Effects of sugarcane wax alcohols in subjects with normal or borderline serum cholesterol levels

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RESUMEN. La reducción de las concentraciones séricas del colesterol transportado por las lipoproteínas de baja densidad (LDL-C) y del colesterol total (CT) ha demostrado reducir la morbilidad y mortalidad coronaria, incluso en sujetos con concentraciones normales o limítrofes de colesterol. Los alcoholes de alto peso molecular de la cera de caña de azúcar (ACCA) han demostrado reducir las concentraciones séricas de LDL-C y CT y aumentar las del colesterol transportado por las lipoproteínas de alta densidad (HDL-C), sin cambios importantes de los triglicéridos (TG), en sujetos normocolesterolémicos e hipercolesterolémicos. Sin embargo, los datos que sustentan los efectos de la dosis de 10 mg/d en individuos con concentraciones séricas de CT limítrofes o normales son relativamente escasos. El objetivo de este estudio aleatorizado, a doble ciegas y controlado con placebo consistió en confirmar la eficacia y seguridad de los ACCA (10 mg/d) en sujetos con concentraciones séricas de CT ≤ 5,9 mmol/L. Cincuenta y cinco hombres y mujeres (edad promedio: 63 años) fueron aleatorizados para recibir tabletas de placebo ó ACCA durante 12 semanas. El tratamiento redujo significativamente las concentraciones de LDL-C (22,1 %, p < 0 000 01), CT (11,7 %, p < 0,000 01) y aumentó las de HDL-C (9,6 %, p < 0,05) con respecto a las iniciales y al grupo placebo. Los indicadores de seguridad no se afectaron. Sólo un sujeto (placebo) abandonó prematuramente el ensayo, pero no a causa de EA, y dos sujetos (un tratado, un placebo) refirieron alguna EA (artralgia) durante el estudio. Este estudio confirma que los ACCA (10 mg/d) administrados durante 12 semanas fueron efectivos en reducir las LDL-C, el CT, el cociente LDL-C /HDL-C y en aumentar las HDL-C, siendo seguros y bien tolerados en sujetos con concentraciones séricas de CT normales o limítrofes.

ABSTRACT. The reduction of serum levels of low-density lipoprotein (LDL-C) and total cholesterol (TC) has been shown to reduce coronary morbidity and mortality, even in subjects with normal or borderline values of serum TC. High-molecular weight sugarcane wax alcohols (SCWA) have been shown to reduce serum LDL-C and TC, and to increase high-density lipoprotein-cholesterol (HDL-C) levels, without substantial changes on triglycerides (TG), in both normocholesterolemic and hypercholesterolemic subjects. Nevertheless, the data supporting the effects of the dose of 10 mg/d in individuals with normal or borderline serum TC levels are relatively scarce. The aim of this randomised, double-blinded and placebo-controlled study was to confirm the efficacy and safety of SCWA (10 mg/d) in subjects with serum TC ≤ 5.9 mmol/L . Fifty five men and women (mean age: 63 years) were randomised to receive placebo or SCWA for 12 weeks. The treatment significantly reduced LDL-C (22.1 %, p < 0.000 01) and TC (11.7 %, p < 0 000 01), and increased HDL-C (9.6 %, p < 0.05) values compared with baseline and placebo. Safety indicators were not affected by therapy. Only one subject (placebo) discontinued prematurely the trial, but not because of adverse effects AE, and two subjects (one treated, one placebo) referred some AE (arthralgia) during the trial. This study confirms that SCWA (10 mg/d) administered for 12 weeks was effective for lowering LDL-C, TC, LDL-C/HDL-C ratio and for increasing HDL-C, being safe and well tolerated in subjects with normal or borderline serum TC levels

