BACKGROUND: Growth differentiation factor 15 (GDF-15) is emerging as a powerful risk indicator in both cardiovascular disease patients and community-dwelling individuals. We investigated GDF-15 concentrations and their changes over 5 years in elderly individuals from the community, together with the underlying conditions and prognostic implications of these measurements.

METHODS: We analyzed GDF-15 concentrations using a sandwich immunoassay in participants from the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study. Measurements were performed at both 70 (n = 1004) and 75 (n = 813) years of age. Median follow-up was 8.0 years.

RESULTS: Over time, GDF-15 concentrations increased by 11.0% (P < 0.001). These changes were related to male sex, hypertension, diabetes, heart failure, renal function, and concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Significant relationships also emerged between changes in GDF-15 and changes in concentrations of NT-proBNP and C-reactive protein (CRP) and renal function between ages 70 and 75. The R² value of the model including all covariates was 0.20. GDF-15 concentrations independently predicted all-cause mortality [hazard ratio 4.0 (95% CI 2.7–6.0)] with results obtained at ages 70 and 75. The change in GDF-15 concentrations over time independently predicted even all-cause mortality occurring after age 75 [hazard ratio 3.6 (95% CI 2.2–6.0)].

CONCLUSIONS: GDF-15 concentrations and their changes over time are powerful predictors of mortality in elderly community-dwelling individuals. GDF-15 concentrations increase with aging, and these changes are explained only partially by cardiovascular risk factors, indicators of neurohumoral activation and inflammation, and renal function. Thus GDF-15 reflects both cardiovascular and other biological processes closely related to longevity.

Growth differentiation factor 15 (GDF-15) is a divergent member of the transforming growth factor-β cytokine superfamily. GDF-15 is secreted at low concentrations from most tissues but may be overexpressed in cardiomyocytes and various vascular cell types under stressful conditions (1). Several recent investigations have demonstrated that circulating GDF-15 concentrations are increased and independently prognostic across a wide spectrum of cardiovascular diseases, including acute and chronic coronary artery disease, congestive heart failure, and ischemic stroke (2–6).

Even in the general population, GDF-15 has been shown to be a powerful predictor of mortality (7–9). We have previously reported that GDF-15 concentrations in community-dwelling individuals are closely related to cardiovascular risk factors and perturbations of cardiac and vascular function (10). However, information on the change in GDF-15 concentrations over time, underlying cardiovascular and metabolic conditions, and the prognostic implications of changes in the general population are lacking so far. We therefore investigated these issues in participants from the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study. The main hypothesis of our analy-
sis was that the changes in GDF-15 concentrations over time would be of prognostic relevance for future mortality.

Methods

STUDY DESIGN

All individuals aged 70 years living in Uppsala, Sweden, were eligible for participation in the PIVUS study. Potential study participants were randomly chosen from the register of community inhabitants. Of the 2025 individuals invited, 1016 participated in the study, with baseline investigations starting in April 2001. All participants recorded their medical history and underwent cardiovascular examinations, including echocardiography and blood sampling for measurement of circulating biomarkers (11). Five years after enrollment, all surviving study participants were invited to a reexamination 1 month after their 75th birthday, and 827 participants (85.8% of all survivors) attended. Written informed consent was obtained from all study participants, and the study protocol was approved by the local ethics committee and complies with the Declaration of Helsinki.

The present analysis was based on 1004 participants with available GDF-15 results at baseline and a subcohort of 813 participants who also had available GDF-15 results at 5-year follow-up.

