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Protective Role Against Restenosis from an Interleukin-1 Receptor Antagonist Gene Polymorphism in Patients Treated With Coronary Stenting

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OBJECTIVES To test the hypothesis that interleukin-1 receptor antagonist (IL-1ra) gene polymorphism contributes to the risk of restenosis after coronary stenting.

BACKGROUND Cytokines of the interleukin-1 (IL-1) family play a central role in regulating inflammatory responses. There is strong evidence to support IL-1 involvement in smooth muscle cell mitogenesis and extracellular matrix metabolism. The IL-1ra counters the proinflammatory effects of IL-1. The interleukin-1 receptor antagonist gene (IL-1RN) contains several well-characterized polymorphic sites that correlate with altered IL-1ra levels.

METHODS In 1,850 consecutive patients, clinical and angiographic measures of restenosis were evaluated over one year after coronary stent placement. Repeat angiography at six months was achieved in 84% of the patients; angiographic restenosis was defined ≤50% diameter stenosis at follow-up. Genotyping for an exon 2 polymorphism (+2,018) of IL-1RN (alleles 1 and 2) was based on a polymerase chain reaction technique.

RESULTS Allele 2 frequency was 0.28. Carriers of allele 2 had a significantly lower risk for angiographic restenosis, odds ratio (OR) of 0.78 (95% confidence interval, 0.63 to 0.97) and target vessel revascularization, OR of 0.73 (0.58 to 0.92) compared with noncarriers. Risk reduction was especially significant in patients <60 years (n = 696), with OR of 0.63 (0.43 to 0.91) for angiographic restenosis and 0.55 (0.39 to 0.78) for target vessel revascularization.

CONCLUSIONS Allele 2 of the IL-1ra gene was associated with a lower incidence of restenosis after coronary stenting, particularly in younger patients. This finding supports a role of inflammation in the development of restenosis after stent placement. (J Am Coll Cardiol 2000;36:2168–73) © 2000 by the American College of Cardiology

There is increasing evidence for an important role of inflammation in coronary artery disease (1). Cytokines of the interleukin-1 (IL-1) family are central regulators in immunoinflammatory mechanisms (2), and intensive work has been focused on IL-1 modifiers that may influence the inflammatory response (3). Data from several studies support IL-1 regulation of endothelial and smooth muscle cell mitogenesis, thrombogenic response of endothelial cells, leukocyte adherence, lipoprotein metabolism, extracellular matrix production and vascular permeability (4,5). With these actions, IL-1 occupies a key place in the cascade of autocrine and paracrine mediators that promote restenosis after percutaneous coronary interventions (6).

Restenosis remains a significant limitation for stenting, affecting around 30% of patients treated with this procedure. It is assumed to be the result of a particularly high degree of arterial injury and inflammatory reaction produced by the stent (7). Due to the potent proinflammatory actions of IL-1, the regulation of IL-1 activity by endogenous biological antagonists may play a significant role in this process. Of particular interest is the naturally occurring IL-1 receptor antagonist (IL-1ra) (8), which is the product of a polymorphic gene (IL-1 receptor antagonist gene [IL-1RN]). Five polymorphic sites have been discovered in the IL-1RN: a variable number tandem repeat (VNTR) polymorphism in intron 2, and four single nucleotide polymorphisms, including one in exon 2, that show a high degree of linkage disequilibrium with the VNTR (9). These IL-1RN polymorphisms have been associated with altered production rates of IL-1ra protein (10–12). In view of the central role of IL-1 in regulation of the inflammatory response and the potent inhibitory effect of IL-1ra in this system, the hypothesis that the IL-1RN locus may contribute genetic risk in inflammatory diseases was proposed (2,13). In recent years this hypothesis has been extensively tested, and significant associations have been found between IL-1RN polymorphism and inflammatory diseases (13). More re-

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Abbreviations and Acronyms

CI	=	confidence interval
IL-1	=	interleukin-1
IL-1ra	=	interleukin-1 receptor antagonist
IL-1RN	=	interleukin-1 receptor antagonist gene
MI	=	myocardial infarction
MLD	=	minimal lumen diameter
OR	=	odds ratio
PTCA	=	percutaneous transluminal coronary angioplasty
TVR	=	target vessel revascularization
VNTR	=	variable number tandem repeat

cently, this polymorphism has been found to be associated with single-vessel coronary artery disease in younger patients (14).

