Associations Between Lipoproteins and the Progression of Coronary and Vein-Graft Atherosclerosis in a Controlled Trial With Gemfibrozil in Men With Low Baseline Levels of HDL Cholesterol

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Background—Lipid-lowering secondary-prevention trials of coronary artery disease (CAD) have implicated triglyceride-rich lipoproteins as the main determinants of angiographic progression after elevated LDL cholesterol levels have been lowered with therapy. The present study focuses on the lipoprotein determinants of angiographic CAD progression in men with low HDL cholesterol concentration as their main baseline lipid abnormality who underwent 32 months of randomized therapy with gemfibrozil or placebo.

Methods and Results—Men who had undergone coronary bypass surgery (n=372) completed a randomized, placebo-controlled study with gemfibrozil 1200 mg/d. They were selected primarily for HDL cholesterol levels that corresponded to the lowest third for middle-aged men. Average baseline lipid and lipoprotein levels were serum triglyceride, 1.60; serum cholesterol, 5.17; ultracentrifugally separated LDL cholesterol, 3.43; HDL₂ cholesterol, 0.41; and HDL₃ cholesterol, 0.61 mmol/L. In the gemfibrozil group, these levels were reduced on average by 40%, 9%, and 6% or increased by 5% and 9%, respectively. On-trial IDL and LDL triglyceride and cholesterol levels significantly predicted global angiographic progression, taking into account changes in native segments and in bypass grafts. HDL₃ but not HDL₂ cholesterol concentration was associated with protection against progression, especially focal disease in native coronary lesions. VLDL was the lipoprotein most predictive of new lesions in vein grafts; IDL was also significantly related.

Conclusions—This study expands the previous evidence of the triglyceride-rich lipoproteins, especially IDL, as predictors of angiographic progression of CAD but does not negate the significance of mildly elevated LDL levels. Of the HDL subfractions, only HDL₃ was protective in this group of men selected for their low initial HDL levels. (Circulation. 1998;98:1993-1999.)

Key Words: coronary disease ■ bypass ■ lipoproteins ■ angiography ■ trials

In recent years, many studies have shown that treatment of dyslipidemia retards the angiographic progression of coronary artery disease (CAD) (reviewed in Reference 1) and reduces mortality and morbidity. Most of these trials used 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Recently, a study suggested a beneficial effect of the fibric acid derivative bezafibrate. We reported similar results with gemfibrozil in the Lopid Coronary Angiography Trial (LOCAT). Despite marked benefits from treating dyslipidemia in CAD patients, most studies, including LOCAT, showed that angiographic progression continued during active therapy, albeit at a slower pace than in patients who received placebo. The present study reports which lipoproteins, separated by preparative ultracentrifugation, predict angiographic progression in the LOCAT study population.

Methods

Patients
The entry criteria and baseline characteristics of the study population have been described. Briefly, 395 men who had previously undergone coronary artery bypass surgery and who had HDL...
cholesterol levels ≤1.1 mmol/L (42.5 mg/dL), LDL cholesterol ≤4.5 mmol/L (174 mg/dL), and serum triglyceride ≤4.0 mmol/L (354 mg/dL) were randomized to receive 1200 mg/d gemfibrozil or placebo. Three hundred seventy-two patients (placebo, 187; gemfibrozil, 185) completed the study with a baseline and follow-up angiogram that were suitable for quantitative analysis, and these patients constitute the population of this report.

### Angiographic Data

As previously reported, we used the average diameters of coronary segments (ADS) to describe changes in diffuse CAD and minimum luminal diameters (MLD) of stenoses to characterize focal CAD. We classified the patients into those showing progression or regression, or no significant change. Those with progression only or a mixed response were considered progressors, and the remaining patients were non-progressors. Progression or regression was defined as a change in ADS or MLD ≥0.40 mm in any native coronary segment.