INTRODUCTION

Elevated serum levels of low-density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) are major coronary risk factors,[1-3] and intervention studies have been shown that lowering LDL-C reduces the coronary risk.[4-10] Therefore, the reduction of LDL-C is a primary target in the control of blood lipids for coronary prevention. Current guidelines emphasize that lipid-modifying therapies must lower serum LDL-C to reach targets as per patients' individual coronary risk, estimated through risk calculation algorithms. This approach has led to establish *"desirable"* rather than *"normal"* serum LDL-C and TC values in the understanding that the lower, the better value. Then, values considered as *"normal"* 10 years ago currently can be high, depending on the individual risk. Current clinical practice focuses in educating the population, even subjects with *"normal"* values, in controlling their LDL-C and TC through the adherence to therapeutic lifestyle changes (TLC) as the first-choice therapy, in which the adherence to a low-fat,

low-cholesterol diet plays a key role.[11-13] This strategy alone, however, may achieve the LDL-C goals in subjects with borderline to mildly elevated values and low risk, but in many others with some non-lipid risk factor, TLC alone is not enough to reach the targets, and cholesterol-lowering therapy is recommended in addition to the TLC.[14,15] Even so, however, to achieve the LDL-C targets is a difficult task, as demonstrated by a retrospective cohort analysis involving 58 223 Europeans treated with lipid-modifying therapies for about 15 months, in which about 60 % of the subjects did not achieve the recommended goals.[16] In addition to LDL-C reduction, it is important to control other lipid variables, so that beneficial changes of the lipid profile include increases of high-density lipoprotein-cholesterol (HDL-C) and reduction of triglycerides (TG).[11-13]

Consistent with all this background, the control of serum LDL-C and TC in subjects with normal to borderline levels should no be ignored, and the effects of lipid-lowering strategies on these subjects, and not only in frankly hypercholesterolemic individuals, should be investigated.

Policosanol is a mixture of eight high molecular weight sugarcane wax alcohols with cholesterol-lowering effects [17] due to the inhibition of cholesterol synthesis by regulating the activity of hydroxymethyl glutaryl Coenzyme (HMG CoA) through the increase of AMP kinase activity,[18-21] and to the increase of LDL receptor-dependent processing and catabolic rate of LDL.[18,19]

The cholesterol-lowering effects of policosanol have been proven in healthy subjects, [22-25] in patients with type II HC or with Type 2 diabetes.[26-43] Some of these studies have investigated the effects of the treatment on the lipid profile of individuals with normal or borderline serum TC levels. [22-25] The first study included 38 subjects with serum TC < 5.7 mmol/L (defined as normocholesterolemic in that time) treated with placebo, or with 10 or 20 mg/d for only 4 weeks,[22] the second one explored the effects of 5 and 10 mg/d for eight weeks on the lipid profile of 69 subjects with serum TC < 5.2 mmol/L,[23] a third study demonstrated the hypocholesterolemic effects of 5 mg/d given for eigth weeks to 100 subjects with a broad range of serum TC (4.8 – 6.0 mmol/L).[24] and a fourth study conducted in young adults (mean age: 18 years) with serum TC between 4.8 and 5.7 mmol/L demonstrated that 5 mg/d for 12 weeks (titrated to 10 mg/day if LDL-C remained ≥ 3.4 mmol/L at week 6 lowered LDL-C and TC.[25] Accordingly, the data supporting the effects of the dose of 10 mg/d are relatively scarce.[22,23]

In light of these issues, this study was undertaken to confirm the cholesterol-lowering effects and the good safety and tolerability of SCWA (10 mg/d) in individuals with TC ≤ 5.9 mmol/L .

PARTICIPANTS AND METHODS

Study design

This prospective, randomized, placebo-controlled and double-blinded study was conducted in the Medical Surgical Research Centre (Havana City, Cuba). The independent Ethics Committee of this centre reviewed and approved study protocol according to the ethical norms of the Helsinski Declaration. The protocol Investigators obtained the subject informed written consent before commencing the trial.

Alter given their informed written consent, women and men (25-70 years old) with serum TC values ≤ 5,9 mmol/L were enrolled at the "Ramón González Coro" (Marianao) and "26 de Julio" (Playa) Policlinics (Havana City) (visit 1). At this visit subjects underwent a complete physical examination and clinical history and were advised to follow a low-fat, low-cholesterol diet (cholesterol < 300 mg/d), for four weeks while total fat, carbohydrates and proteins should be about 10, 55 and 15 %, respectively, of the total calories intake.

After concluding this baseline period, lipid profile was determined twice within 15 d, and when samples for the second determination were drawn, aliquots for safety laboratory tests were taken. Eligible patients were randomized (visit 2), under double-blind conditions, to placebo or SCWA (10 mg/d) for 12 weeks, and attended to control visits after complete 6 and 12 weeks on therapy (visits 3 and 4, respectively).

