Rosuvastatin for Primary Prevention Among Individuals With Elevated High-Sensitivity C-Reactive Protein and 5% to 10% and 10% to 20% 10-Year Risk

Implications of the Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial for "Intermediate Risk"

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Background—Recent primary prevention guidelines issued in Canada endorse the use of statin therapy among individuals at "intermediate risk" who have elevated levels of high-sensitivity C-reactive protein (hsCRP). However, trial data directly addressing whether this recommendation defines a patient population in which statin therapy is effective have not previously been published.

Methods and Results—In the Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which demonstrated a 44% reduction in first vascular events when rosuvastatin 20 mg was compared with placebo among 17 802 primary prevention patients with LDL cholesterol <130 mg/dL and hsCRP ≥2 mg/L, 6091 participants (2525 women, 3566 men) had baseline estimated 10-year Framingham risks of 5% to 10% and 7340 participants (1404 women, 5936 men) had baseline estimated Framingham risk of 11% to 20%. In these 2 "intermediate risk" subgroups, relative risk reductions consistent with the overall trial treatment effect were observed (hazard ratio, 0.55; 95% confidence interval, 0.36 to 0.84; 5-year number needed to treat=40, $P=0.005$ for those with 5% to 10% risk; hazard ratio, 0.51; 95% confidence interval, 0.39 to 0.68, 5-year number needed to treat=18, $P<0.0001$ for those with 11% to 20% risk). Use of the Reynolds Risk Score to stratify the study population gave similar results but reclassified large numbers of individuals into lower- or higher-risk groups. The majority of women with elevated hsCRP who benefited from rosuvastatin were at 5% to 10% 10-year risk at study entry using either global risk scoring system.

Conclusions—Consistent with recent evidence-based Canadian Cardiovascular Society guidelines for primary prevention, the JUPITER trial demonstrates that rosuvastatin 20 mg significantly reduces major cardiovascular events among men and women with elevated hsCRP and "intermediate risk" defined either as 5% to 10% or 10% to 20% 10-year risk.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00239681.

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In 2009, the Canadian Cardiovascular Society issued new primary prevention guidelines recommending measurement of high-sensitivity C-reactive protein (hsCRP) along with LDL cholesterol and HDL cholesterol among otherwise healthy men and women at "intermediate risk."[1] These new practice guidelines extend prior recommendations issued by the American Heart Association and the Centers for Disease Control and Prevention in 2003 that endorsed the use of hsCRP as an adjunct to global risk prediction among individuals at "intermediate risk,"[2] a population defined at that time as having estimated Framingham 10-year risk between 5% and 20%.[3] Both of these guidelines reflect evidence that hsCRP has been found useful in reclassifying risk for intermediate risk men and women in several cohorts including the Women's Health Study, the Physicians' Health Study, the Framingham Heart Study, the Uppsala Longitudinal Study of Adult Men, the MONICA-Augsberg cohort, the EPIC Norfolk study, the Atherosclerosis Risk in Communities study,

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and the Heart and Soul cohort.[4–11] As demonstrated in a 2010 meta-analysis of 54 prospective cohort studies, the adjusted magnitude of risk associated with a 1–standard deviation increase in hsCRP (hazard ratio [HR], 1.4; 95% confidence interval [CI], 1.3 to 1.5) is if anything larger than that associated with a similar increase in cholesterol (HR, 1.2; 95% CI, 1.1 to 1.3).[12]

The new Canadian Cardiovascular Society guidelines for primary prevention go an important step further by recommending the use of statin therapy to prevent vascular events among intermediate risk individuals with elevated hsCRP, even if LDL cholesterol levels are within the normal range. This evidence-based recommendation in part reflects data from the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, in which random allocation of rosuvastatin among 17 802 primary prevention patients with LDL cholesterol <130 mg/dL and hsCRP ≥2 mg/L was associated with a 54% reduction in myocardial infarction, a 48% reduction in stroke, a 47% reduction in need for angioplasty or bypass surgery, a 43% reduction in venous thrombosis, and a 20% reduction in all-cause mortality.[13,14] To date, however, presentation of the JUPITER trial data stratified by underlying level of vascular risk has not been available for review by the preventive cardiology community.