The objective of this study was to test for association between IL-1ra gene polymorphism and risk for restenosis after coronary stent placement in a large cohort of patients.

METHODS

Patients. The study included 1,850 consecutive Caucasian patients with symptomatic coronary artery disease who underwent coronary stent implantation at our institutions during the period between January 1996 and June 1997. All patients were scheduled for angiographic follow-up at 6 months; they gave written informed consent for the intervention, follow-up angiography and genotype determination. The study protocol conformed to the Declaration of Helsinki and was approved by the institutional ethics committee at our institution. Adjunct pharmacologic therapy consisted of aspirin (100 mg twice daily, indefinitely) and ticlopidine (250 mg twice daily for four weeks). Patients considered at a higher risk for stent thrombosis received adjunct therapy with the glycoprotein-IIb/IIIa blocker abciximab given as bolus injection during stent insertion procedure and as a 12-h continuous infusion thereafter.

Determination of the IL-1RN genotype. Genomic DNA was extracted from 200 μl of peripheral blood leukocytes with the QIAamp Blood Kit (Qiagen, Hilden, Germany) and the High Pure PCR Template Preparation Kit (Boehringer Mannheim, Mannheim, Germany).

Interleukin-1 receptor antagonist gene genotyping was performed with the ABI Prism Sequence Detection System (PE Applied Biosystems, Weiterstadt, Germany). The IL-1RN (+2,018), a single base pair polymorphism in exon 2, was the polymorphism typed in this study (9). The nucleotide sequences of primers and probes were as follows: forward primer 5′ GGG ATG TTA ACC AGA AGA CCT TCT ATC T 3′, reverse primer 5′ CAA CCA CTC ACC TTC TAA ATT GAC ATT 3′, allele 1 probe 5′ AAC AAC CAA CTA GTT GCT GGA TAC TTG CAA 3′, allele 2 probe 5′ ACA ACC AAC TAG TTG CCG GAT ACT TGC 3′. Genotype validation was performed by repeating the determination in 20% of the patients using a duplicate DNA sample with a novel subject code unrelated to the original subject code. There was a 100% matching between the two results.

Angiographic assessment. Quantitative computer-assisted angiographic analysis was performed off-line using the automated edge-detection system CMS (Medis Medical Imaging Systems, Nuenen, the Netherlands). Operators were unaware of the patient's IL-1RN genotype. Acute lumen gain was calculated as the difference between minimal lumen diameter (MLD) at the end of intervention and MLD before the intervention. Late lumen loss was calculated as the difference between MLD at the end of intervention and MLD at the time of follow-up angiography. Loss index was calculated as the ratio between late lumen loss and acute lumen gain.

Definitions and study end points. The primary end point of the study was restenosis. Two definitions of restenosis were assessed: the incidence of a diameter stenosis of $\geq$50% at six-month follow-up angiography and the need for target vessel revascularization (TVR) (percutaneous transluminal coronary angioplasty [PTCA] or bypass surgery) due to symptoms or signs of ischemia in the presence of angiographic restenosis at the stented site over one year after stent placement. Other major adverse events evaluated were death from any cause and nonfatal myocardial infarction (MI). The diagnosis of acute MI was based on the presence of new pathological Q waves or a value of creatine kinase or its MB isoenzyme at least 3 times the upper limit (15). Clinical events were assessed on the basis of the information provided by hospital readmission records, referring physician or phone interview with the patient. For all patients who presented cardiac symptoms during the interview, at least one clinical and electrocardiographic evaluation was performed at the outpatient clinic or by the referring physician.

