

Concordance between Carotid and Femoral Ultrasound for the Diagnosis of Subclinical Atherosclerosis in Patients with Low or Intermediate Cardiovascular Risk

Concordancia entre la ecografía carotídea y la femoral para el diagnóstico de aterosclerosis subclínica en pacientes con riesgo cardiovascular bajo o intermedio

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ABSTRACT

Background: Approximately 50% of coronary events and sudden death occur in patients with low or intermediate cardiovascular risk, as determined by the Framingham risk score. Subclinical atherosclerosis in the carotid and femoral territories is a powerful predictor of cardiovascular events. Identifying patients with subclinical atherosclerosis allows reclassification of the cardiovascular risk in an individualized manner.

Objective: The aim of this study was to investigate the prevalence of subclinical atherosclerosis in patients with low or intermediate cardiovascular risk, to evaluate the diagnostic agreement between carotid and femoral Doppler ultrasound, and to determine the independent predictors of subclinical atherosclerosis in both locations.

Methods: Patients with low or intermediate risk of the Framingham risk score underwent carotid and femoral Doppler ultrasound for the diagnosis of subclinical atherosclerosis; patients with diabetes and those treated with statins were excluded.

Results: A total of 207 patients were included; 50.2% were classified as low-risk patients, 50.2% were women, and mean age was 52 ± 9 years. The prevalence of subclinical atherosclerosis was 42.5%. The concordance between carotid and femoral Doppler ultrasound was weak (κ 0.28; 95% CI, 0.13-0.44). Age and sex were independent predictors of subclinical atherosclerosis in both territories, while smoking was an independent and powerful predictor only in the femoral arteries.

Conclusions: Approximately 40% of patients with low or intermediate cardiovascular risk of the Framingham risk score have evidence of subclinical atherosclerosis. Concordance between the carotid and femoral Doppler ultrasound is weak, implying that the two methods identify subclinical atherosclerosis in different populations of patients.

Key words: Plaque, Atherosclerotic - Femoral Artery - Carotid Arteries - Ultrasonography, Doppler

RESUMEN

Introducción: Aproximadamente el 50% de los eventos coronarios y la muerte súbita tienen lugar en pacientes con riesgo cardiovascular bajo o intermedio del puntaje de Framingham. La aterosclerosis subclínica en los territorios carotídeo y femoral es un potente indicador de eventos cardiovasculares. La identificación de los pacientes con aterosclerosis subclínica permite reclasificar el riesgo cardiovascular de manera individual.

Objetivos: Investigar la prevalencia de aterosclerosis subclínica en pacientes con riesgo cardiovascular bajo o intermedio, evaluar la concordancia entre el eco-Doppler carotídeo y el femoral para su diagnóstico y determinar los indicadores independientes en ambas localizaciones.

Material y métodos: Se realizó eco-Doppler carotídeo y femoral a pacientes con riesgo bajo o intermedio del puntaje de Framingham para detectar aterosclerosis subclínica; se excluyeron los pacientes diabéticos y los tratados con estatinas.

Resultados: Se incluyeron 207 pacientes; el 50,2% eran de riesgo bajo, el 50,2% eran mujeres y la edad media fue de 52 ± 9 años. La prevalencia de aterosclerosis subclínica fue del 42,5%. La concordancia entre el eco-Doppler carotídeo y el femoral fue débil (coeficiente κ 0,28, IC 95% 0,13-0,44). La edad y el sexo fueron indicadores independientes de aterosclerosis subclínica en ambos territorios, mientras que el tabaquismo fue un poderoso indicador solo en las arterias femorales.

Conclusiones: Aproximadamente el 40% de los pacientes con riesgo cardiovascular bajo o intermedio del puntaje de Framingham tienen evidencia de aterosclerosis subclínica. La concordancia entre el eco-Doppler carotídeo y el femoral es débil, lo que implica que ambos métodos identifican aterosclerosis subclínica en diferentes poblaciones de pacientes.