WHAT IS KNOWN

- Although the Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrates that statin therapy significantly reduces vascular risk in primary prevention among those with LDL cholesterol <130 mg/dL but high-sensitivity C-reactive protein (hsCRP) >2 mg/L, analyses of this trial stratified by underlying level of absolute risk has not been available.

WHAT THE STUDY ADDS

- In primary prevention patients with low LDL cholesterol but elevated hsCRP who are at 5% to 10% or 11% to 20% 10-year risk using either the Framingham or Reynolds risk scores, rosuvastatin 20 mg significantly reduces the risk of future cardiovascular events.
- These data provide evidence-based support for recommendations from the Canadian Cardiovascular Society that "intermediate risk" individuals with elevated hsCRP be considered for statin therapy, even if LDL cholesterol levels are low to normal.

Methods

The study population derived from Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), a randomized, double-blind, placebo-controlled trial designed to investigate whether rosuvastatin 20 mg daily compared with placebo decreases the rate of first-ever cardiovascular events among apparently healthy men age 50 or over and women age 60 or over with LDL cholesterol <130 mg/dL at increased vascular risk caused by hsCRP ≥2 mg/L.[13]

Full details of the trial protocol, procedures, and methods of confirming clinical end points and ascertaining adverse events have been previously presented. Trial exclusion criteria included use within the 6 weeks before screening any lipid-lowering therapies, current use of postmenopausal hormone replacement therapy, evidence of hepatic dysfunction, creatinine >2.0 mg/dL, diabetes, uncontrolled hypertension or hypothyroidism, cancer within 5 years before enrollment, or another serious medical condition that might compromise safety or successful completion of the study. Because a core scientific hypothesis of JUPITER related to underlying low-grade inflammation as evidenced by hsCRP levels ≥2.0 mg/L, individuals with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded.

For the purposes of this analysis, all study participants were classified according to 10-year global risk estimates using the Framingham Risk Score as published in the ATP-III[15] and using the Reynolds Risk Scores as derived for women from the Women's Health Study[4] and for men from the Physicians Health Study.[5] As previously described, the Framingham Risk Score estimates 10-year global cardiovascular risk on the basis of age, sex, smoking status, blood pressure, and total and HDL cholesterol, whereas the Reynolds Risk Score estimates global 10-year cardiovascular risk on the basis of these covariates as well as hsCRP and parental history of premature atherothrombosis.

Baseline clinical characteristics of the study population as well as lipid and hsCRP levels were calculated according to baseline levels of Framingham Risk and according to baseline levels of Reynolds Risk. In stratified analyses according to estimated levels of global risk at study entry, Cox proportional hazards models were used to calculate HRs and 95% CIs for the comparison of event rates between those allocated to rosuvastatin or placebo. All analyses were performed on an intention-to-treat basis using the JUPITER prespecified primary trial end point of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed cardiovascular death. Number-needed-to-treat [NNT] values were calculated as the reciprocal of the absolute difference between risks of the outcome of interest based on Kaplan–Meier estimates. Estimated 95% CIs for the NNT were based on inversion of the CIs for risk differences with standard errors of risks estimated by the Greenwood formula. Consistent with prior JUPITER publications, 5-year NNT values were computed on the basis of 4-year absolute rates projected over an average 5-year period according to the methods of Altman and Andersen.[16]

Role of the Funding Source

JUPITER was an investigator initiated trial. The sponsor of the study collected the trial data and monitored the study sites but had no access to unblinded data until after drafting of the trial primary report. All statistical analyses were done by the investigators and the academic study statistician (R.J.G.). Both the trial Principle Investigator (P.M.R.) and R.J.G. had full access to all study data and had final responsibility for the decision to submit these data for publication.