LABORATORY ANALYSIS

By use of an immunoradiometric assay, we measured GDF-15 concentrations in frozen (not previously thawed) samples of EDTA-plasma obtained at baseline and 5-year follow-up. The detection limit of this assay is 20 ng/L; the assay is linear from 200 to 50 000 ng/L and has intra- and interassay imprecisions of ±12.2% (12). We measured N-terminal pro–B-type natriuretic peptide (NT-proBNP) using the Elecsys proBNP sandwich immunoassay on an Elecsys 2010 instrument (Roche Diagnostics) and C-reactive protein (CRP) on an Architect ci8200 analyzer (Abbott Laboratories). We measured cardiac troponin I (cTnI) concentrations with a high-sensitivity assay (Beckman Coulter) and dichotomized them at the level of detection of 6.0 ng/L (13), considering that 38.7% of the study participants had undetectable concentrations. We measured estimated glomerular filtration rate (eGFR) according to the 4-variable Modification of Diet in Renal Disease equation (14).

ECHOCARDIOGRAPHY

Echocardiography was performed with an Acuson XP124 cardiac ultrasound unit, as described previously (15). We calculated left ventricular (LV) volumes according to the Teichholz method and, from those, determined the LV ejection fraction. We calculated LV mass index according to the recommendations of the American Society of Echocardiography (16).

STATISTICAL ANALYSIS

Data for continuous variables are presented as median (25th, 75th percentile) or mean (SD). We used the Mann–Whitney U-test for between-group comparisons and the Wilcoxon signed rank test for within-group comparisons of continuous variables. Correlations between continuous variables were determined by the Spearman rank correlation. Categorical variables are expressed as frequencies and percentages. All differences in categorical variable frequencies were analyzed with the χ² test.

We defined the change in GDF-15 concentrations from age 70 to 75 first, as the ln-transformed relative difference between concentrations at each time. This change criterion was chosen because it approximated a normal distribution to a greater extent than other relative or absolute change criteria (Shapiro–Wilk W-test statistic = 0.95). Second, we defined different change patterns considering published data on the biological variability of GDF-15 (17): decreasing, change in GDF-15 concentrations ≤−20%; increasing, change in GDF-15 concentrations ≥+40%; or unchanged, change in GDF-15 concentrations between −19% and 39%. Independent predictors of changes were identified by multiple linear regression analysis and multivariable regression analysis, as appropriate. Tested covariates included sex, hypertension (defined as blood pressure >140/90 mmHg at rest or antihypertensive treatment), diabetes (defined as fasting blood glucose >110 mg/dL (6.1 mmol/L) or antidiabetic treatment including diet), HDL cholesterol, LDL cholesterol, current smoking, previous smoking, body mass index, abnormal electrocardiographic findings (defined as presence of ST-segment depression (Minnesota codes 4-1 and 4-2), T-wave inversion (Minnesota codes 5-1, 5-2, or 5-3), pathologic Q-waves (Minnesota code 1-1), or left bundle branch block (Minnesota code 7-1) on a conventional 12-lead electrocardiogram (18)), previous myocardial infarction, self-reported heart failure, previous coronary revascularization, previous stroke, NT-proBNP, CRP, cTnI (≥6.0 ng/L), eGFR, LV ejection fraction, LV mass index, intercurrent cardiovascular events (defined as hospitalizations for myocardial infarction, stroke, or coronary revascularization occurring between the examinations at baseline and 5-year follow-up), and GDF-15 at baseline. If necessary, continuous variables were ln-transformed to achieve a normal distribution. The adjusted models included all covariates demonstrat-
ing a univariate association to ln(GDF-15) at \( P \leq 0.10 \). In an extended model, we also included the changes in concentrations of NT-proBNP and CRP and the eGFR (defined as the absolute difference of ln-transformed results at both measurements) from age 70 to 75 as covariates.

The primary outcome examined in this analysis was all-cause mortality. In secondary analyses, we assessed the associations of GDF-15 with cardiovascular and noncardiovascular mortality. Cardiovascular mortality was defined as death resulting from myocardial infarction, stroke, heart failure, other documented cardiovascular diseases, sudden death, and death not clearly attributable to noncardiovascular disease. Information on outcome was obtained from the Swedish Registry on Mortality and the medical records for Uppsala County, and outcome data were complete for all participants. Two follow-up periods were considered: from the baseline investigation until censor date at end of December 2010 [median 8.0 (25th, 75th percentile 7.1, 8.9) years], and from the 5-year follow-up examinations until censor date [2.9 (2.1, 3.8) years], which enabled us to investigate the prognostic implications of changes in GDF-15 concentrations.