Statistical analysis. Discrete variables are expressed as counts or percentages and compared with the chi-square or Fisher exact test, as appropriate. Continuous variables are expressed as mean $\pm$ standard deviation and compared by means of the unpaired, two-sided *t*-test or analysis of variance for more than two groups. Risk analysis was performed calculating the odds ratio (OR) and the 95% confidence interval (CI). The main analysis consisted in comparing combined heterozygous and homozygous carriers of the IL-1RN*2 allele with homozygous carriers of the IL-1RN*1 allele. A multivariate logistic regression model was applied to adjust for those clinical and lesion-related characteristics for which the comparison between carriers and noncarriers of the IL-1RN*2 allele yielded a p value $\leq$0.30. Since the relative contribution of genetic factors to multifactorial processes such as restenosis may decrease with the age, we carried out an additional prespecified subgroup analysis of patients $<$60 years. Successively, we used a test for trend for assessing gene dose effect, i.e. a stepwise increasing or decreasing phenotypic response with the presence of 0, 1 or 2 putative alleles. Statistical significance was accepted for p values $<$0.05.

Table 1. Baseline Clinical Characteristics

	IL-1RN 1/2 or 2/2 (n = 896)	IL-1RN 1/1 (n = 954)	p Value
Age, yr	63.4 ± 10.0	62.6 ± 10.0	0.11
Women, %	22.4	19.9	0.19
Arterial hypertension, %	67.2	68.9	0.44
Diabetes, %	22.7	19.4	0.08
Current or former smoker, %	38.7	41.2	0.28
Elevated total cholesterol, %	42.5	43.1	0.81
Acute myocardial infarction, %	20.3	20.2	0.97
Unstable angina, %	27.9	27.8	0.95
Prior bypass surgery, %	10.6	11.5	0.53
Number of diseased coronary vessels			0.39
1 vessel, %	29.2	27.3	
2 vessels, %	32.9	31.9	
3 vessels, %	37.8	40.9	

Data are proportions or mean ± standard deviation.

RESULTS

Patients characteristics. The observed IL-1RN genotypes in the study population were 1/1 in 954 (51.6%), 1/2 in 742 (40.1%) and 2/2 in 154 (8.3%). Thus, the frequency for the allele 2 was 0.28. Main baseline characteristics of the patients are listed in Table 1. There was only a trend toward a higher frequency of diabetes among carriers of the IL-1RN*2 allele. The angiographic and procedural characteristics at the time of intervention are listed in Table 2 and show no significant differences between carriers and noncarriers of the IL-1RN*2 allele.

IL-1RN polymorphism, mortality and MI after stenting. Table 3 shows similar adverse clinical event rates in carriers and noncarriers of the IL-1RN*2 allele during the first 30 days after coronary stenting. However, this study was not sufficiently powered to assess the potential influence of the IL-1ra gene polymorphism on 30-day events.

One-year follow-up (complete in 98.4% of the patients) also indicated that there was no correlation between the presence of the IL-1RN*2 allele and mortality or incidence of MI after the intervention. The graph in the left panel of Figure 1 displays the OR for these events associated with the presence of the IL-1RN*2 allele. During the one-year period, the mortality rate was 2.8% in the combined group of IL-1RN 1/2 and IL-1RN 2/2 patients and 2.2% in IL-1 1/1 patients (p = 0.42). The incidence of nonfatal MI was 3.5% in IL-1RN*2 allele carriers and 3.9% in homozygous carriers of the IL-1RN*1 allele (p = 0.54).

IL-1RN polymorphism and restenosis after stenting. Six-month follow-up angiography was performed in 84% of the patients, in a similar proportion among carriers and noncarriers of the IL-1RN*2 allele. Table 4 lists the results of the quantitative assessment of six-month angiograms. The presence of the IL-1RN*2 allele was associated with a 22% decrease in the risk for restenosis, OR 0.78 (95% CI, 0.63 to 0.97; Fig. 1). More specifically, the restenosis rate was 35.6% in IL-1RN 1/1, 30.4% in IL-1RN 1/2 and 29.1% in IL-1RN 2/2 patients (p = 0.03, test for trend). Clinical restenosis requiring TVR was also significantly lower, 17.7% in IL-1RN*2 allele carriers versus 22.7% in homozygous patients for the IL-1RN*1 allele (p = 0.03), yielding an OR of 0.73 (0.58 to 0.92), as shown in Figure 1. Target vessel revascularization rates were 22.7% in IL-1RN 1/1, 18.3% in IL-1RN 1/2 and 14.9% in IL-1RN 2/2 patients (p = 0.005, test for trend).