Palabras clave: Placa aterosclerótica - Arteria femoral - Arterias carótidas - Ultrasonografía, Doppler

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Abbreviations

SCA	Subclinical atherosclerosis	HDL-C	High density lipoprotein-cholesterol
CV	Cardiovascular	LDL-C	Low density lipoprotein-cholesterol

INTRODUCTION

Cardiovascular (CV) disease continues to be the leading cause of death in developed countries (1) and accounts for 35% of deaths in Argentina. (2) For this reason, efforts should focus on diagnosing the early stages of atherosclerosis to prevent its progression and complications.

Currently, several risk scores are used, based on the presence of CV risk factors, to identify patients who are at risk of CV events. (4-7) However, the sensitivity and specificity of these scores to predict CV events in patients with low or intermediate risk is limited. (3, 8, 9) As an example, 60–70% of patients who suffer an acute myocardial infarction or sudden death have no known atherosclerotic disease and their risk is categorized into low or intermediate according to the Framingham risk score at the time of the event. (1, 10)

Subclinical atherosclerosis (SCA) is an expression of CV disease that reflects the consequences of chronic exposure to risk factors in genetically predisposed patients. (3) The presence of SCA in the carotid and femoral territories is a powerful predictor of coronary heart disease and CV events. (11) For this reason, detection of SCA allows refinement of risk estimate to adjust the intensity of preventive treatment. (12)

There are many imaging methods for the diagnosis of SCA, as computed tomography (coronary calcium score), (13) magnetic resonance imaging (14), positron emission tomography (15), and two- or three-dimensional ultrasound of the peripheral vessels. (16)

Ultrasound is ideal for the detection of subclinical CV disease at the population level because it is inexpensive, does not use radiation, is widely available, is sensitive for the detection of plaques, and does not require the use of contrast agents. (16, 17) In clinical practice, screening for SCA is usually performed using carotid Doppler ultrasound. We hypothesized that adding the evaluation of the femoral arteries, which only prolongs the procedure for a few minutes, would permit the diagnosis of SCA in a larger number of patients, thus enabling a more accurate estimate of their individual CV risk.

The primary endpoint of this study was to determine the diagnostic agreement between carotid and femoral Doppler ultrasound for the detection of SCA in a group of patients with low or intermediate risk, and to determine whether both procedures would identify the same group of patients, or whether SCA might be present in different territories according to different CV risk factors. In the latter case, both studies would be needed to evaluate the presence of SCA. Specifically we evaluated:

1. The prevalence of SCA in patients with low or intermediate CV risk, according to the Framingham risk score.
2. The concordance between the two methods in the diagnosis of SCA.
3. The independent predictors of SCA in each territory.

METHODS

We conducted a cross-sectional study of patients prospectively enrolled between May 2013 and September 2014. The study population consisted of asymptomatic patients with low or intermediate Framingham risk score who were referred to the Cardiovascular Prevention Department at a private teaching hospital for a carotid ultrasound study to detect SCA. Patients at high CV risk (10-year risk >20%), with history of CV disease (infarction, coronary revascularization, stroke, or peripheral vascular disease), diabetes, and those under treatment with statins were excluded.

Subclinical atherosclerosis was assessed using high-resolution Phillips 5500™ and Phillips I33™ ultrasound devices with a 7 MHz linear transducer. Longitudinal and cross-sectional two-dimensional echocardiographic images were obtained by applying standardized and validated scanning protocols. (16) The carotid ultrasound procedure included the bilateral evaluation of the common carotid, carotid bifurcation, carotid sinuses, and internal and external territories. During the procedure, both common femoral arteries were also assessed at the bifurcation and were scanned over a distance of 1.5 cm proximally and distally from this landmark. (11)

Subclinical atherosclerosis was defined as the presence of atherosclerotic plaques in the carotid or femoral territories. Atherosclerotic plaque was defined as a focal structure of the inner vessel wall with a thickness of at least 0.5 mm, or >50% of the surrounding intima-media thickness, or any intima-media thickness ≥ 1.5 mm. (18)

Medical records were reviewed for the assessment of risk factors (hypertension, diabetes, smoking and dyslipidemia), medical treatments, blood pressure obtained during the last visit and total cholesterol, HDL-C and LDL-C levels from the most recent laboratory tests available.