New lesions and new total occlusions were also defined as progression. Venous aortocoronary bypass grafts were taken into account by defining a new graft lesion as progression. The rationale for this post hoc classification, rather than one based only on changes in the luminal diameters (MLD) of stenoses to characterize focal CAD. We defined a new graft lesion as progression. The rationale for this post hoc classification, rather than one based only on changes in the nonbypassed native vessels and segments distal to graft insertions as we originally planned, was a report by the Cholesterol Lowering Atherosclerosis Study (CLAS) investigators showing that a global coronary score that takes into account all native segments and bypass grafts predicts future clinical events in postbypass patients.

We also calculated per-patient mean changes in ADS and MLD (∆ADS and ∆MLD) in all native coronary segments and stenoses available for analysis. An additional outcome variable was the appearance of new lesions in vein grafts.

### Lipoprotein and Other Risk-Variable Data

Blood samples were obtained after an overnight fast at the randomization visit, 1 year after randomization, and ≥2 years after randomization. Lipoproteins (VLDL, d<1.006 g/mL; IDL, d=1.006 to 1.019 g/mL; LDL, d=1.019 to 1.063 g/mL; HDL, d=1.063 to 1.210 g/mL; and the HDL subfractions HDL₂, d=1.063 to 1.120 g/mL; and HDL₃, d=1.120 to 1.210 g/mL) were separated by preparative ultracentrifugation as described elsewhere. Triglyceride, cholesterol, free (nonesterified) cholesterol, and phospholipid were measured in unfractionated serum and in the lipoprotein fractions, and protein was measured in the fractions. Cholesterol ester concentrations were calculated as 1.67×(total minus free cholesterol [in mg/dL]). Lipoprotein compositions were calculated as the percentages of triglyceride, esterified cholesterol, free cholesterol, phospholipid, and protein (all in mg/dL) of the sum of these constituents. Serum apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)] concentrations were determined as described.

Triglyceride and cholesterol in serum and lipoproteins and serum apoB were measured at both 1- and 2-year visits and averaged. On-trial data for other lipoprotein constituents and Lp(a) were available only at the 1-year visit.

An oral glucose tolerance test with glucose, insulin, and C-peptide measurements was performed at baseline as described, and fasting insulin was also measured at the final study visit. Height was measured at baseline; weight, waist and hip circumferences, blood pressure, and heart rate were determined at each visit.

### Statistical Analyses

Data were given as mean±SD or median (25th, 75th percentile). Unpaired t tests were used to compare on-trial lipoprotein data in the randomized groups after logarithmic transformations for skewed data. Categorical variables were compared by the χ² test. Simple correlations were assessed by Pearson’s coefficients. Associations between risk factors and the global progressor status were evaluated by logistic regression analyses. All analyses were adjusted for the time interval between the baseline and follow-up angiograms. For the calculation of odds ratios, lipoprotein data were made comparable by transformation to standardized z scores (they have the same distribution as the original data but a mean value of zero and SD=1). Other logistic models were created to control for the randomization group and to study the associations in the placebo and gemfibrozil groups separately. The continuous outcome variables (ΔADS and ΔMLD) were analyzed by linear regression, controlling for the time between angiograms and the baseline values of the dependent natural logarithms for the statistical comparisons.

