

Lipoprotein(a) screening in young and middle-aged patients presenting with acute coronary syndrome

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Abstract

Background: *Elevated lipoprotein(a) [Lp(a)] is an independent risk factor for coronary artery disease (CAD). However, its role in real-world practice and implications for clinical care remains limited. Under investigation herein, are the clinical characteristics associated with increased Lp(a) levels in patients presenting with acute coronary syndrome (ACS).*

Methods: *Lp(a) was measured at admission in patients ≤ 65 years of age presenting with ACS in a single center. Logistic regression model was used to determine the independent association of clinical characteristics with elevated Lp(a).*

Results: *A total of 134 patients were screened for Lp(a); 83% males, mean age 52 ± 8 years. Median Lp(a) level was 46 nmol/L (interquartile range [IQR] 13–91). Elevated Lp(a) > 72 nmol/L (30 mg/dL) was documented in 32% and associated with younger age at CAD diagnosis. In a multiple logistic regression model, premature CAD (odds ratio [OR] 3.85, 95% confidence interval [CI] 1.48–10.07, $p = 0.06$), previous revascularization (OR 2.56, 95% CI 1.17–5.59, $p = 0.019$) and probable/definite familial hypercholesterolemia (FH) (OR 3.18, 95% CI 1.10–9.21, $p = 0.033$), were independently associated with elevated Lp(a). In contrast, Lp(a) levels were not associated with other traditional cardiovascular risk factors, previous statin treatment, C-reactive protein level or ACS type.*

Conclusions: *In young and middle-aged patients presenting with ACS, premature CAD, previous revascularization and FH were independently associated with elevated Lp(a), indicating progressive CAD and higher cardiovascular risk. These results, are in accordance with guideline based recommendations for Lp(a) screening, and may be of importance in addressing residual cardiovascular risk in young ACS patients, in light of the novel emerging therapies targeting Lp(a). (Cardiol J 2019; 26, 5: 511–518)*

Key words: lipoprotein(a), acute coronary syndrome, coronary artery disease, familial hypercholesterolemia

Introduction

Lipoprotein(a) [Lp(a)] consists of an apolipoprotein B containing low-density lipoprotein (LDL) like particle, covalently linked to plasminogen-like glycoprotein apo(a) [1]. Lp(a) is mainly determined genetically by the LPA gene, and is considered proatherogenic, proinflammatory and potentially antifibrinolytic [2]. Evidence from epidemiological and clinical analyses in both primary and secondary prevention populations show an independent asso-

ciation between Lp(a) and risk for cardiovascular disease (CVD) and death [3–8], results that are further supported by genetic studies indicating that Lp(a) has a causal role in the development of coronary artery disease (CAD) [9–11]. Nevertheless, despite these associations, the value of Lp(a) as a prognostic biomarker remains controversial and is incompletely defined due to lack of standardized assays [12], the limited therapeutic options for significantly lowering Lp(a) and the need of outcome data showing the benefit of lowering Lp(a) levels [13].

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Although screening for Lp(a) is recommended by professional societies in selected patients [14], there is wide variation in the clinical utility of Lp(a) measurement among health care providers, and real-life data regarding the screening for Lp(a) levels in patients with established CAD is limited. It is therefore important to identify clinical characteristics and risk factors associated with elevated Lp(a), as well as high-risk populations in whom future preventive strategies and emerging therapies will be applied [15]. In addition, screening for Lp(a) in the younger population presenting with acute coronary syndrome (ACS) may serve as an opportunity to identify residual cardiovascular risk, with long-term implications.

In light of these considerations, the aim of the current study was to investigate the clinical features associated with elevated Lp(a) in young and middle-aged patients ≤ 65 years presenting with ACS. Moreover, as Lp(a) levels were suggested to be related to pro-inflammatory conditions [16, 17], their association with C-reactive protein (CRP) levels at presentation with ACS will be analyzed.