Framingham sex-specific equations were used to predict the 10-year risk of fatal and non-fatal CV events. Low risk was defined as a 10-year CV risk score <10% and intermediate risk as a risk score between 10–20%. (4)

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or median and interquartile range (25–75) and the differences were compared using analysis of variance or the Mann-Whitney test, as appropriate. Categorical variables were expressed as percentages and were compared using the Irwin-Fisher test. Agreement between carotid and femoral Doppler ultrasound was assessed using the kappa concordance coefficient. A logistic regression analysis was performed to identify the association of the independent variables with the presence of atherosclerotic plaques in the carotid and

femoral territories. A p value < 0.05 was considered statistically significant. All the statistical calculations were performed using MedCalc 10.2.0.0 software package.

Ethical considerations

The study protocol was approved by the institutional Ethics Committee.

RESULTS

From a total of 357 patients enrolled, 207 were included in the study (Figure 1); 49.8% (103) were men and mean age was 52 ± 9 years. Forty-six patients (22.2%) had hypertension, 50 (24.1%) were smokers, mean cholesterol level was 219 ± 45 mg/dL, and mean HDL-C was 54 ± 16 mg/dL. Baseline characteristics according to the CV risk category are shown in Table 1.

One hundred and four patients (50.2%) had low CV risk and 103 (49.8%) had intermediate CV risk.

The prevalence of SCA in the entire cohort was 42.5% (88 patients), 28% (29 patients) in the low CV risk group and 57% (59 patients) in the intermediate CV risk group. Subclinical atherosclerosis was detected only in the carotid territory in 41% of cases (36 patients), only in the femoral arteries in 27% (24 patients), and in both territories in 32% (28 patients)

(Figure 2).

The agreement between femoral and carotid ultrasound was weak for the entire cohort (kappa index 0.28, 95% confidence interval 0.13–0.44), as well as for the low and intermediate CV risk subgroups, indicating a lack of concordance between both locations of atherosclerotic plaques (Figure 3).

The prevalence of different clinical variables according to the presence or absence of SCA is shown in Table 2.

Age, male sex and smoking habits were the variables that differed significantly between the groups and were found to be independent predictors of SCA. Age and male sex were predictors of SCA in both territories, whereas smoking was a powerful predictor of SCA only in the femoral arteries (Table 3).

DISCUSSION

The findings of our study show that 42.5% of asymptomatic patients with low or intermediate Framingham risk score have evidence of SCA detectable by carotid or femoral Doppler ultrasound. In addition, we found that there is a weak agreement between the presence of atherosclerotic plaques in both vascular territories,

Fig. 1. Patient enrollment and distribution according to the cardiovascular risk category