Results

Table 1 presents clinical characteristics of the JUPITER trial according to baseline levels of Framingham Risk Score; Table 2 presents similar data according to baseline levels of the Reynolds Risk Score. Because the JUPITER population was selected on the basis of having LDL cholesterol <130 mg/dL, none would have qualified for statin therapy according to guidelines in effect at study entry in 2003. As anticipated, those with higher global risk estimates were older, more likely to have hypertension and metabolic syndrome, and less likely to have elevated HDL cholesterol. Whereas the median 10-year risk for JUPITER participants was approximately 10% using either the Framingham Risk Score or the Reynolds Risk Score, the latter global risk algorithm reclas-

Table 1. Baseline Clinical Characteristics of Participants in the JUPITER Trial According to Estimated 10-Year Risk Defined by the Framingham Risk Score

Baseline Characteristic	<5% 10-Year Risk (n=2791)	5% to 10% 10-Year Risk (n=6091)	11% to 20% 10-Year Risk (n=7340)	>20% 10-Year Risk (n=1555)
Age, y	65 (62–68)	64 (58–69)	67 (61–73)	74 (66–78)
Female, %	93.8	41.5	19.1	15.6
Body mass index, kg/m^2	28.6 (25.2–32.4)	28.3 (25.1–32.1)	28.4 (25.4–31.7)	28.4 (25.8–31.6)
Hypertension, %	36.4	50.4	64.9	86.5
Blood pressure, mm Hg				
Systolic	125 (118–135)	130 (121–141)	138 (130–149)	146 (136–160)
Diastolic	80 (70–82)	80 (75–86)	80 (76–88)	83 (79–90)
Current smoking, %	5.5	10.6	20.8	31.8
Family history of premature CHD,* %	12.0	12.4	11.1	9.3
Metabolic syndrome, %	30.0	35.1	46.1	68.6
hsCRP, mg/L	4.4 (2.9–7.2)	4.2 (2.8–7.0)	4.3 (2.8–7.1)	4.7 (3.1–7.9)
Total cholesterol, mg/dL	190 (172–204)	186 (168–201)	184 (169–198)	181 (167–194)
LDL-C, mg/dL	107 (92–118)	107 (92–119)	109 (96–120)	109 (97–119)
HDL-C, mg/dL	58 (50–69)	53 (44–64)	45 (38–53)	38 (34–44)
Triglycerides, mg/dL	106 (79–142)	109 (79–154)	127 (91–183)	152 (109–221)

CHD indicates congestive heart disease; LDL-C, LDL cholesterol; and HDL-C, HDL cholesterol.

All values are median (interquartile range) or n (%). For hsCRP, values are based on the average of the screening and randomization visits.

*CHD in a male first-degree relative before age 55 or in a female first-degree relative before age 65.

sified more participants into lower (<5%) and higher (>20%) 10-year risk categories.

Table 3 presents data on the JUPITER primary end point of nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed cardiovascular death according to baseline level of Framingham estimated 10-year risk. All Framingham groups had relative risk reductions with rosuvastatin comparable to the overall trial treatment effect observed in JUPITER. With regard to those at intermediate risk, the HRs for rosuvastatin

Table 2. Baseline Clinical Characteristics of Participants in the JUPITER Trial According to Estimated 10-Year Risk Defined by the Reynolds Risk Score

Baseline Characteristic	<5% 10-Year Risk (n=3583)	5% to 10% 10-Year Risk (n=6436)	11% to 20% 10-Year Risk (n=5040)	>20% 10-Year Risk (n=2651)
Age, y	64 (60–67)	63 (58–69)	67 (63–72)	74 (69–78)
Female, %	73.7	41.2	22.8	12.3
Body mass index, kg/m^2	28.2 (25.0–32.0)	28.7 (25.4–32.6)	28.4 (25.5–31.7)	27.8 (25.0–30.8)
Hypertension, %	41.3	53.7	63.7	76.1
Blood pressure, mm Hg				
Systolic	124 (117–132)	130 (122–140)	139 (130–150)	149 (138–160)
Diastolic	80 (70–82)	80 (75–87)	81 (76–88)	83 (78–90)
Current smoking, %	5.8	14.6	20.2	24.0
Family history of premature CHD,* %	5.2	9.8	14.0	19.6
Metabolic syndrome, %	28.5	41.6	46.9	50.2
hsCRP, mg/L	3.8 (2.7–6.1)	4.2 (2.8–7.0)	4.4 (2.9–8.6)	4.9 (3.1–8.6)
Total cholesterol, mg/dL	187 (168–202)	185 (169–200)	185 (169–199)	184 (170–197)
LDL-C, mg/dL	105 (89–117)	108 (93–119)	110 (96–120)	110 (98–120)
HDL-C, mg/dL	57 (47–69)	49 (41–60)	46 (38–56)	43 (37–52)
Triglycerides, mg/dL	104 (77–139)	118 (86–167)	126 (90–182)	131 (92–192)