Physical examination was conducted at each visit, treatment compliance and adverse experiences (AE) were controlled after 6 and 12 weeks on therapy and the effects on the lipid profile and blood safety indicators were assessed at starting and at treatment completion.

The randomized, double-blind, placebo-controlled design was chosen as being the gold standard in clinical trials for minimising study bias.

Participants

Enrolled subjects were eligible for randomization whether at the end of the baseline period they show the following values (mmol/L): CT ≥ 4.5; ≤ 5.9 mmol/L, TG ≤ 2.2 mmol/L .

Patients with active renal, liver or/and gallbladder diseases, diagnosed neoplasias, uncontrolled diabetes or hypertension (diastolic pressure ≥ 100 mmHg), habitual alcoholic state, or with any of the following laboratory values: aspartate (ASAT) or alanine amino (ALAT) transferases > 45 U/L, glucose > 7 mmol/L, creatinine > 130 μmol/L, were excluded from the trial. Also, pregnant or nursing women, or any subject with a previous history of myocardial infarction, instable angina, coronary surgery, transient ischemic attacks, stroke, or any major surgery within six months prior to the trial were also excluded.

Premature withdrawals were pre-defined as those subjects who dropped out the trial because of any AE due to other causes (unwillingness to follow-up, protocol violations like compliance < 85 %, infringement of laboratory tests schedule and conditions, and/or consumption of forbidden concomitant drugs, among others).

Treatment

Eligible subjects were randomized to placebo or SCWA (10 mg/d). Tablets should be taken once daily with the evening meal. Drug randomization was computer-generated, with balanced blocks and allocation ratio 1 : 1. Treatments were indistinguishable. At randomization, codified treatments identically packed were given to subjects.

Compliance with study drugs was assessed through tablet count and subject interview, and considered as acceptable if drug consumption was ≥ 85 %.

Consumption of any lipid-lowering drug other than study medications was prohibited from the enrolment up to study completion.

Efficacy variables

The primary efficacy variable was to obtain a significant LDL-C reduction of at least 10 % compared with placebo, considering that subjects normal to borderline levels. Significant reductions of serum TC, TG and of LDL-C/HDL-C ratio, and increases of HDL-C were secondary efficacy variables.

Safety and tolerability

Data from physical (body weight, pulse rate, blood pressure) and laboratory (AST, ALT, glucose, creatinine) safety indicators and AE were analysed.

Any undesirable event occurred in the trial, disregarding if it was or not drug-related, was considered as an AE, being classified as mild, moderate or serious according to their intensity. Mild AE did not require discontinuation or dosage change and/or specific treatment of the AE, moderate AE required discontinuation of study drugs and/or specific treatment of the AE. Serious AE (SAE) were those leading to death and/or hospitalizations.

Laboratory examinations

Blood venous samples were drawn after a 12 h fasting condition. Serum TC, TG and HDL-C were determined through enzymatic methods using reagent kits. LDL-C values were calculated using the Friedewald equation.[44]

Blood biochemistry parameters were determined through routine enzymatic methods and reagent kits, in the Hitachi 719 autoanalyzer (Tokyo, Japan) of the Surgical Medical Research Centre. Systematic quality control was performed throughout the study.

Statistical analysis

Statistical analyses were performed through Intention to Treat (ITT). Continuous variables were analyzed with non-parametric tests, the Wilcoxon test for paired samples (within group comparisons) and the Mann Whitney U test (between group comparisons). Categorical variables were analyzed with the Fisher´s Exact Probability test.

The statistical analyses were performed using the Statistics for Windows software (Version 4,2 Stat Soft). All statistical tests were two-tailed. A difference of $p < 0.05$ was considered as statistical significant.

RESULTS

Baseline characteristics and study premature withdrawals

After concluding the baseline period, 55 of 60 enrolled subjects were eligible for randomization. Five subjects were not eligible because of TG values > 2.20 mmol/L . Of the 55 randomized, 54 individuals (98.2 %) completed the study.