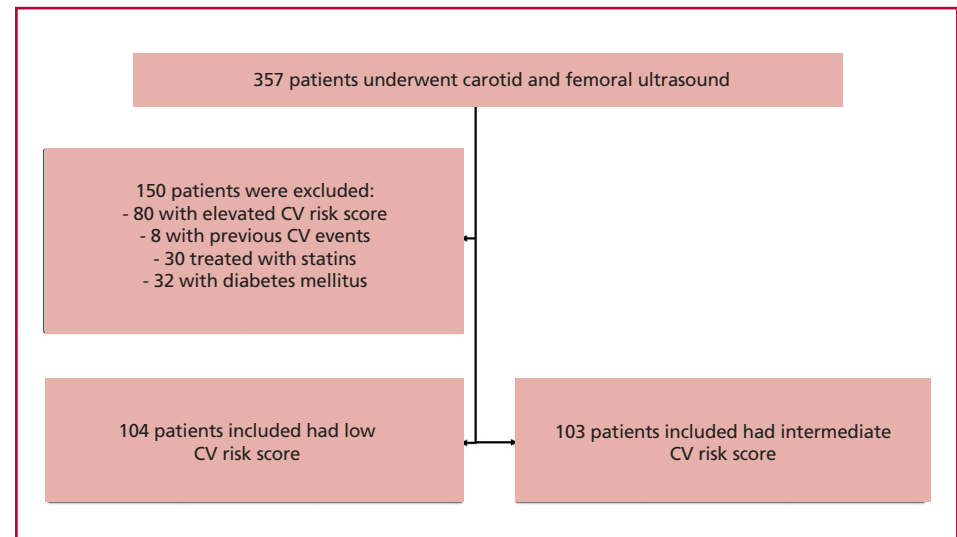


Table 1. Baseline characteristics according to the cardiovascular risk category

	Total population	Low risk	Intermediate risk	p
Patients, n (%)	207	104 (50.2)	103 (49.8)	0.93
Age, years, mean	52±9	49±8	55±9	<0.0001
Male sex, n (%)	103 (49.8)	39 (37.5)	64 (62.1)	0.0007
Hypertension, n (%)	46 (22.2)	14 (13.5)	32 (31.1)	0.004
Smokers, n (%)	50 (24.1)	12 (11.5)	38 (36.9)	<0.0001
Total cholesterol, mean	219±45	216±44	220±46	0.52
HDL-C, mean	54±16	58.8±17.7	49.7±12.5	<0.0001
Subclinical atherosclerosis	88 (42.5)	29 (28)	59 (57)	<0.0001
Carotid atherosclerosis	64 (30.9)	22 (21.2)	42 (40.8)	0.0037
Femoral atherosclerosis	52 (25.1)	15 (14.4)	37 (35.9)	0.0007

HDL-C: High density lipoprotein-cholesterol.

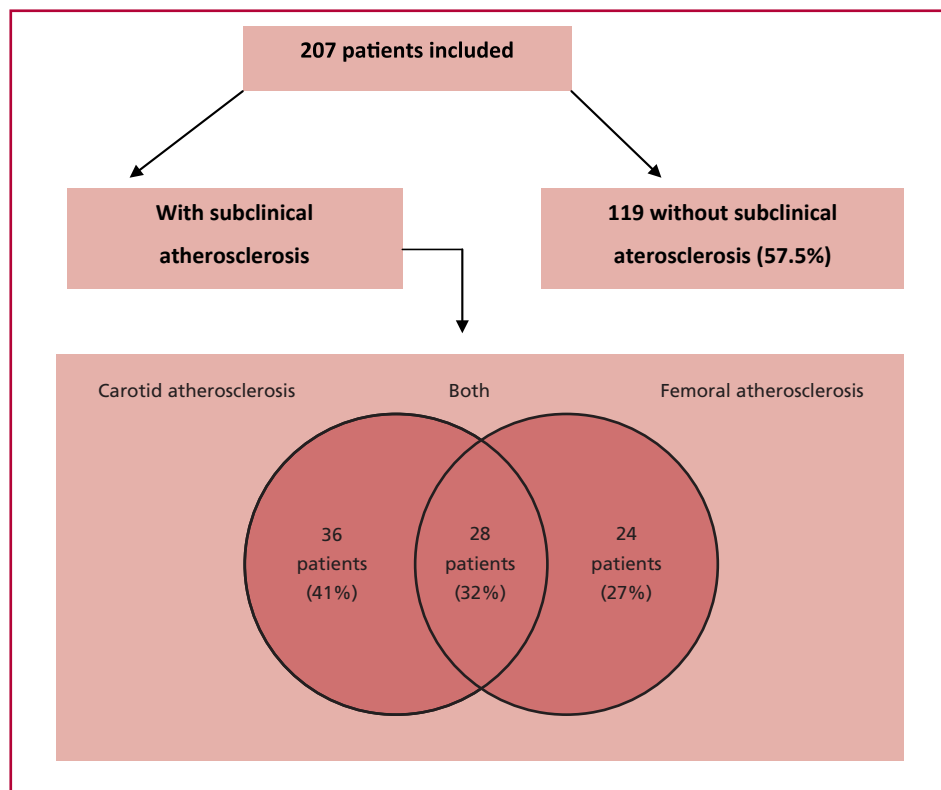


Fig. 2. Prevalence and distribution of subclinical atherosclerosis according to the vascular territory