The prognostic value of ln-transformed GDF-15 was assessed by Cox proportional hazard models adjusting for established cardiovascular risk indicators: sex, hypertension, diabetes, HDL cholesterol, LDL cholesterol, current smoking, body mass index, previous cardiovascular disease, ln(CRP), and ln(eGFR). Additional adjustment was made for cTnI \( \geq 6.0 \) ng/L and ln(NT-proBNP). In these models, we included ln(GDF-15) concentrations, as well as all confounders from both age 70 and 75 in an updated covariate fashion. This procedure creates 2 rows for each observation in the data set, 1 for the period between ages 70 and 75, and 1 for the period between age 75 and the censor date. With this approach, information on measurements performed at both age 70 and 75 could be used to increase the precision of the prognostic estimates and also take changes over time into account in an appropriate fashion. The models assessing the prognostic implications of changes in GDF-15 concentrations over time applied the same set of covariates, including ln(GDF-15) at baseline.

We constructed Kaplan–Meier curves to illustrate the timing of events. The incremental value of GDF-15 to a risk model based on established cardiovascular risk indicators was investigated by calculation of the C statistics, with comparison of differences by the method described by DeLong et al. (19). In addition, we assessed the integrated discrimination improvement (IDI) and the category-free net reclassification improvement (NRI) as described by Pencina and colleagues (20, 21).

In all tests, a 2-tailed \( P \) value <0.05 was considered significant. The software packages SPSS 19.0 (SPSS Inc) and Stata 11 (Stata Corp) were used for statistical analyses.

### Results

**GDF-15 Concentrations at Baseline and Their Relation to Clinical Characteristics**

Results for GDF-15 were available in 1004 participants at baseline and ranged from 450 to 9338 ng/L, median 1135 (95% CI 948–1390) ng/L. The clinical characteristics of the studied population are demonstrated in Table 1, and the univariate associations of these variables to baseline GDF-15 concentrations are presented in Supplemental Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol59/issue7.
In total, 813 participants had available results for GDF-15 from both baseline and 5-year follow-up. None of these individuals had suffered from an intercurrent cardiovascular event within the 28 days preceding the follow-up visit. Considering baseline characteristics, participants in the follow-up examinations tended to be somewhat healthier than nonparticipants, in particular in terms of lower prevalence of diabetes and current smoking, lower LV mass index, and lower concentrations of NT-proBNP (see online Supplemental Table 2).

GDF-15 concentrations at baseline and 5-year follow-up correlated strongly ($r = 0.70; P < 0.001$). Median concentrations increased by 11.0%, from 1102 (938–1348) ng/L at baseline to 1238 (991–1697) ng/L at 5-year follow-up ($P < 0.001$). By multiple linear regression with the change in GDF-15 concentrations as the dependent variable, male sex, hypertension, diabetes, self-reported heart failure, ln(eGFR), and ln(NT-proBNP) were independently and consistently associated with the changes in GDF-15 (Table 2; models 1 and 2). In an extended model that also included biomarker results obtained at age 75, additional significant relationships emerged between changes in GDF-15 and changes in NT-proBNP, CRP, and eGFR (Table 2; model 3). The $R^2$ value of model 3 was 0.20. Intercurrent cardiovascular events ($n = 85, 10.5\%$) were not associated with an increase in GDF-15 concentrations upon univariate analysis. Neither were the initiation of lipid-lowering medication ($n = 98, 12.1\%$), antihypertensive medication ($n = 248, 30.5\%$), or coronary revascularization ($n = 27, 3.3\%$) between the examinations at baseline and 5-year follow-up associated with decreasing GDF-15 concentrations (data not shown).

Applying our predefined criteria, 176 participants (21.6%) had increasing concentrations (40%), 576 participants (70.9%) had unchanged concentrations (19% to 39%), and 61 participants (7.5%) had decreasing concentrations (20%).