The two groups were statistically similar regarding to all demographic characteristics at baseline (Table 1). Despite the enrollment was focused to a broad age range, most subjects (45/55; 81.8 %) were ≥ 60 years old, and most of them (38/55; 69,1 %) were women. Consistent with their age, the study population had non-modifiable risk factors, since 94.7 % (36/38) randomized women were postmenopausal, 14/17 (82.4 %) men were older than 45 years, and 11/55 (20 %) randomized subjects reported family history of coronary heart disease (CHD). Hypertension (28/55; 50.9 %) was frequent among study population and the frequency of smokers 8/55 (14.5 %) was somewhat high.

Concomitant medications were well matched in both groups. Consistent with the frequency of hypertension, antihypertensive drugs were the concomitant therapy most frequently consumed.

Efficacy analysis

Both groups were well matched at randomisation and treatment compliance was very good (≥ 90 %). No significant changes on LDL-C values were found in the placebo group. After 12 weeks on treatment, SCWA 10 mg/d significantly lowered serum LDL-C, the primary efficacy variable, by 22.1 % ($p < 0.000\,01$) compared with baseline and placebo. The frequency of treated subjects with LDL-C reductions >10 % (21/27; 77.8 %) was significantly greater ($p < 0.000\,1$) than in placebo (2/28; 7.1 %). The treatment also reduced significantly ($p < 0.000\,01$) serum

Table 1. Baseline characteristics of study subjects.

Characteristics	Placebo (n = 28)		SCWA (n = 27)	
Age (years) (X ± DE)	61 ± 11		64 ± 6	
Body mass index (kg/m^2) (X ± SD)	25.8 ± 3.7		25.8 ± 4.4	
Gender	n	%	n	%
Females	18	64.3	20	74.1
Males	10	35.7	7	25.9
Personal history				
Postmenopausal women	17	60.7	19	70.4
Hipertensión	15	53.6	13	48.1
Men > 45 years old	7	25.0	7	25.9
Family history of CHD	6	21.4	5	18.5
Smokers	5	17.9	3	11.1
Diabetes mellitus	3	10.7	1	3.7
Concomitant therapy[1]				
Inhibitors of the angiotensin converting enzyme	7	25.0	8	29.6
Diuretics	6	21.4	6	22.2
β-blockers	3	10.7	2	7.4
Aspirin	2	7.1	1	3.7
Nitrates	2	7.1	1	3.7

SCWA sugarcane wax alcohols. n Number of subjects. X Mean. SD Standard deviation. CHD Coronary heart disease. [1]The table includes concomitant therapy consumed by ≥ three subjects. All comparisons were not significant.

TC *versus* baseline and placebo (11.7 %) and LDL-C/HDL-C ratio (27.9 %), raised HDL-C (9.6 %) ($p < 0.01$) *versus* baseline and $p < 0.05$ *versus* placebo, but unaffected TG values (Table 2).

Safety and tolerability

Treatments were safe and well tolerated. Only one subject (placebo) dropped out the study, the reason was unwillingness to follow. Only two individuals (one SCWA, one placebo) experienced mild AE (articulation pain in both cases).

Safety indicators were well balanced in both groups at baseline and did not change significantly with the therapy as compared to placebo. Individual vales remained within normal ranges in both groups, however, glucose values significantly, but mildly, decreased compared to baseline (Table 3).

DISCUSSIÓN

This study confirms that SCWA (10 mg/d) consumed for 12 is effective for lowering LDL-C (the primary efficacy variable) in subjects with normal or borderline serum TC values (≤ 5.9 mmol/L), and that produces additional benefits in the lipid profile of these subjects, like the reduction of TC and the LDL-C/HDL-C ratio, and the increase of HDL-C.

Most study subjects were middle-aged and older subjects, all with normal to borderline serum TC values, but presenting non-lipid risk factors like age enough to be considered as a risk factor in women (94.7 % were postmenopausal) and men (82.4 % older than 45 years) and hypertension (about 51 % of study population) as the most remarkable. This situation is consistent with the fact that most included subjects were ≥ 60 years (81.8 %), a fact not planned, but that happened and that can be related with a higher motivation and conscience of health care than younger individuals. Then, the present results can be extrapolated to similar populations, which are more amenable to control lipid values as a part of a coronary prevention attitude, for which addition of SCWA to habitual TLC should be a good alternative.

Since demographic characteristics and all study variables were well matched in the two groups at baseline, random allocation of treatments can be considered as satisfactory and both groups as homogeneous for comparisons, which supports that the effects on efficacy variables here shown are actually treatment-related.