### Table 1: Baseline and On-Trial Concentrations of Triglyceride and Cholesterol in Serum and in Lipoprotein Fractions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline, Placebo, mmol/L</th>
<th>On-trial, Placebo, mmol/L</th>
<th>Baseline, Gemfibrozil, mmol/L</th>
<th>On-trial, Gemfibrozil, mmol/L</th>
<th>Percentage Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triglyceride</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.61±0.83</td>
<td>1.60±0.68</td>
<td>1.59±0.67</td>
<td>0.95±0.37†</td>
<td>-40 (52, -26)</td>
</tr>
<tr>
<td>VLDL</td>
<td>1.06±0.72</td>
<td>1.06±0.60</td>
<td>1.05±0.59</td>
<td>0.52±0.30†</td>
<td>-51 (64, -35)</td>
</tr>
<tr>
<td>IDL</td>
<td>0.11±0.04</td>
<td>0.12±0.04</td>
<td>0.12±0.05</td>
<td>0.09±0.03†</td>
<td>-19 (35, 0)</td>
</tr>
<tr>
<td>LDL</td>
<td>0.26±0.08</td>
<td>0.25±0.06</td>
<td>0.25±0.07</td>
<td>0.20±0.05†</td>
<td>-21 (31, -9)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.16±0.04</td>
<td>0.16±0.03</td>
<td>0.16±0.04</td>
<td>0.13±0.03†</td>
<td>-17 (30, -7)</td>
</tr>
<tr>
<td>HDL₂</td>
<td>0.07±0.02</td>
<td>0.07±0.02</td>
<td>0.07±0.02</td>
<td>0.06±0.01†</td>
<td>-21 (35, 0)</td>
</tr>
<tr>
<td>HDL₃</td>
<td>0.09±0.03</td>
<td>0.09±0.02</td>
<td>0.09±0.02</td>
<td>0.07±0.02†</td>
<td>-17 (30, 0)</td>
</tr>
<tr>
<td><strong>Cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.21±0.71</td>
<td>5.33±0.74</td>
<td>5.13±0.72</td>
<td>4.74±0.68†</td>
<td>-9 (15, 0)</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.49±0.33</td>
<td>0.52±0.33</td>
<td>0.50±0.32</td>
<td>0.24±0.17†</td>
<td>-54 (66, -33)</td>
</tr>
<tr>
<td>IDL</td>
<td>0.22±0.13</td>
<td>0.23±0.12</td>
<td>0.23±0.13</td>
<td>0.16±0.15†</td>
<td>-35 (50, -7)</td>
</tr>
<tr>
<td>LDL</td>
<td>3.46±0.62</td>
<td>3.57±0.58</td>
<td>3.40±0.55</td>
<td>3.25±0.60†</td>
<td>-6 (15, 6)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.04±0.18</td>
<td>1.00±0.16</td>
<td>1.00±0.16</td>
<td>1.09±0.22†</td>
<td>9 (3, 19)</td>
</tr>
<tr>
<td>HDL₂</td>
<td>0.42±0.15</td>
<td>0.42±0.13</td>
<td>0.41±0.13</td>
<td>0.44±0.17†</td>
<td>5 (10, 27)</td>
</tr>
<tr>
<td>HDL₃</td>
<td>0.62±0.09</td>
<td>0.58±0.08</td>
<td>0.59±0.11</td>
<td>0.65±0.10†</td>
<td>9 (-1, 22)</td>
</tr>
</tbody>
</table>

Data are mmol/L, mean±SD. On-trial values are averages of visits 1 and 2 years after randomization.

*Per-patient change in the gemfibrozil group from baseline to on-trial average, median (25th, 75th percentile).

†P<0.001, †P<0.03, on-trial placebo vs gemfibrozil. All triglyceride values and VLDL and IDL cholesterol values were transformed to their natural logarithms for the statistical comparisons.
variables. These analyses were performed for the whole study population and for the randomized groups separately. Further analyses were adjusted for the treatment group. For linear regression analyses, skewed variables were logarithmically transformed. Finally, we performed multivariate stepwise linear regression analyses.

**Results**

**Lipoprotein Triglyceride, Cholesterol, and Apolipoprotein Concentrations**

The randomized groups had similar triglyceride and cholesterol levels in total serum and in the lipoprotein fractions separated by ultracentrifugation at baseline (Table 1). The median change in serum triglyceride concentrations in the gemfibrozil group was $240\%$, and triglyceride reductions were highly significant in all lipoprotein classes. Cholesterol levels were also reduced in serum and in all apoB-containing lipoproteins, especially VLDL (Table 1).

The change in serum and VLDL triglyceride values in the gemfibrozil group was highly correlated with the baseline value (Figure 1A). In 170 patients (92%), VLDL triglyceride levels decreased during active therapy. For HDL cholesterol, there was also a significant, albeit weaker, correlation between the baseline value and treatment response (Figure 1B). Although most patients ($n=126, 68\%$), as expected, experienced an increase in HDL cholesterol levels, a substantial minority were nonresponders. For the HDL$_2$ subfraction, 111 patients (60%) had an increase during gemfibrozil therapy, and for HDL$_3$, 129 patients (70%) (Figure 1C). LDL cholesterol levels decreased during gemfibrozil therapy in 113 patients (61%), and the change in LDL cholesterol was also related to the baseline value ($r=-0.430, P<0.001$).