Methods

Study design

This study is a retrospective observational cohort analysis performed in a single center at Lady Davis Carmel Medical Center, Haifa, Israel. 134 patients were included, aged 65 years and under who presented to the Cardiology Department with ACS between June 2016 to November 2017 and were tested for Lp(a) levels. Blood analysis was performed at a single laboratory with samples collected within 24 h of hospital admission. Laboratory blood tests included Lp(a) levels, routine lipid panel, kidney function tests and CRP levels. LDL cholesterol was calculated by the Friedwald formula. Lp(a) was measured using a particle-enhanced quantitative turbidimetric immunoassay (PETIA) (Tina-quant[®] Lipoprotein (a) Gen.2, Roche Diagnostics International Ltd.), on a COBAS automated chemistry analyzer. Lp(a) levels were reported in nmol/L units, according to recent recommendations [13]. Levels above 72 nmol/L were considered elevated (estimated conversion factor from molar to mass based concentration: $1 \text{ nmol/L} \times 0.4167 = \text{mg/dL}$), consistent with traditional thresholds for elevated Lp(a) above 30 mg/dL which approximate the 75th percentile in white populations, and also reflect epidemiological data of CVD risk thresholds [4, 18].

Additional demographic and clinical characteristics as well as traditional cardiovascular risk factors were recorded from computerized data of patient files. Patients were assessed for clinical indications to Lp(a) measurement, as recommended by customary guidelines [14], including (1) premature CAD (male age < 55 years and female age < 60 years), (2) family history of premature CAD, (3) familial hypercholesterolemia (FH) and (4) markers of progressive CAD including previous revascularization, presence of multi-vessel CAD and need for cardiac surgery. The clinical diagnosis of FH was established using the Dutch Lipid Clinic Network (DLCN) algorithm [19]. Peak LDL cholesterol level documented in each patient's history was used to calculate the DLCN score. FH was considered probable or definite if the total score was ≥ 6 points. The study was approved by the Lady Davis Carmel Medical Center Institutional Ethics Committee in Haifa, Israel, with a waiving of the need for individual patient consent.

Data analysis

Continuous data are presented as means \pm \pm standard deviation or median and interquartile range (IQR), and categorical variables as numbers and percentages. The independent-samples T-test or Mann-Whitney test was used to compare continuous variables and the χ^2 test to compare categorical variables. The Fisher exact test was used in cases of small sample size. Information on covariates was complete except for CRP levels, missing in 3 patients. Spearman's correlation coefficient was used to investigate the relationship between Lp(a) and CRP levels at admission.

Multivariate logistic regression model was used to determine the independent association between clinical characteristics and elevated Lp(a), defined as $> 72 \text{ nmol/L}$. Included in the multivariable model were variables with a significance level < 0.20 in the univariate analysis. Odds ratio were further adjusted for age, gender and statin treatment prior to hospitalization. Lp(a) levels were additionally analyzed according to distribution into tertiles. The results were considered statistically significant when the 2-sided p-value was < 0.05 . SPSS statistical software version 20.0 was used to perform all statistical analyses.

Results

Lipoprotein(a) was measured in 134 patients aged 65 years and under presenting with ACS. Un-

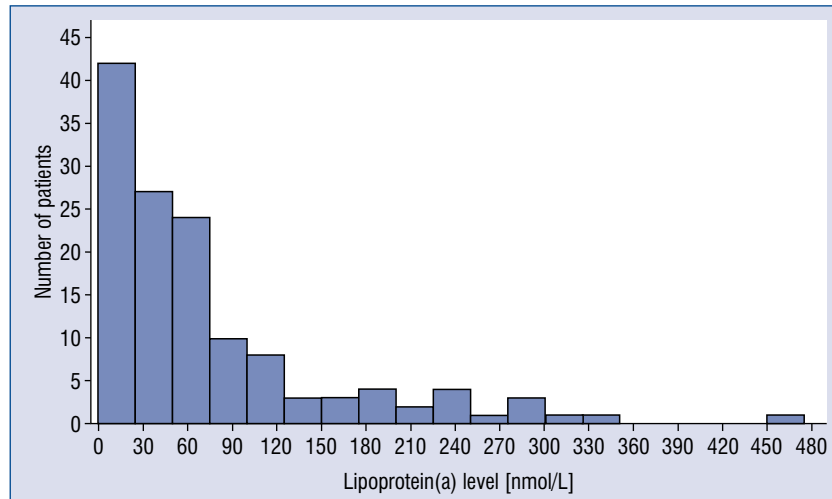


Figure 1. Lipoprotein(a) level distribution in study population.