The LDL-C reduction with SCWA 10 mg/day (22.1 % vs. baseline; 25.4 % vs. placebo) achieved the predefined efficacy criterion and agreed with previous results in subjects with similar serum TC values.[22-25] The decrease of LDL-C was consistent to the reductions obtained with 5 (19.9 %)[24] or 10 mg/d (20.2 %)[23] given for eight weeks to middle-aged and older subjects with normal or borderline serum TC, although inferior to the LDL-C decrease (32.6 %) observed in young adults treated with 5 mg/d titrated to 10 mg/d for 12 weeks,[25] a fact that could be influenced by the age and general conditions of the population included in this study compared with the others.

Nevertheless, it should be noted that the dose of 10 mg/d significantly reduced serum TC, but not LDL-C, in the first study conducted in normocholesterolemic subjects, a result that can be related to the short duration of the treatment (only four weeks), so in that trial only the highest dose (20 mg/d) was able to reduce significantly serum LDL-C values.[22]

Overall, the decrease of LDL-C here found is consistent with most results obtained in dyslipidemic patients (26-43), and with the weighted estimate of LDL-C reduction (23.7 %) calculated in a meta-analysis of randomised controlled trials of policosanol (5-40 mg/d), 1 528 patients (29 eligible studies) ($p < 0.000\ 1$ cumulative p compared

Table 2. Effects on the lipid profile.

Treatment	Baseline	Week 12	Changes (%)
	LDL-C (mmol/L)		
SCWA	3.44 ± 0.44	2.68 ± 0.62$^{****+++}$	-22.1^{++++}
Placebo	3.33 ± 0.46	3.44 ± 0.51	+3.3
	TC (mmol/L)		
SCWA	5.39 ± 0.40	4.76 ± 0.61^{****++}	-11.7^{++++}
Placebo	5.31 ± 0.39	5.36 ± 0.47	+0.9
	HDL-C (mmol/L)		
SCWA	1.46 ± 0.33	1.60 ± 0.33^{**+}	+9.6^{+}
Placebo	1.43 ± 0.36	1.36 ± 0.30	-4.9
	Triglycerides (mmol/L)		
SCWA	1.35 ± 0.38	1.32 ± 0.53	-2.2
Placebo	1.49 ± 0.49	1.52 ± 0.54	+2.0
	LDL-C/HDL-C		
SCWA	2.51 ± 0.75	1.81 ± 0.74$^{******++}$	-27.9^{++++}
Placebo	2.52 ± 0.84	2.67 ± 0.81	+6.0

SCWA Sugarcane wax alcohols. Results are expressed as (X ± SD). X Mean. SD Standard deviation. $^{**}p < 0{,}01$; $^{****}p < 0{,}000\ 01$ Comparison with baseline (Wilcoxon test for paired samples). $^{+}p < 0{,}05$; $^{++}p < 0{,}01$; $^{+++}p < 0{,}000\ 1$; $^{++++}p < 0{,}000\ 01$ Comparison with placebo (Mann Whitney U test).

Table 3. Effects on safety indicators.

Treatment	Baseline	Week 6	Week 12
Physical safety indicators			
		Body weight (kg)	
SCWA	66.92 ± 9.91	67.06 ± 9.41	66.02 ± 9.61
Placebo	69.96 ± 13.10	70.07 ± 12.97	69.80 ± 13.01
		Pulse (beats/min)	
SCWA	73.56 ± 8.81	73.85 ± 6.07	72.78 ± 7.73
Placebo	77.07 ± 8.56	78.00 ± 10.17	75.63 ± 7.85
		Blood systolic pressure (mmHg)	
SCWA	128.52 ± 14.33	125.56 ± 11.88	126.30 ± 15.48
Placebo	128.57 ± 14.07	126.79 ± 10.56	126.67 ± 13.52
		Blood diastolic pressure (mmHg)	
SCWA	76.30 ± 9.26	76.30 ± 8.39	76.30 ± 6.29
Placebo	80.00 ± 11.55	78.93 ± 7.37	80.93 ± 9.31
Blood biochemistry safety indicators			
		ALT (U/L)	
SCWA	19.77 ± 6.38		20.63 ± 10.46
Placebo	22.36 ± 7.23		21.63 ± 17.92
		AST (U/L)	
SCWA	23.74 ± 9.42		25.48 ± 7.92
Placebo	23.93 ± 9.38		26.59 ± 8.07
		Glucose (mmol/L)	
SCWA	4.68 ± 0.69		4.41 ± 0.70*
Placebo	4.84 ± 0.74		4.48 ± 0.94*
		Creatinine (μmol/L)	
SCWA	83.15 ± 18.42		84.85 ± 18.75
Placebo	90.29 ± 18.97		88.63 ± 20.21