Serum apoB concentration at baseline was $102\pm19$ mg/dL in the placebo group and $102\pm18$ mg/dL in the gemfibrozil group. On-trial values (averages of 1- and 2-year visits) were $108\pm19$ and $88\pm17$ mg/dL in the placebo and gemfibrozil groups, respectively ($P<0.001$). Lp(a) concentrations [median (25th, 75th percentile)] at baseline were 173 (63, 440) and 161 (76, 412) and after 1 year of randomized therapy 176 (66, 466) and 181 (75, 411) mg/L in the placebo and gemfibrozil groups, respectively (not significant).

**Lipoprotein Compositions**

All lipoprotein classes were significantly depleted of triglyceride by gemfibrozil (Table 1, Figure 2). In the triglyceride-rich lipoproteins (VLDL and IDL), all lipid constituents were markedly reduced (Table 2). In VLDL, the protein concentration also fell (from $24.0\pm8.7$ to $18.6\pm9.2$ mg/dL), suggesting that VLDL particles were both decreased in number and depleted of lipid. By contrast, there was no suggestion of any reduction in IDL particle numbers. For LDL, there was
also no change in protein concentrations (Table 2), but there was a significant increase in the placebo group (data not shown), resulting in 11% lower levels in the gemfibrozil group during randomized therapy. On-trial concentrations of all LDL lipid components were lower in the gemfibrozil than in the placebo group, and the differences ranged from 7% (free cholesterol) to 21% (triglyceride).

HDL₃ protein concentrations remained unchanged during gemfibrozil therapy (Table 2), indicating no change in particle numbers, but there was some depletion of triglyceride and phospholipid and a concomitant increase in esterified and free cholesterol contents (Figure 2). HDL₂ protein concentrations increased, suggesting an increased number of these particles. The particles were depleted of triglyceride and enriched in esterified cholesterol (Figure 2).

**Global Angiographic Progression**

In the placebo group, 95 patients were classified as showing progression only, 31 had a mixed response, 40 had no significant change, and 21 had regression only. In the group allocated to gemfibrozil therapy, 61 subjects had progression only; 40, a mixed response; 57, no change; and 27, regression only (χ² P = 0.007). Thus, 126 placebo and 101 gemfibrozil patients had any progression and 61 and 84 patients, respectively, had no progression (odds ratio for progression in the gemfibrozil versus placebo group, 0.582; 95% CI, 0.382 to 0.887; P = 0.012).

Age, body mass index, waist-to-hip circumference ratio, heart rate, known duration of CAD, and history of hypertension, myocardial infarction, or angina at baseline were not related to global progression. There was also no significant relation between disease progression and blood pressure values or glucose, insulin, or C-peptide concentrations.

Total serum cholesterol and both triglyceride and cholesterol in the IDL and LDL fractions were positively and significantly associated with the risk of progression (Figure 3, Table 3). HDL cholesterol concentration was not associated with protection against progression. HDL₂ cholesterol had, if anything, a positive relation, and only HDL₁ had a borderline-significant protective effect.

On-trial apoB concentration was a predictor of progression in the whole study population (P = 0.002) and also after adjustment for study group (P = 0.018). Lp(a) levels were not related to global progression (data not shown).

**Quantitative Changes of Lumen Diameters in Native Coronary Vessels**

On-trial concentrations of the components of apoB-containing lipoproteins, especially IDL, were related to angiographic progression, both diffuse (ΔADS, Table 4) and focal (ΔMLD, Table 5). In many instances, these associations remained significant after adjustment for the randomized group allocation. Tables 4 and 5 also show that total HDL concentrations were not associated with protection from progression. HDL₂ levels even tended to be positively related to the risk of luminal narrowing. Conversely, concentrations of esterified cholesterol in the HDL₃ fraction were strongly and inversely related to progression of focal disease (Table