stable angina was diagnosed in 11% of the patients, non ST-segment elevation myocardial infarction (NSTEMI) in 58%, and ST-segment elevation myocardial infarction (STEMI) in 31%. Mean age was 52 ± 8 years and 83% were males. Mean LDL cholesterol level at admission with ACS was 123 ± 52 mg/dL, and high-density lipoprotein (HDL) cholesterol 35 ± 9 mg/dL. Median Lp(a) level was 46 (IQR 13–91) nmol/L. Lp(a) level distribution in the study population is presented in Figure 1, showing a skewed distribution with a tail towards the highest levels. Younger patients under 45 years of age ($n = 24$) had significantly higher Lp(a) levels than middle-aged patients between 45 and 65 years ($n = 110$): mean 105 ± 119 nmol/L, median (IQR) 61 (24–120) nmol/L vs. mean 65 ± 70 nmol/L, median (IQR) 40 (11–83) nmol/L, $p = 0.027$, respectively. Similarly, their mean LDL-cholesterol levels were higher: 143 ± 66 mg/dL vs. 119 ± 48 mg/dL, $p = 0.037$, respectively.

Elevated Lp(a) > 72 nmol/L was documented in 43 patients with ACS (32%) and associated with younger age and premature CAD (men < 55 years and women < 60 years) (Table 1). In addition, elevated Lp(a) was associated with previous revascularization (42% vs. 22%, $p = 0.017$) and more prevalent clinical diagnosis of probable/definite FH (21% vs. 8%, $p = 0.027$). In contrast, elevated Lp(a) was not related to other traditional risk factors such as hypertension, diabetes, smoking, chronic kidney disease, as well as family history of premature CAD; nor was it associated with previous statin treatment or ACS type (Table 1). Triglyceride and cholesterol levels at admission were comparable in both Lp(a) groups. In addition, performance rates of cardiac surgery and angiographic evidence of 3 ves-

sel CAD were also similar between patients with and without elevated Lp(a) levels. In a multiple logistic regression model, previous revascularization, premature CAD and probable/definite FH remained independently and significantly associated with high Lp(a) levels, after additional adjustment to age, gender and previous statin therapy (Table 2). These independent risk markers of progressive CAD were also associated with Lp(a) levels stratified by tertiles (Fig. 2). Moreover, an increase in 20 nmol/L in Lp(a) was associated with significant increase in the adjusted odds ratio (OR) for premature CAD (OR 1.237, 95% confidence interval [CI] 1.014–1.509, $p = 0.036$), but not the other two risk predictors.

C-reactive protein levels measured at admission of patients with ACS were not correlated with elevated Lp(a), both when analyzed as a continuous variable (Spearman's correlation coefficient 0.136, $p = 0.120$) or as a categorical variable (high CRP levels observed in 27% of those with elevated Lp(a) compared to 23% with normal Lp(a), $p = 0.630$). Repeat Lp(a) was measured ≥ 2 months after discharge in 5 patients with significantly high admission Lp(a) levels, and remained elevated in all subjects (Fig. 3).

Discussion

In the present study of patients presenting with ACS, elevated Lp(a) was evident in a third of the population and was associated with younger age, premature CAD and previous revascularization indicating progressive CAD. Furthermore, high Lp(a) was related to clinical diagnosis of probable/

Table 1. Patient characteristics according to lipoprotein(a) [Lp(a)] level.