### Table 2. Multiple linear regression: variables associated with change in GDF-15 concentrations.$^a$

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Model 1 (n = 813)</th>
<th>Model 2 (n = 682)</th>
<th>Model 3 (n = 800)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>$\beta$ 0.092</td>
<td>$P = 0.02$</td>
<td>$\beta$ 0.082</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$\beta$ 0.111</td>
<td>$P = 0.002$</td>
<td>$\beta$ 0.115</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$\beta$ 0.147</td>
<td>$P &lt; 0.001$</td>
<td>$\beta$ 0.103</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>$\beta$ −0.036</td>
<td>$P = 0.36$</td>
<td>$\beta$ −0.038</td>
</tr>
<tr>
<td>Body mass index</td>
<td>$\beta$ 0.069</td>
<td>$P = 0.06$</td>
<td>$\beta$ 0.023</td>
</tr>
<tr>
<td>Heart failure</td>
<td>$\beta$ 0.088</td>
<td>$P = 0.02$</td>
<td>$\beta$ 0.132</td>
</tr>
<tr>
<td>ln(NT-proBNP)</td>
<td>$\beta$ 0.133</td>
<td>$P &lt; 0.001$</td>
<td>$\beta$ 0.112</td>
</tr>
<tr>
<td>Change in NT-proBNP</td>
<td>$\beta$ 0.101</td>
<td>$P = 0.01$</td>
<td>$\beta$ 0.087</td>
</tr>
<tr>
<td>ln(eGFR)</td>
<td>$\beta$ 0.091</td>
<td>$P = 0.01$</td>
<td>$\beta$ 0.037</td>
</tr>
<tr>
<td>Change in eGFR</td>
<td>$\beta$ 0.038</td>
<td>$P = 0.07$</td>
<td>$\beta$ 0.38</td>
</tr>
<tr>
<td>LV mass index$^b$</td>
<td>$\beta$ 0.09</td>
<td>$P = 0.07$</td>
<td>$\beta$ 0.38</td>
</tr>
</tbody>
</table>

$^a$ Model 1 was adjusted for ln(GDF-15) at baseline and candidate covariates with an univariate association to the change in GDF-15 concentrations at $P \leq 0.10$, excluding echocardiographic variables. Model 2 was adjusted as model 1 plus: including echocardiographic candidate covariates with an univariate association to the change in GDF-15 concentrations at $P \leq 0.10$, excluding ln(NT-proBNP). Model 3 was adjusted as model 1 plus: change in NT-proBNP, change in CRP, ln(CRP) at baseline, and change in eGFR. Changes in NT-proBNP, CRP, and eGFR were defined as the absolute difference between ln-transformed concentrations at baseline and 5-year follow-up.

$^b$ Assessed in model 2 in the 825 participants with complete echocardiographic examinations at baseline.

MORTALITY IN RELATION TO GDF-15 CONCENTRATIONS

In total, 111 participants (11.0%) died during the total follow-up period. Cardiovascular death occurred in 75
Table 3. Cox proportional hazard regression model evaluating the risk of mortality using ln(GDF-15) at both 70 and 75 years in a model for updated covariates together with established cardiovascular risk indicators (n = 1794).

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
<th>Noncardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>z score</td>
<td>P</td>
</tr>
<tr>
<td>ln(GDF-15)</td>
<td>4.0 (2.7–6.0)</td>
<td>6.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.2 (0.7–1.5)</td>
<td>0.87</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.8 (0.5–1.1)</td>
<td>−1.37</td>
<td>0.17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.1 (0.6–1.9)</td>
<td>0.34</td>
<td>0.74</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.0 (0.9–1.0)</td>
<td>−1.89</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.2 (0.7–2.0)</td>
<td>0.75</td>
<td>0.46</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>1.0 (0.8–1.2)</td>
<td>−0.18</td>
<td>0.86</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.6 (1.0–2.6)</td>
<td>1.75</td>
<td>0.08</td>
</tr>
<tr>
<td>ln(CRP)</td>
<td>1.1 (0.9–1.3)</td>
<td>1.09</td>
<td>0.28</td>
</tr>
<tr>
<td>ln(eGFR)</td>
<td>1.2 (0.6–2.4)</td>
<td>0.45</td>
<td>0.65</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td>1.7 (1.0–2.8)</td>
<td>2.11</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>z score</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3 (1.1–5.0)</td>
<td>2.09</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>5.1 (3.2–8.2)</td>
<td>6.81</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