**Figure 3.** Influence of serum and lipoprotein lipid concentrations on global angiographic outcome in whole study population, adjusted for time interval between baseline and follow-up angiograms. Standardized averages of values obtained after 1 and 2 years of treatment were used. Standardization does not change distribution of a variable, but it renders various lipoprotein constituents comparable by setting mean of each variable to 0 and SD to 1. ■, Odds ratios of being classified as a progressor as lipid variable changes by 1 SD. Horizontal lines indicate 95% CIs. When CIs do not include unity (vertical line), association is significant at P < 0.05. TG indicates triglyceride; C, cholesterol.
and this relationship persisted after adjustment for group allocation. Essentially similar results were obtained when the randomized groups were analyzed separately (data not shown).

New Lesions in Vein Grafts

Nineteen patients in the placebo group had 1 new lesion and 4 patients had 2 new lesions in their vein grafts in the follow-up angiogram; in the gemfibrozil group, 4 patients had 1 new vein-graft lesion ($P$ = 0.001). Total serum triglyceride concentration was a powerful predictor of new vein-graft lesions in the whole study population (standardized odds ratio, 1.774; 95% CI, 1.303 to 2.414; $P$ = 0.001). When study group allocation was taken into account, both triglyceride level ($P$ = 0.042) and the grouping factor ($P$ = 0.013) independently predicted the appearance of new lesions. Total cholesterol also predicted new lesions in logistic regression analyses unadjusted (odds ratio, 1.899; 95% CI, 1.259 to 2.864; $P$ = 0.002) and adjusted ($P$ = 0.075) for the grouping factor ($P$ = 0.007). The lipoproteins responsible for these associations were VLDL (both triglyceride and cholesterol, $P$ < 0.001) and IDL (triglyceride, $P$ = 0.036; cholesterol, $P$ = 0.096). LDL and HDL levels were not associated with new vein-graft lesions.

Multivariate Models

The strongest univariate predictor of $\Delta$MLD in each lipoprotein class (VLDL phospholipid, IDL triglyceride, LDL tri-
1998  Lipoproteins and CAD Progression on Gemfibrozil

**TABLE 5. Lipoprotein and CAD Progression on Gemfibrozil**

<table>
<thead>
<tr>
<th>Triglyceride*</th>
<th>Cholesterol</th>
<th>Cholesteryl Ester</th>
<th>Free Cholesterol</th>
<th>Phospholipid</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude†</td>
<td>Adjusted‡</td>
<td>Crude†</td>
<td>Adjusted‡</td>
<td>Crude†</td>
<td>Adjusted‡</td>
</tr>
<tr>
<td>Total</td>
<td>0.004</td>
<td>0.148</td>
<td>0.016</td>
<td>0.179</td>
<td>0.028</td>
</tr>
<tr>
<td>VLDL*</td>
<td>0.014</td>
<td>0.331</td>
<td>0.005</td>
<td>0.152</td>
<td>0.001</td>
</tr>
<tr>
<td>IDL*</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.010</td>
<td>0.006</td>
</tr>
<tr>
<td>LDL</td>
<td>&lt;0.001</td>
<td>0.012</td>
<td>0.100</td>
<td>0.372</td>
<td>0.080</td>
</tr>
<tr>
<td>HDL</td>
<td>0.009</td>
<td>0.130</td>
<td>0.274</td>
<td>0.658</td>
<td>0.287</td>
</tr>
<tr>
<td>HDL₂</td>
<td>0.036</td>
<td>0.290</td>
<td>0.414</td>
<td>0.342</td>
<td>0.488</td>
</tr>
<tr>
<td>HDL₃</td>
<td>0.034</td>
<td>0.224</td>
<td>&lt;0.001</td>
<td>0.009‡</td>
<td>0.001§</td>
</tr>
</tbody>
</table>

Data are P values of linear regression analyses with ΔMLD as dependent variable.