Variable	Total (n = 134)	Lp(a) < 72 nmol/L (n = 91)	Lp(a) > 72 nmol/L (n = 43)	P
Age [years] (range 29–65)	52.2 ± 8.0	53.1 ± 7.8	50.3 ± 8.3	0.056
Age at CAD diagnosis	49.9 ± 9.0	51.3 ± 8.9	47.1 ± 8.6	0.010
Gender (male)	111 (83%)	75 (82%)	36 (84%)	0.852
Family history of premature CAD	75 (56%)	51 (56%)	24 (54%)	0.980
Dyslipidemia	100 (75%)	69 (76%)	31 (72%)	0.643
Hypertension	71 (53%)	46 (51%)	25 (58%)	0.411
Diabetes mellitus	42 (31%)	27 (30%)	15 (35%)	0.544
Obesity (BMI > 30 kg/m ²)	51 (39%)	39 (43%)	12 (29%)	0.105
Current smoking	69 (52%)	51 (56%)	18 (42%)	0.125
Chronic kidney disease	13 (10%)	7 (8%)	6 (14%)	0.348
Stroke	5 (4%)	4 (4%)	1 (2%)	0.484
Previous revascularization	38 (28%)	20 (22%)	18 (42%)	0.017
LDL cholesterol [mg/dL]	123 ± 52	123 ± 52	124 ± 52	0.909
Triglycerides [mg/dL]	225 ± 218	223 ± 201	228 ± 251	0.902
HDL cholesterol [mg/dL]	35 ± 9	34 ± 9	37 ± 10	0.116
Peak LDL cholesterol [mg/dL]	165 ± 46	163 ± 47	171 ± 44	0.364
Probable/definite FH	16 (12%)	7 (8%)	9 (21%)	0.027
Previous statin therapy	65 (49%)	41 (45%)	24 (56%)	0.245
Cardiac surgery	23 (17%)	16 (17%)	7 (16%)	0.341
Unstable angina	15 (11%)	8 (9%)	7 (16%)	
NSTEMI	77 (58%)	55 (60%)	22 (51%)	0.381
STEMI	42 (31%)	28 (31%)	14 (33%)	
Three-vessel CAD	53 (40%)	35 (39%)	18 (42%)	0.707
Premature CAD	93 (69%)	56 (61%)	37 (86%)	0.004

BMI — body mass index; CAD — coronary artery disease; FH — familial hypercholesterolemia; HDL — high-density lipoprotein; LDL — low-density lipoprotein; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

Table 2. Multivariate regression analysis showing independent associations between clinical characteristics and elevated lipoprotein(a)*.

Variable	Odds ratio	95% CI	P
Previous revascularization	2.56	1.17–5.59	0.019
Premature CAD	3.85	1.48–10.07	0.06
Probable/definite FH	3.18	1.10–9.21	0.033

*Multivariable logistic regression model was adjusted to age, gender and previous statin therapy. CAD — coronary artery disease; CI — confidence interval; FH — familial hypercholesterolemia

definite FH. In contrast, traditional cardiovascular risk factors were not associated with elevated Lp(a), and no correlation was observed between admission CRP levels during ACS and Lp(a).

Plasma levels of Lp(a) are similar in men and women and show a skewed distribution in the popu-

lation with a tail towards the highest levels. Lp(a) concentration is lower in non-Hispanic Caucasians and Asian populations, and higher in Hispanic and Black ethnic populations [18]. Individual studies used different thresholds to define elevated Lp(a), with common thresholds of 30 mg/dL and 50 mg/dL, corresponding to the 75th and 80th percentiles in the general population. In the setting of a large referral center, Lp(a) levels > 30 mg/dL and > 50 mg/dL were shown to be fairly common, present in 35% and 24% of the subjects, respectively [20]. This is in line with the current study, in which 32% of the patients presenting with ACS at a relatively young age had Lp(a) levels above a cutoff equivalent to 30 mg/dL.

Although there is an exponential relationship between Lp(a) levels and cardiovascular risk, in epidemiological and Mendelian randomization studies increased cardiovascular risk starts at a level as low as 20 mg/dL or 50 nmol/L, especially when