Multivariate analysis of the correlates of angiographic

Table 2. Lesion and Procedural Characteristics at the Time of Intervention

	IL-1RN 1/2 or 2/2 (n = 896)	IL-1RN 1/1 (n = 954)	p Value
Target coronary vessels			0.89
Left main, %	1.3	1.6	
LAD, %	40.1	39.3	
LCx, %	19.9	20.0	
RCA, %	32.6	31.9	
Venous bypass graft, %	6.1	7.2	
Complex lesions, %	75.2	74.1	0.58
Restenotic lesions, %	25.3	23.3	0.30
Before stenting			
Reference diameter, mm	3.02 ± 0.53	3.05 ± 0.54	0.29
Diameter stenosis, %	79.1 ± 14.9	78.7 ± 15.7	0.57
Lesion length, mm	12.1 ± 6.9	12.1 ± 6.6	0.98
Procedural data			
Measured balloon diameter, mm	3.2 ± 0.5	3.2 ± 0.5	0.45
Maximal balloon pressure, atm	13.9 ± 3.3	13.8 ± 3.2	0.20
Stent type:			0.89
Inflow*, %	33.5	34.3	
JOSTENT†, %	5.6	6.5	
MULTI-LINK‡, %	5.8	6.6	
NIR§, %	13.1	12.5	
Palmaz-Schatz‖, %	15.6	15.5	
PURA-A¶, %	20.1	18.0	
other, %	6.4	6.6	
Stented segment length, mm	20.0 ± 14.3	20.3 ± 13.6	0.70
Periprocedural abciximab therapy, %	19.8	19.6	0.93
Immediately after stenting			
Diameter stenosis, %	5.2 ± 9.1	5.4 ± 7.6	0.47

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Data are proportions or mean ± standard deviation.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; complex lesions were defined as ACC/AHA lesion types B2 and C, according to the American College of Cardiology/American Heart Association grading system.

Table 3. Incidence of Adverse Events Recorded During the Early 30 Days

	IL-1RN 1/2 or 2/2 (n = 896)	IL-1RN 1/1 (n = 954)	p Value
Death, %	0.9	0.9	0.91
Nonfatal myocardial infarction, %	3.3	2.6	0.52
Q_wave, %	1.1	0.7	0.39
non-Q_wave, %	2.2	1.9	0.60
Target vessel revascularization, %	3.0	2.3	0.34

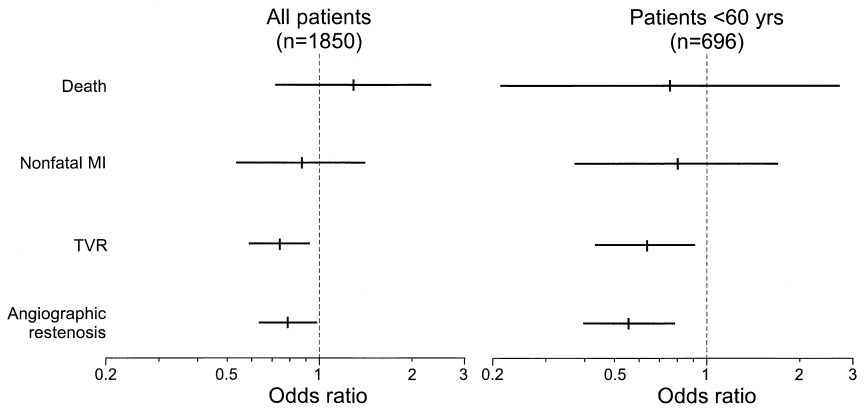

Figure 1. Graph showing on a logarithmic scale the odds ratios for clinical events and angiographic restenosis associated with the presence of the IL-1RN*2 allele for the entire population **(left panel)** and patients <60 years **(right panel)**. ILRN = interleukin-1 receptor antagonist gene; MI = myocardial infarction; TVR = target vessel revascularization.

restenosis was performed with the variables age, gender, diabetes, smoking, restenotic lesions and vessel size (all variables differing in univariate analysis by a p value ≤0.30) along with the presence or absence of the IL-1RN*2 allele. The presence of the IL-1RN*2 allele was independently ($p < 0.001$) correlated with a decreased risk for restenosis with an adjusted OR of 0.81 (0.71 to 0.92). In addition, there was a significant interaction between the presence of the IL-1RN*2 allele and age ($p = 0.009$) as reflected by a progressively stronger protective effect of this allele in younger patients.