*Transformed to natural logarithms.
†Adjusted for baseline value of the dependent variable and time between angiograms.
‡Adjusted for study group allocation (placebo vs gemfibrozil), baseline value of the dependent variable, and time between angiograms.
§Inverse (protective) association. All other significant associations were directly associated with luminal narrowing (progression).

glyceride, HDL₂ triglyceride [all log-transformed], and HDL₃ cholesterol; Table 5) was entered into a stepwise linear regression model, adjusted for baseline MLD and the time between angiograms. IDL triglyceride (P = 0.001) and HDL₃ cholesterol (inverse, P = 0.003) were retained in the model as significant predictors of the progression of focal coronary atherosclerosis. When the grouping factor was included in the model, it was not independently related to angiographic progression (P = 0.405), whereas IDL triglyceride (P = 0.002) and HDL₃ cholesterol (inverse, P = 0.013) were.

**Discussion**

In this study of 372 male postbypass patients, gemfibrozil therapy markedly reduced absolute and relative triglyceride concentrations in all lipoprotein classes. The drug also caused significant reductions in VLDL and IDL cholesterol levels, a marginal lowering of LDL cholesterol, and a moderate increment of HDL₃ cholesterol.

The on-trial concentrations of the triglyceride-rich lipoproteins VLDL and IDL were strong determinants of CAD progression in the present study. VLDL components were especially strong predictors of new vein-graft lesions, and IDL was the individual lipoprotein class most closely associated with progression in native coronary vessels. In previous studies, IDL and a lipoprotein fraction containing IDL and small VLDL particles have been associated with the angiographic severity and presence of CAD. Despite marked differences in enrollment criteria and interventions used, 3 previous secondary-prevention trials have found IDL to predict the angiographic progression of CAD. Markers of triglyceride-rich lipoproteins have been further associated with CAD progression in CLAS and with atherosclerosis progression in coronary and carotid arteries in the Monitored Atherosclerosis Regression Study (MARS). Finally, the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) showed benefits from fibrate therapy associated with marked reductions of triglyceride-rich lipoproteins and no change in LDL levels.

Taken together, the available evidence unequivocally implicates triglyceride-rich lipoproteins, especially IDL, in the progression of CAD. This relationship is particularly strong when LDL levels have been efficiently reduced, as in CLAS and in MARS and when baseline LDL values are relatively normal, as in LOCAT. Although in the present study IDL levels were markedly reduced by gemfibrozil therapy, this lipoprotein class remained a significant risk factor after adjustment for the treatment group and within the gemfibrozil group. Therefore, therapeutic measures that reduce IDL levels even more aggressively might provide further benefits in preventing the progression of CAD.

On average, LDL levels changed little in the present study. Although subjects with grossly elevated LDL cholesterol levels (>4.5 mmol/L) were excluded at baseline, LDL cholesterol was significantly related to the angiographic outcome. This is compatible with subgroup data from the Cholesterol and Recurrent Events trial, which showed benefits from LDL lowering with pravastatin in patients with baseline LDL cholesterol levels >3.2 mmol/L (125 mg/dL), closely corresponding to the mean on-trial value of our gemfibrozil group. Also, the Post Coronary Artery Bypass Graft trial showed that aggressive LDL cholesterol lowering (a goal of 1.6 to 2.2 mmol/L) conferred superior protection against progressing vein-graft disease compared with moderate lowering (to 3.4 to 3.6 mmol/L). It is therefore reasonable to speculate that reaching lower LDL levels than was possible with gemfibrozil therapy might have improved the outcome of the present trial.

A specific goal of LOCAT was to test the hypothesis that increasing low HDL levels prevents the progression of CAD. We found no evidence of any protective effect of HDL. Conversely, the on-trial concentration of HDL₃ cholesterol was a strong protective factor against progression, especially that of focal CAD. This raises the possibility that enhanced cholesterol efflux from coronary lesions into HDL precursors and its subsequent esterification is reflected in higher HDL₃ cholesterol levels. HDL₃ was associated with protection against CAD progression also in the St Thomas’ Atherosclerosis Regression Study and in MARS. In conclusion, our results add to growing evidence of the atherogenicity of triglyceride-rich lipoproteins, especially IDL, and antiatherogenic influence of HDL₃. Notably, reduc-
tions of triglyceride levels that are commonly considered normal seem to provide protection against progressive CAD.

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References
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