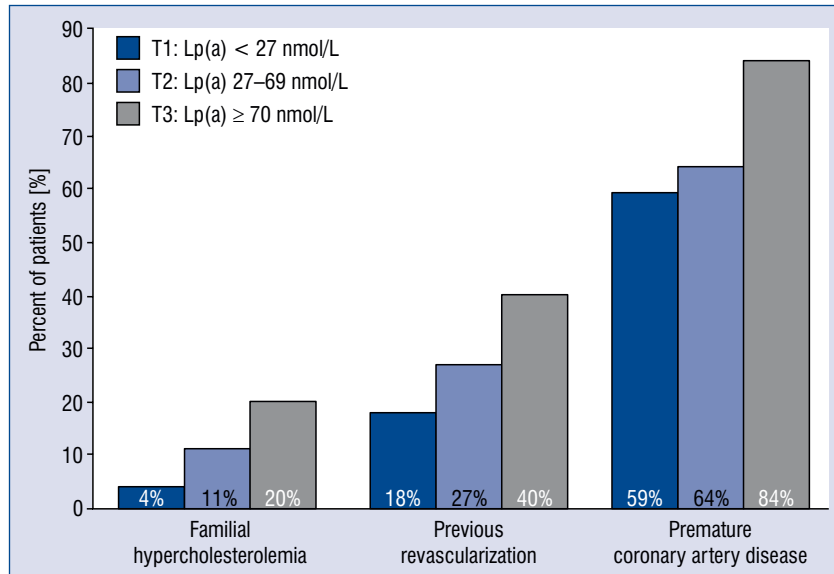


Figure 2. Prevalence of independent clinical risk markers according to lipoprotein(a) [Lp(a)] tertiles.

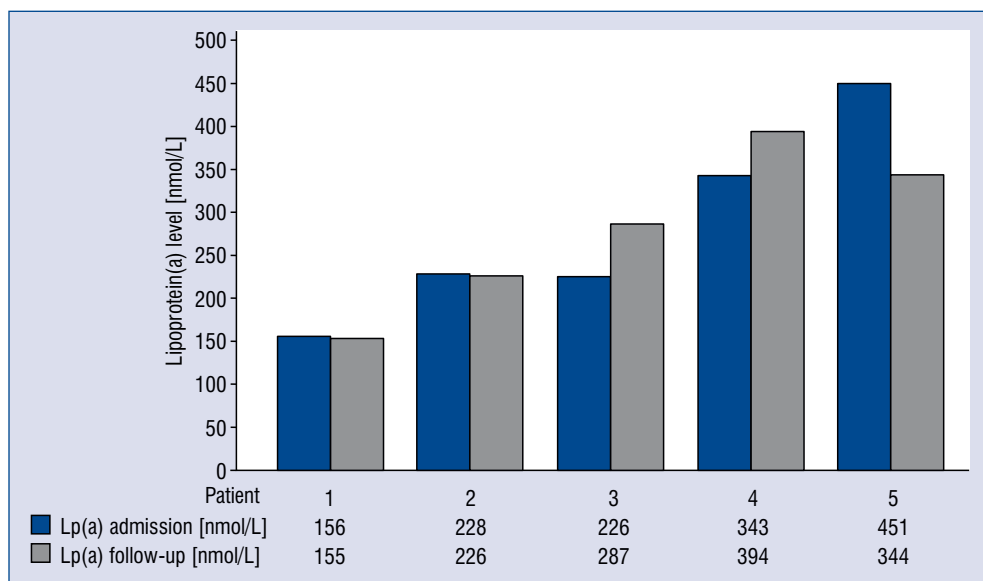


Figure 3. Admission versus post-hospitalization repeat lipoprotein(a) [Lp(a)] levels in 5 patients with acute coronary syndrome and elevated lipoprotein(a).

evaluated in primary care populations [10, 13, 18, 21]. In the setting of ACS, there are non-conclusive findings. Past studies have demonstrated an association between baseline Lp(a) concentrations and increased risk of cardiac death in patients admitted with ACS [22]. Lp(a) was also shown to be independently associated with ACS and subsequent cardiovascular events in younger and middle aged individuals below 60 years old [23–25]. However, data from sub-analyses of large prospec-

tive randomized trials of lipid-modifying therapies in patients with ACS or established CAD, showed conflicting results with some reporting no association between Lp(a) concentration and adverse cardiovascular outcomes [26–28], while others have demonstrated that Lp(a) was associated with increased cardiovascular risk [8, 29, 30]. Future studies with antisense oligonucleotides targeting apo(a), recently shown to reduce Lp(a) levels by 80% in phase 2 trials, may further shed light on

the impact of Lp(a) reduction on cardiovascular outcomes in patients with CAD [15]. The present findings of a stepwise association between tertiles of Lp(a) with premature and progressive CAD support the role of Lp(a) as a risk marker also in patients with ACS.