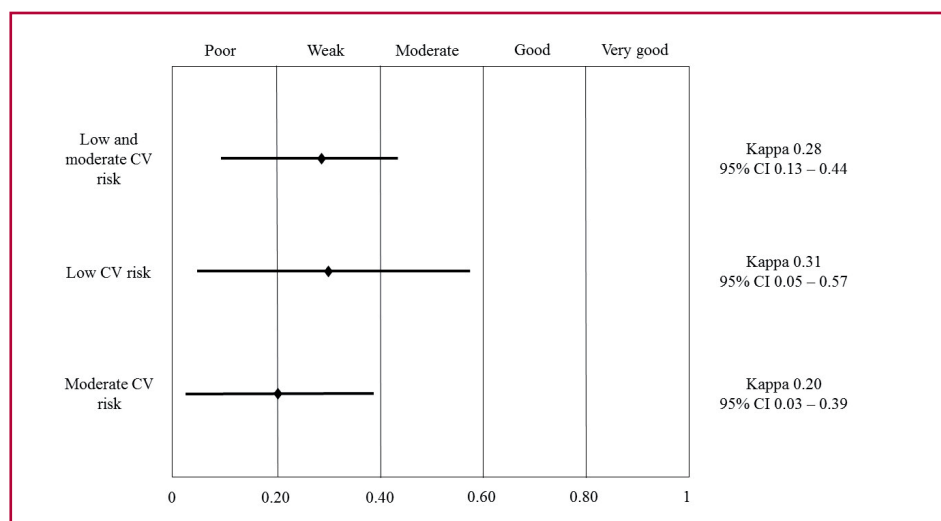


Fig. 3. Concordance between carotid and femoral Doppler ultrasound according to cardiovascular risk using kappa concordance coefficient.

implying that both carotid and femoral arteries need to be assessed when screening for SCA. Finally, we found that age and sex are independent predictors of SCA in both locations, whereas smoking is a powerful predictor only in the femoral arteries.

This study corroborates the lack of specificity of a low or intermediate Framingham risk score to exclude SCA. (17) The fact that a low or intermediate Framingham risk score underestimates the presence of SCA has been confirmed in studies using calcium score and computed tomography angiography, (19) but few studies have assessed the prevalence of subclinical

atherosclerotic plaques in this low-risk population using Doppler ultrasound of the carotid and femoral arteries. It is important to identify SCA because it is a strong predictor of CV events that is independent of traditional risk factors and CV risk scores. (11, 13) We found a prevalence of 42.5%, which is similar to that reported by Postley et al. (42%) and higher than that described by Belcaro et al. (10%). (11) The lower prevalence reported by these authors is probably due to a population at lower risk that did not include patients with diabetes, hypertension, or cholesterol levels >200 mg/dL. (11) >

Table 2. Patients' characteristics according to the presence or absence of subclinical atherosclerosis

	SCA (-)	SCA (+)	p
Patients, n (%)	119 (57.5)	88 (42.5)	-
Age, years, mean	50±8	55±9	<0.0001
Male sex, n (%)	51 (42.8)	52 (59.1)	0.02
Total cholesterol, mean	221±40	218±52	0.63
HDL-C, mean	54.9±17.6	52±13.2	0.19
Hypertension, n (%)	24 (20.2)	22 (25)	0.51
Smokers, n (%)	25 (21)	25 (28.4)	0.28

ASC (-): Absence of subclinical atherosclerosis. ASC (+): Presence of subclinical atherosclerosis. HDL-C: High density lipoprotein-cholesterol.

Table 3. Independent predictors of subclinical atherosclerosis according to the vascular territory involved

	Odds ratio	95% CI
Femoral SCA		
Age	1.10	1.05-1.15
Male sex	3.41	1.44-8.03
Smokers	2.52	1.16-5.49
Hypertension	1.02	0.43-2.42
Total cholesterol	0.99	0.98-1.01
HDL-C	0.98	0.95-1.01
Carotid SCA		
Age	1.06	1.02-1.11
Male sex	2.25	1.09-4.63
Smokers	1.03	0.48-2.23
Hypertension	1.76	0.85-3.66
Total cholesterol	0.99	0.99-1.01
HDL-C	0.99	0.97-1.02

SCA: Subclinical atherosclerosis. HDL-C: High density lipoprotein-cholesterol.