The results of the analysis in the prespecified subgroup of patients <60 years (n = 696) are presented in Table 5, Figure 1 and Figure 2. The frequency for the allele 2 among these patients was 0.27, and there were no significant differences in baseline characteristics between allele 2 carriers and homozygous patients for allele 1. During the one-year follow-up period, 17.1% of the IL-1RN*2 allele carriers and 24.9% of the homozygous IL-1RN*1 allele carriers needed TVR ($p = 0.01$). Thus, the presence of the IL-1RN*2 allele was associated with a 37% risk reduction (OR, 0.63 [0.43 to 0.91], Fig. 1) of the need of reinterventions. Quantitative data obtained for six-month angiography (performed in 590 or 85% of patients <60 years) are displayed in Table 5. The incidence of angiographic restenosis was 25.6% in the combined group of IL-1RN 1/2 and IL-1RN 2/2 patients and 38.5% among IL-1RN 1/1 patients ($p < 0.001$), which corresponds to a 45% risk reduction (OR, 0.55 [0.39 to 0.78], Fig. 1). Figure 2 illustrates the gene dose effect verified in the subgroup of younger patients. The incidence of restenosis decreased progressively with heterozygosity and homozygosity for the IL-1RN*2 allele. The rate of angiographic restenosis was 38.5% in IL-1RN 1/1 patients, 26.3% in IL-1RN 1/2 patients and 22.4% in IL-1RN 2/2 patients ($p = 0.001$, test for trend; Fig. 2). Target vessel revascularization rates were 24.9% in IL-1RN 1/1 patients, 17.9% in IL-1RN 1/2 patients and 13.2% in IL-1RN 2/2 patients ($p = 0.01$, test for trend; Fig. 2).

DISCUSSION

Restenosis remains the major limitation of coronary stenting and other percutaneous interventions. Restenosis is not a random phenomenon, and certain patients are at increased risk of developing it (16). There are several clinical and lesion-related factors that serve to explain part of the risk for restenosis (17). However, a significant portion of this process can not be predicted based on conventional risk factors (18). Recent studies have provided evidence on the emerging role of genetic factors in determining the risk for restenosis after coronary interventions (19).

In this study we assessed the association between a polymorphism in the gene encoding IL-1ra and both angiographic and clinical restenosis after coronary stent implantation in a large and consecutive series of patients with systematic angiographic control study at 6 months achieved in a very high proportion of patients. The rationale for choosing IL-1RN as a candidate gene in restenosis after coronary stenting came from the evidence of the role of

Table 4. Results at Follow-up Angiography

	IL-1RN 1/2 or 2/2 (n = 758)	IL-1RN 1/1 (n = 798)	p Value
Late lumen loss, mm	1.16 ± 0.82	1.24 ± 0.86	0.07
Loss index	0.53 ± 0.38	0.59 ± 0.45	0.009
Diameter stenosis, %	41.8 ± 26.2	45.2 ± 28.7	0.02
Restenosis rate, %	30.2	35.6	0.02

Data are proportions or mean ± standard deviation.

Table 5. Results at Follow-up Angiography in Patients <60 Years

	IL-1RN 1/2 or 2/2 (n = 273)	IL-1RN 1/1 (n = 317)	p Value
Late lumen loss, mm	1.08 ± 0.77	1.27 ± 0.93	0.008
Loss index	0.49 ± 0.35	0.59 ± 0.48	0.003
Diameter stenosis, %	39.3 ± 24.1	46.7 ± 30.5	0.001
Restenosis rate, %	25.6	38.5	<0.001

Data are proportions or mean ± standard deviation.