CHD indicates congestive heart disease; LDL-C, LDL cholesterol; and HDL-C, HDL cholesterol.

All values are median (interquartile range) or n (%). For hsCRP, values are based on the average of the screening and randomization visits.

*CHD in a male first-degree relative before age 55 or in a female first-degree relative before age 65.

Table 3. Event Rates and Hazard Ratios for the Primary Trial End Point According to Baseline Levels of Estimated 10-Year Risk According to Either the Framingham Risk Score or the Reynolds Risk Score

		Rosuvasatatin		Placebo				
	n	Events	Rate	Events	Rate	HR	(95% CI)	*P*
Framingham 10-y risk <5%	2791	6	0.22	9	0.34	0.64	(0.23–1.81)	0.40
Framingham 10-y risk 5% to 10%	6091	32	0.50	59	0.92	0.55	(0.36–0.84)	0.005
Framingham 10-y risk 11% to 20%	7340	74	0.95	145	1.84	0.51	(0.39–0.68)	0.0001
Framingham 10-y risk >20%	1555	29	1.72	38	2.41	0.70	(0.43–1.14)	0.15
Reynolds 10-y risk <5%	3583	9	0.26	14	0.41	0.62	(0.27–1.43)	0.26
Reynolds 10-y risk 5% to 10%	6436	30	0.44	69	1.00	0.45	(0.29–0.68)	0.0001
Reynolds 10-y risk 11% to 20%	5040	59	1.07	87	1.65	0.65	(0.47–0.90)	0.009
Reynolds 10-y risk >20%	2651	42	1.55	81	2.84	0.55	(0.38–0.80)	0.001

Rate is per 100 person-years.

as compared with placebo for the primary trial end point were 0.55 (95% CI, 0.36 to 0.84; $P=0.005$) for those with 5% to 10% risk and 0.51 (95% CI, 0.39 to 0.68; $P<0.0001$) for those with 11% to 20% risk.

Table 3 also presents similar data when the Reynolds Risk Score was used to define 10-year risk groups rather than the Framingham Risk Score. In this analysis, the HRs for rosuvastatin as compared with placebo for the primary trial end point were 0.45 (95% CI, 0.29 to 0.68; $P=0.0001$) for those with 5% to 10% risk and 0.65 (95% CI, 0.47 to 0.90; $P=0.009$) for those with 11% to 20% risk.

Tables 4 and 5 provide data further stratified by sex. At all levels of 10-year risk by either Framingham and Reynolds stratum, the point estimates of effect associated with rosuvastatin remain consistent with the overall trial treatment effect, although the 95% CIs are wider for several subgroups that have small numbers of events. As shown in Table 4, the great majority of men enrolled in JUPITER had baseline Framingham Risk Scores of either 5% to 10% (n=3566) or 11% to 20% (n=5936), with only 173 men having baseline risk <5%. In marked contrast, 2618 women had baseline Framingham Risk Scores <5%, 2525 had baseline Framingham Risk Scores of 5% to 10%, and only 1404 had Framingham Risk Scores of 11% to 20% (Table 5). Use of the Reynolds Risk Score gave similar results such that with either global scoring system, most women with elevated hsCRP who benefited from rosuvastatin had baseline 10-year risks of 5% to 10%.