The CAFES-CAVE study followed-up 10,000 Italian women and men with low CV risk. (11) All the patients were asymptomatic with no known CV disease. Patients with hypertension, diabetes, or an abnormal lipid profile were excluded and preventive therapy was not initiated. Screening of atherosclerotic plaques was performed using carotid and femoral Doppler ultrasound. As expected, the 10-year risk of CV events for the entire cohort was low (7.1%). The 10-year rate of CV events of those with atherosclerotic plaques was 57% vs. 1% in those without atherosclerotic plaques ($p < 0.001$), confirming that, even in a very low-risk population, the presence of SCA in the femoral or carotid territories confers a substantial CV risk at 10 years. These patients could benefit from preventive treatment with statins and aspirin, but most do not meet the criteria, according to the 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults. (20) Nasir et al. showed that 78% of patients with significant SCA

did not meet the criteria for pharmacological therapy, according to the NCEP-ATP III guidelines. (19)

In clinical practice, screening for SCA with Doppler ultrasound is frequently performed by evaluating only the carotid vessels. Evaluation of the femoral arteries adds only a few minutes to the procedure and can potentially increase the likelihood of diagnosing SCA. In order to determine whether the assessment of the femoral arteries identifies a different population of patients with SCA, we evaluated the agreement of both procedures in diagnosing atherosclerotic plaques and found a weak agreement between both procedures. Screening for SCA with carotid Doppler ultrasound would have missed a substantial subgroup of patients (27%) who had SCA only in the femoral arteries. Conversely, 41% of the patients with SCA would have been misclassified if screening had been performed only in the femoral arteries. These findings are similar to those described by Postley et al. and to those published in the Bogalusa Heart Study, which reported a weak agreement between Doppler ultrasound in both territories (kappa coefficient 0.19). (21)

The high prevalence of plaque only in the femoral or the carotid arteries advocates screening both vascular territories. The fact that SCA may be present exclusively in one vascular territory is reinforced by the finding that smoking was a predictor of femoral but not of carotid SCA. Even though the traditional risk factors are likely to affect both vascular territories, the impact of a given risk factor is probably dissimilar, as carotid arteries are predominantly elastic vessels, while the femoral arteries are mainly muscular vessels with distinctive regional blood flow and hydrostatic conditions. (21) As expected, age was an independent and progressive predictor of SCA in both territories, as has been reported by other authors. (17, 22)

Some limitations of this study should be noted. Firstly, we used the Framingham risk score, which has not been validated in the Latin American population. Although the Argentine Society of Cardiology recommends the use of the cardiovascular risk score developed by the World Health Organization and the Pan American Health Organization for Latin America, adapted to zone B, where Argentina is found, we decided not to use it because it was never validated in

large prospective studies in this country. Even more, Christen et al. reported similar findings to ours in the study performed by the Argentine Society of Cardiology study using the Framingham-ATP III score. (2) Nevertheless, the Framingham risk score remains as the most widely used method to estimate CV risk worldwide. Secondly, the number of patients evaluated was not large enough for us to categorically recommend the use of both tests to detect SCA; however, considering the minimal added time for assessing the femoral territory, we believe it is reasonable to evaluate both territories when screening for SCA. Thirdly, the fact that we did not consider intima-media thickness between 0.8 and 1.5 mm as a surrogate of SCA could be another limitation. Our decision was based on considering it as an expression of physiological aging rather than a precursor of atherosclerosis. (23, 24) The correlation between increased intima-media thickness and CV events is weak and questionable, (24, 25) while its estimation requires adequate training to achieve reliable results and several technical limitations might compromise its interpretation. (26) Furthermore, intima-media thickness measurements are not recommended for the routine assessment of CV risk in the 2013 ACC/AHA guidelines. (27)

Given that more than half of CV events occur in individuals who are not identified by the CV risk scores and are not eligible for preventive treatment according to current guidelines, screening for SCA to refine CV risk is essential. (1, 20) Vascular Doppler ultrasound is a widely available and inexpensive technique that can be used at the population level to identify those patients who can potentially benefit from more aggressive, preventive treatment. On the basis of our findings, exploring only one vascular territory misses atherosclerotic plaques present in the other vascular territory in approximately 30–40% of cases. Therefore, combining carotid and femoral Doppler ultrasound provides incremental prediction of SCA.

CONCLUSIONS

The prevalence of SCA in this low and intermediate CV risk group of patients was 42.5%. There was a weak concordance between carotid and femoral Doppler ultrasound, which implies that different populations of patients with SCA were identified. Age and sex were independent predictors of SCA in both vascular territories, whereas smoking was a powerful predictor of SCA only in the femoral arteries

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

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