SCWA Sugarcane wax alcohols. Results are expressed as (X ± SD). X Mean. SD Standard deviation. *p < 0,05 Comparison with baseline (Wilcoxon test for paired samples).

with placebo).[45]

The effect of SCWA on serum TC was coherent with the effect on LDL-C values, although less marked, which agrees with previous results in subjects with normal to borderline values of serum TC[22-25] or in dyslipidemic patients.[26-43] Thus, previous studies demonstrated that policosanol at 5 and 10 mg/d for eight weeks significantly lowered TC by 10.5 to 12.4 % in subjects with normal or borderline serum TC,[23,24] and at 10 mg/d for only four weeks produced a significant TC reduction of 10.7 % to normocholesterolemic individuals.[22] In the study conducted in young subjects, however, administration with 5 mg/d titrated to 10 mg/d for 12 weeks higher reductions were found (21.9 %), which can be related, as stated, to the characteristics of this population, different form those included in the other trials.[25]

The changes on LDL-C and TC were beneficial, even for subjects with normal to borderline values. Indeed, mean baseline levels of TC were 5.39 and 5.31 mmol/L in the treated and placebo groups, respectively, and LDL-C were 3.44 and 3.33 mmol/L, respectively. After 12 weeks on therapy, both TC (5.36 mmol/L) and LDL-C values (3.44 mmol/L) were unaffected in the placebo group, but decreased to more desirable values (TC 4.76 mmol/L; LDL-C 2.68 mmol/L) in the treated group, which supports that SCWA assists in the management of healthy TC and LDL-C values

The other benefit of SCWA 10 mg/d on the lipid profile of study subjects was the significant increase of HDL-C (9.6 %), which generally matches with previous data despite in this study it was assessed HDL-C values through a direct method using kits, instead of assessing cholesterol levels in the supernatant obtained after precipitating β-lipoproteins,[46] as was done in previous trials.[22-43]

In fact, an HDL-C increase of about 10 % in subjects with normal to borderline serum TC treated with 5 mg/d for eight weeks has been observed[23,24] including the study in young adults in which 5 mg/d was titrated to 10 mg/d,[25] although a higher increase (15.2 %) was found in normocholesterolemic subjects treated with 10 mg/d for eight weeks.[23] Only in the study in which the treat-

ment was given for only four weeks the dose of 10 mg/d did not raise significantly HDL-C values, probably because the treatment duration was too short for obtaining a significant increase with such a dose.[22]

Consequently with the decrease of LDL-C and the increase of HDL-C, SCWA also produced a beneficial reduction of the LDL-C/HDL/C ratio in the study population.

SCWA unchanged serum TG values, in agreement with most previous data,[23,25] although significant reductions of TG have been found in two studies in subjects with normal or borderline serum TC values treated with 10 or 5 mg/d .[22,24] Overall, the effects of the therapy on this target have been marginal or null.

The treatment was safe and well tolerated. The frequency of withdrawals was very low (only one placebo subject dropped out the trial) and only two subjects (one of each group) reported a mild and common AE (arthralgia). Also, the treatment did not affect safety indicators compared with placebo, and the small but significant decrease of serum glucose can be considered as clinically non relevant since also occurred in placebo and these values are included in the normal range, probably indicating a bias on the assessment of this variable. Then, the safety results here shown agree with previous clinical data[22-43] including post-marketing studies,[47-49] demonstrating the excellent safety and tolerability of the treatment.

CONCLUSIONS

This study confirms that SCWA (10 mg/d) administered for 12 weeks was effective for lowering LDL-C, TC, LDL-C/HDL-C ratio and for increasing HDL-C, which provides more desirable values in subjects with normal or borderline serum TC levels, being safe and well tolerated.

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