As would be anticipated, absolute risk reductions increased with increasing level of global risk as assessed by either the Framingham Risk Score or the Reynolds Risk Score. The estimated 5-year NNT among men and women with elevated hsCRP and 5% to 10% 10-year Framingham risk was 40 (95% CI, 22 to 206), whereas the comparable 5-year NNT value among men and women with 11% to 20% 10-year Framingham risk was 18 (95% CI, 12 to 32). These NNT values correspond to estimated absolute risk differences between the rosuvastatin and placebo groups at 5 years of 2.5 and 5.7 events per 100 person-years for those with baseline Framingham risks of 5% to 10% and 11% to 20%, respectively.

Within the JUPITER trial, we found no evidence that the safety profile of rosuvastatin differed significantly according to baseline level of global risk estimated by either the Framingham Risk Score or the Reynolds Risk Score.

Discussion

In the present analysis of the JUPITER trial, men and women with LDL cholesterol levels <130 mg/dL and hsCRP levels ≥2 mg/L had similar relative risk reductions associated with rosuvastatin as compared with placebo regardless of underlying level of absolute risk as calculated by either the

Table 4. Event Rates and Hazard Ratios for the Primary Trial End Point According to Baseline Levels of Estimated 10-Year Risk According to Either the Framingham Risk Score or the Reynolds Risk Score

		Rosuvasatatin		Placebo				
	n	Events	Rate	Events	Rate	HR	(95% CI)	*P*
Framingham 10-y risk <5%	173	0	…	0	…	…	(…)	…
Framingham 10-y risk 5% to 10%	3566	21	0.57	34	0.89	0.64	(0.37–1.10)	0.1
Framingham 10-y risk 11% to 20%	5936	58	0.91	114	1.77	0.52	(0.38–0.71)	0.0001
Framingham 10-y risk >20%	1313	23	1.61	33	2.40	0.67	(0.39–1.14)	0.1
Reynolds 10-y risk <5%	944	1	0.11	4	0.44	0.25	(0.03–2.25)	0.17
Reynolds 10-y risk 5% to 10%	3785	21	0.52	43	1.03	0.51	(0.30–0.86)	0.009
Reynolds 10-y risk 11% to 20%	3889	43	1.00	63	1.54	0.65	(0.44–0.96)	0.03
Reynolds 10-y risk >20%	2324	36	1.51	71	2.81	0.54	(0.36–0.81)	0.002

Rate is per 100 person-years. Data shown for men only.

Table 5. Event Rates and Hazard Ratios for the Primary Trial End Point According to Baseline Levels of Estimated 10-Year Risk According to Either the Framingham Risk Score or the Reynolds Risk Score

		Rosuvasatatin		Placebo				
	n	Events	Rate	Events	Rate	HR	(95% CI)	*P*
Framingham 10-y risk <5%	2618	6	0.24	9	0.36	0.65	(0.23–1.84)	0.4
Framingham 10-y risk 5% to 10%	2525	11	0.42	25	0.96	0.44	(0.22–0.89)	0.02
Framingham 10-y risk 11% to 20%	1404	16	1.09	31	2.20	0.50	(0.27–0.91)	0.02
Framingham 10-y risk >20%	242	6	2.31	5	2.47	0.87	(0.26–2.88)	0.8
Reynolds 10-y risk <5%	2639	8	0.31	10	0.40	0.76	(0.30–1.94)	0.6
Reynolds 10-y risk 5% to 10%	2651	9	0.33	26	0.96	0.35	(0.16–0.74)	0.003
Reynolds 10-y risk 11% to 20%	1151	16	1.33	24	2.05	0.65	(0.35–1.23)	0.18
Reynolds 10-y risk >20%	327	6	1.91	10	3.07	0.61	(0.22–1.68)	0.3

Rate is per 100 person-years. Data shown for women only.

Framingham Risk Score or the Reynolds Risk Score. However, as demonstrated in these data, individuals with elevated hsCRP who are otherwise at 5% to 10% or 10% to 20% 10-year risk had substantive absolute risk reductions, suggesting that this group—currently outside treatment guidelines and with a mean entry LDL cholesterol of only 104 mg/dL—might well be considered candidates for statin therapy. By contrast, our data also demonstrate that men and women estimated to be at low risk (<5% 10-year risk estimates) had concomitantly low absolute risk reductions and hence represent a group where the absolute benefit of statin therapy is small.