The European Society of Cardiology/European Atherosclerosis Society has given a Class IIa recommendation for measuring Lp(a) in patients with premature CVD, FH, family history of premature CVD or elevated Lp(a), as well as in those with recurrent CVD despite optimal lipid-lowering therapy, and also for risk reclassification in subjects with borderline risk [14]. Nevertheless, in many countries assays for Lp(a) measurement are not routinely available in clinical practice, often performed only at dedicated lipid clinics, and there is low awareness for the risk associated with high Lp(a). Current results are consistent with the above recommendations, demonstrating an independent association between the majority of these risk groups and high Lp(a) also in the setting of ACS. However, although the plasma level of Lp(a) is, to a major extent, genetically determined, no similar association was observed between Lp(a) and family history of premature CAD. This may have been affected by the use of an electronic chart diagnosis for defining positive family history and not by directly questioning the patients and preparing a family tree when appropriate.

Familial hypercholesterolemia is an autosomal co-dominant genetic disorder associated with raised concentrations of LDL cholesterol from birth and an elevated risk of premature CVD [31]. Concentrations of Lp(a) are raised in patients with FH compared with individuals with normal lipid levels, and data in patients with FH shows that high Lp(a) levels further increase cardiovascular risk [32, 33]. Prospective data from 46,200 individuals from the Copenhagen General Population Study showed that the risk of myocardial infarction (MI) was highest in patients classified as having both FH and high Lp(a) values, concluding that high Lp(a) concentrations represent a novel risk factor for clinical FH, and suggesting that all individuals with FH should have their Lp(a) measured in order to identify those with the highest concentrations, and as a result, the highest risk for MI [34]. The present results, demonstrate that a clinical diagnosis of probable/definite FH is independently associated with elevated Lp(a) and premature CAD in patients presenting with ACS, are compatible with a recent investigation concluding that the combination of elevated Lp(a) and phenotypic FH is commonly

encountered in patients with premature CAD admitted to the coronary care unit [35]. Overall, this data supports the routine screening for both FH and elevated Lp(a) in young patients hospitalized in cardiac units for evaluation or treatment of CAD. This will also serve as an opportunity to perform cascade-screening of relatives of identified index-cases, due to the genetic nature of both disorders [36].

Past small-scale studies have reported conflicting findings regarding the associations between Lp(a) levels and inflammatory markers following MI, with both increases or no change in Lp(a) levels as a function of increasing CRP levels [16, 17, 37]. In patients with rheumatoid arthritis, high Lp(a) levels were related to an active inflammatory disease [38, 39]; while following an acute ischemic stroke, Lp(a) levels were shown to remain stable [40]. A more recent, far larger analysis, in the setting of the general population, reported only minimal increases in Lp(a) with increasing CRP levels [41]. Furthermore, the ability of elevated Lp(a) to predict ischemic heart disease and MI was not affected by markers of inflammation. In the current study, no correlation between CRP and Lp(a) concentration was found at admission of patients with ACS. In addition, in a small number of patients with significantly high Lp(a), repeat levels measured more than 2 months from the acute event remained high. These findings should be confirmed in larger studies, and could be clinically relevant, as Lp(a) measurement performed during the acute phase may lead to intensification of treatment such as with proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies and possibly future apo(a) antisense therapy, in addition to a more aggressive management of modifiable cardiovascular risk factors [15].

Limitations of the study

Several limitations of the current study should be acknowledged. This is a retrospective analysis of a single center, with a relatively small sample size. Nevertheless, Lp(a) levels are not routinely measured in the study region, and there is low awareness of the health care providers to Lp(a) and its associated risk. In addition, as Lp(a) level varies among different races, and results may not be generalizable to other races or geographical areas. No genetic testing was performed for diagnosing FH, although a customary algorithm for phenotypically diagnosing probable and definite FH was used. Finally, it should be noted that the independent associations between clinical variables

and Lp(a) levels described in this analysis do not prove causation.

Conclusions

In young and middle-aged patients ≤ 65 years of age presenting with ACS, previous revascularization, premature CAD and FH were independently associated with elevated Lp(a). These findings, limited by a small sample size, are in accordance with guideline based recommendations for Lp(a) screening, and suggest that testing for Lp(a) in young patients in the setting of ACS may address residual cardiovascular risk, with potential clinical benefit in light of the novel emerging therapies targeting Lp(a).

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Conflict of interest: None declared

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