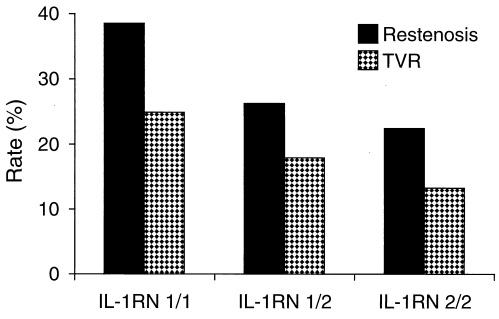

Figure 2. Bar graph showing the decrease in the incidence of restenosis and TVR in patients <60 years with the increase in the number of IL-1RN*2 alleles. ILRN = interleukin-1 receptor antagonist gene; TVR = target vessel revascularization.

inflammation in this process, the central role of the IL-1 system in inflammatory regulation, the previous evidence of IL-1RN polymorphism as a genetic risk factor in other inflammatory diseases and the therapeutic prospects offered by IL-1 antagonist approaches.

Previous evidence on the relation between IL-1 family and restenosis. Interleukin-1 is a key mediator of immunoinflammatory responses and is considered to be extraordinarily potent since a very low level of binding to the signaling (type I) IL-1 receptor is sufficient to elicit a full response (5). Interleukin-1 has been established as a significant determinant of intimal hyperplasia and has been demonstrated to stimulate the thrombogenic response in endothelial cells as well as the production of endothelial-derived growth factor (4). Coronary angioplasty evokes marked monocyte activation (20). The capacity of in vitro-stimulated monocytes to produce IL-1 has been demonstrated to correlate with lumen renarrowing after PTCA (21). In an IL-1RN knockout mouse model, extensive inflammatory cell infiltrate, which is characteristic of the restenotic response, was observed in the aorta and its major branches, including the coronary arteries (22). In addition, the use of recombinant human IL-1ra inhibited vascular smooth muscle cell proliferation in cell cultures (23).

IL-1ra gene polymorphism and restenosis after stenting. In this study, which included 1,850 consecutive patients with coronary stent implantation, we found that the presence of allele 2 in the IL-1ra gene was significantly associated with a lower risk of both angiographic and clinical restenosis. This association was even stronger in younger patients. A clear gene dose effect was found; the incidence of restenosis decreased with heterozygosity and even more so with homozygosity for the IL-1RN*2 allele. The presence of allele 2 has been shown to be associated with higher blood levels or higher monocyte production rates of IL-1ra (10–12) but not in all populations (12) and not when measured as IL-1RN RNA (9). Interleukin-1 receptor antagonist production increases with age (24) and this may explain, at least in part, the more powerful genetic association in younger patients. In terms of biological function, however, the genotype associated with restenosis in this study cannot yet be confidently defined as specifying a high or low IL-1 production phenotype because gene activation patterns are often tissue specific. It is not possible to extrapolate from studies on blood levels or in vitro monocyte production the effect of genotype on concentration of IL-1ra at coronary artery sites after stenting. In addition, as with other clinical studies on genetic associations, the data presented here do not provide evidence for a causal role of the IL-1RN polymorphism in the complex process of restenosis after coronary stenting. Interleukin-1 receptor antagonist gene lies on a 430kB stretch of chromosome 2 (25), and there is a strong haplotype effect in the region (26), so unknown genes may well be in linkage disequilibrium with IL-1RN. In this case the IL-1RN polymorphism would be serving as a marker for an unknown etiological gene. We cannot claim more than this based on presently available data. However, as described above, there is a biological rationale for IL-1 as a mediator of arterial disease and, therefore, a role for IL-1RN.

Study limitations. Despite the tissue specificity of IL-1ra gene activation patterns discussed above, the lack of measurements of blood levels or monocyte production of IL-1ra should be considered a limitation because they might have provided some mechanistic insights into the association observed in this study. A second limitation to acknowledge is the incomplete six-month angiographic follow-up (present in only 84% of the patients), which may inadvertently have introduced a bias in our angiographic restenosis analysis. However, this bias is not expected to be relevant given the concordance between the angiographic and clinical measures of restenosis.

Conclusions. The results of this study showed a significant association between IL-1RN polymorphism and restenosis after coronary stenting and that IL-1RN*2 carriage has a protective effect, especially in patients <60 of age. For reasons given above, the biological mechanism underlying this genetic finding is, at present, difficult to define in the current state of knowledge. The finding does, however, lend support to the hypothesis that genetic programming of the inflammatory response may be relevant to the pathogenesis of restenosis after stenting. The finding may provide not only a genetic marker for risk stratification but also the rationale for the assessment of the value of IL-1 antagonists as a preventive strategy against restenosis.

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