Clinically, our data provide consistent support for the position taken by the American Heart Association and Centers for Disease Control that the use of hsCRP probably is best among those at 5% to 10% and 10% to 20% 10-year risk, groups in which controversy is present regarding the utility and effectiveness of statin therapy.[2] In this regard, our data are also consistent with prior recommendations that those already known to be at "low risk" (ie, 10-year estimates <5%) benefit little from evaluation of hsCRP because such individuals are unlikely to be treated irrespective of the additional information provided. Within JUPITER, use of the Reynolds Risk Score rather than the Framingham Risk Score gave similar results for those at "intermediate risk." However, the Reynolds Risk Score (which takes into account hsCRP and family history) placed a larger number of individuals into the lower and higher risk categories.

Our data also provide support for evidence-based guidelines issued in October 2009 from the Canadian Cardiovascular Society that for the first time advocate prophylactic statin therapy for men over 50 and women over 60 who have Framingham Risk Scores above 10% and who have hsCRP ≥2 mg/L.[1] One potential limitation of the new Canadian approach is that by limiting hsCRP evaluation to those with a Framingham Risk Score above 10%, few women will be screened. As shown in these data, most women who benefited from rosuvastatin within JUPITER had Framingham Risk Scores of 5% to 10%, a group in which the concomitant finding of an elevated hsCRP was associated with considerably higher absolute risk. Thus, if the concept of "intermediate risk" is expanded to include those at 5% to 10% as well as 10% to 20% 10-year risk, then the use of hsCRP in that group would provide an evidence-based method to pick up women as well as men with a proven benefit from statin therapy.

All participants in JUPITER had elevated hsCRP, a decision made on the basis of prior work indicating that absolute risk among those with low LDL cholesterol and low hsCRP is usually below a 5% 10-year risk threshold.[17,18] In this regard, the multiethnic Atherosclerosis Risk in Communities (ARIC) study has recently confirmed that those with low LDL cholesterol but high hsCRP have substantially higher vascular risk than those with low LDL cholesterol and low hsCRP, despite both groups having identical Framingham Risk Scores.[19] Similarly, in the large scale CORONA trial, statin therapy was only effective among those with hsCRP >2 mg/L, whereas no clinical benefit was observed among those with lower levels.[20] Nonetheless, because JUPITER did not randomly assign those with low hsCRP, the trial cannot exclude the possibility that individuals with intermediate risk, low LDL cholesterol, and low hsCRP might benefit from statin therapy. However, in an analysis of the primary prevention AFCAPS/TexCAPS trial comparing lovastatin with placebo, no efficacy of statin therapy was observed in terms of event reduction for those with low LDL cholesterol and low hsCRP, and such individuals were again found to be at very low absolute risk.[21] Thus, in the absence of positive evidence and in the presence of low absolute risk as seen in ARIC and earlier studies, arguments to treat such low-risk individuals with statin therapy remain speculative.

As in any analysis of a completed trial, caution must be used when interpreting subgroups. For example, as shown in Table 3, among JUPITER participants with low LDL cholesterol who nonetheless had Framingham Risk Scores >20% at study entry, a 30% relative risk reduction in major vascular events was observed that was not statistically significant (HR, 0.70; 95% CI, 0.43 to 1.14; $P=0.15$), probably because of the small number of events recorded (38 on placebo, 29 on rosuvastatin among a total of 1555 trial participants). However, as also shown in Table 3, when the Reynolds Risk Score was used to define those at "higher risk," 81 events were observed on placebo and 42 on rosuvastatin among 2651 study classified as >20% 10-year risk, an effect that was now statistically significant and consistent with the magnitude of

risk reduction observed in the trial as a whole (HR, 0.55; 95% CI, 0.38 to 0.80; $P=0.001$).

In sum, in primary prevention patients with low LDL cholesterol and elevated hsCRP who are at 5% to 10% or 10% to 20% 10-year risk using either the Framingham or Reynolds risk scores, rosuvastatin 20 mg significantly reduces the risk of future cardiovascular events.

Disclosures

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