According to Cox regression analysis with ln(GDF-15) concentrations at both 70 and 75 years in an updated covariate fashion and adjusting for established cardiovascular risk indicators (n = 1794), ln(GDF-15) independently predicted all-cause mortality with a hazard ratio (HR) of 4.0 (95% CI 2.7–6.0), P < 0.001 (Table 3). Additional adjustment for ln(NT-proBNP) and cTnI ≥6.0 ng/L did not affect this association considerably [3.7 (2.4–5.0), P < 0.001]. Adjusting for cardiovascular risk indicators, the HR for cardiovascular mortality was 2.3 (1.1–5.0), P = 0.04, and the HR for noncardiovascular mortality, 5.1 (3.2–8.2), P < 0.001.

Baseline GDF-15 concentrations also improved discrimination and reclassification regarding all-cause mortality when added to a risk model based on established cardiovascular risk indicators. The C statistic increased from 0.65 to 0.71 (P = 0.006), the IDI was 0.030 (P = 0.004), and the category-free NRI was 0.281 (P = 0.006). Addition of GDF-15 to our risk model would have resulted in the correct up-classification of 52.7% of participants who died and the correct down-classification of 61.3% of survivors. In addition, a good goodness-of-fit was seen for the model including GDF-15 and cardiovascular risk indicators (Hosmer–Lemeshow test, P = 0.59).

Mortality in relation to the change in GDF-15 concentrations

Among the 813 participants with available GDF-15 results from both baseline and 5-year follow-up, 32 deaths (3.9%) occurred between the 5-year follow-up examinations and censor date at the end of December 2010. Given the limited number of deaths, we assessed only all-cause mortality in this part of the analysis.

Applied as a continuous variable, the change in GDF-15 concentrations over time exhibited a significant association with all-cause mortality in a model adjusted for sex and ln(GDF-15) at baseline [HR 3.6 (95% CI 2.2–6.0), P < 0.001]. The risk estimate was not considerably affected after additional adjustment for either established cardiovascular risk indicators [3.8 (2.7–6.1), P < 0.001] or cardiovascular risk indicators ln(NT-proBNP) and cTnI ≥6.0 ng/L [3.6 (2.0–6.5), P < 0.001]. The IDI of the change in GDF-15 concentrations in a model adjusting for established cardiovascular risk indicators and ln(GDF-15) at baseline was 0.042 (P = 0.006), and the category-free NRI was 0.468 (P = 0.009) with a corresponding correct up-classification of 59.4% of participants who died and a correct down-classification of 64.4% of survivors.

Applying our predefined GDF-15 change criteria, 2 participants (3.3%) with decreasing concentrations and 14 participants (2.4%) with unchanged concentrations died. Sixteen participants (9.1%) with increasing concentrations died; Fig. 1 demonstrates that the risk for all-cause mortality was significantly increased in these participants compared to those with unchanged GDF-15 concentrations.
Discussion

The results from our study demonstrate that GDF-15 is a powerful predictor of mortality in elderly individuals from the community. As such, our data are consistent with recent investigations (7–9) but also present new evidence, as they demonstrate that both single GDF-15 results and changes in GDF-15 concentrations over time are prognostically important.

