pressure reduction was independent from any changes in insulin sensitivity.

Ghazzi *et al.*²² reported negligible changes in left ventricular mass in patients with type 2 DM after 48 weeks therapy with troglitazone. Similarly in the present study, left ventricular mass did not change significantly during the follow-up period in either group. Recent studies have demonstrated that left ventricular mass is not associated with insulin levels or insulin sensitivity in patients with type 2 DM²⁶ as well as in non-diabetic individuals^{27,28}. Similarly, in the present study, there was no correlation between baseline left ventricular mass, plasma insulin levels and insulin sensitivity.

Treatment with troglitazone 800 mg/day²² was associated with an increase in high-density lipoprotein cholesterol, and a decrease in triglycerides levels in patients with type 2 DM. However, administration of troglitazone 200 mg/day was not associated with improvement of lipid profile in patients with type 2 DM²⁹. Furthermore, a 12-week administration of 400 mg troglitazone in non-diabetic individuals with insulin resistance revealed no changes in low-density lipoprotein, high-density lipoprotein and triglyceride levels²³. Similarly, in the present study, administration of troglitazone 200 mg/day was not associated with significant changes in lipid profile.

Although data suggest that troglitazone (400 mg/day) may improve insulin sensitivity in patients with type 2 DM and insulin resistance³⁰, little is known about the effect of troglitazone on insulin sensitivity in insulin-resistant non-diabetic individuals with normal oral glucose tolerance test. In a small study, after administration of 400 mg/day troglitazone to 9 obese, non-diabetic individuals with insulin resistance and normal oral glucose tolerance test, an improvement of insulin sensitivity was observed²³. In the present study, administration of troglitazone was not associated with significant improvement of insulin sensitivity. However, the dose of 200 mg troglitazone was lower compared to that usually given to patients with type 2 DM, or to those with impaired glucose tolerance.

Insulin resistance occurs frequently in patients with type 2 DM, but may also exist in the presence of either impaired or normal glucose tolerance. Insulin resistance itself is often associated with specific cardiovascular risk factors, and is considered as a risk factor for atherosclerosis even in the absence of type 2 DM^{31,32}. It has been suggested that improvement of insulin sensitivity by lifestyle modification or administration of insulin-sensitiz-

ing pharmacologic agents might delay or prevent cardiovascular complications in non-diabetic individuals with insulin resistance. This study showed that the long-term effects of insulin sensitizing drugs on the cardiovascular system in such individuals must be considered.

CONCLUSIONS

It is concluded that no significant favorable effects on the cardiovascular parameters measured in the present study were observed after 48 months administration of 200 mg troglitazone to non-diabetic African-Americans with insulin resistance and normal oral glucose tolerance test. In addition, administration of 200 mg troglitazone was associated with an increase in the PWV, consistent with a decrease in the elastic properties of the aorta. Since increased PWV may be a risk factor for cardiovascular disease, the long-term therapy with troglitazone or similar agents for the prevention of cardiovascular complications to non-diabetic individuals with insulin resistance needs to be critically evaluated.

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