We and others have previously reported that GDF-15 concentrations in the general population are reflective of cardiovascular risk factors and perturbations in cardiac and vascular function (7, 8, 10). In the current longitudinal study, changes in GDF-15 concentrations were associated with similar entities, i.e., cardiovascular risk factors (male sex, hypertension, diabetes), indices of neurohumoral activation (baseline NT-proBNP concentrations and their changes over time), and indices of inflammation (changes in CRP concentrations over time). Our results support the notion that GDF-15 integrates information on several relevant aspects and pathways in cardiovascular disease. The prominent anti-apoptotic, antihypertrophic, and anti-inflammatory actions of GDF-15 in cardiovascular disease models (22–24) indicate that this cytokine exerts protective effects in the context of acute cardiovascular injury. Whether chronic increases in GDF-15 concentrations in elderly individuals play an adaptive or maladaptive role remains to be investigated.

In the present study, GDF-15 demonstrated strong associations with mortality risk, independent of established clinical and biochemical risk indicators, and enhanced prognostic discrimination and reclassification. Even the changes in GDF-15 over time were independently predictive despite the rather short observation period with the highest mortality seen in participants with the most pronounced increases. Notably, intercurrent cardiovascular events after the baseline investigations did not contribute to increasing GDF-15 concentrations over time, and only 20% of the variability of the changes in GDF-15 concentrations was explained by the cardiovascular risk indicators and biomarkers entered into the multiple regressions.

Moreover, GDF-15 predicted both cardiovascular and noncardiovascular mortality in line with data from previous investigations (7, 25). Our results indicate that GDF-15 is probably related not only to cardiovascular abnormalities but also to other prognostically adverse pathobiological processes. For example, GDF-15 concentrations are increased in renal failure, an entity associated with an increased risk for both cardiovascular and noncardiovascular death (26). Increased GDF-15 concentrations are also seen in rheumatoid arthritis (27) and several malignancies (28) and have been related to shortened telomere length, an indicator of premature aging (23). These entities share some pathobiological pathways with cardiovascular disease (e.g., oxidative stress and inflammation) that might in-

**Fig. 1.** Cumulative incidence of all-cause mortality after 5-year follow-up in relation to the relative change in GDF-15 concentrations.

Decreasing GDF-15 concentrations, change ≤−20%; unchanged GDF-15 concentrations, change between −19% and 39%; increasing GDF-15 concentrations, change ≥40%. Analyses were adjusted for sex and ln(GDF-15) at baseline.
duce GDF-15 via p53 signaling, the main driver of GDF-15 transcription (29). Although the design of our study does not permit further exploration of these issues, our data suggest that the prognostic importance of GDF-15 concentrations is mediated by mechanisms beyond cardiovascular disease.

Some limitations to this analysis should be acknowledged. The PIVUS study was limited to whites aged 70 years. We are therefore unable to evaluate the impact of age and ethnicity on GDF-15 concentrations and its changes. In addition, the selection of such an elderly population inevitably mitigates the powerful influence of age on risk, thereby increasing the relative prognostic importance of other covariates, including circulating biomarkers. However, our data are strikingly similar to results from age-adjusted analyses from the Rancho Bernardo Study, assessing another community population (7). The participants in the 5-year follow-up examinations represented a somewhat healthier subset of the entire study population, which is unavoidable in longitudinal studies assessing elderly populations. Results obtained from this cohort therefore cannot be extrapolated to the entire study population, but likely underestimate the true associations between GDF-15 concentrations and outcome. We lack more detailed data on the cause of death in participants dying from noncardiovascular causes. Finally, we cannot exclude the possibility that our modeling approach might have affected the prognostic estimates of GDF-15 given the somewhat low event rates for some outcomes.

In conclusion, GDF-15 concentrations and their changes over time independently predicted both cardiovascular and noncardiovascular mortality in an elderly population from the community. GDF-15 concentrations increased with aging, and these changes were explained only partially by cardiovascular risk factors, renal function, inflammation, and neurohumoral activation. Our data therefore indicate that GDF-15 and its changes reflect both cardiovascular perturbations and independent pathobiological processes that are closely related to prognosis.

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