**Original Article**

**Helicobacter pylori and cardiovascular risk: Only a dead Helicobacter is a good Helicobacter?**

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**Abstract**

**Objectives:** Helicobacter pylori (H. pylori) and cardiovascular (CV) disease share common symptoms and underlie many general medical complaints. Preliminary studies suggest an association between H. pylori positivity and CV risk, and gastroenterological guidelines recommend eradication of H. pylori in patients with manifest atherosclerosis. Therefore, the aim of this study was to examine the reciprocal association of H. pylori positivity and CV risk for their independence of shared risk factors.

**Methods:** We included 3284 asymptomatic participants of a colorectal cancer screening cohort who were offered and underwent upper gastrointestinal endoscopy. We calculated the 10-year risk for a CV event using the novel SCORE2 for each patient. We evaluated the association between H. pylori positivity and CV risk assessed by SCORE2 using both multilevel logistic and linear regression. We adjusted for age, sex and the concomitant diagnosis of metabolic syndrome. Lastly, we assessed the association between H. pylori status and mortality using proportional hazard Cox regression.

**Results:** In total, 2659 patients were H. pylori negative and 625 H. pylori positive. Helicobacter pylori positivity was associated with SCORE2 and remained so (r = .33; 95% CI 0.09–0.57; p = .006) after adjustment for age, sex, and the diagnosis of metabolic syndrome. Also, SCORE2 was associated with higher odds for H. pylori positivity (aOR 1.03 95% CI 1.01–1.05; p = .02) even after multivariable adjustment. Helicobacter pylori positivity was associated with neither CV (HR 0.60 95% CI 0.14–2.63; p = .50) nor all-cause (HR 1.20 95% CI 0.77–1.87; p = .43) mortality during a median follow-up of 9 years.

**Conclusions:** In our study, H. pylori positivity and CV risk were independently associated. This did not translate into a dissimilar CV mortality between H. pylori positive and H. pylori negative patients. However, the overwhelming majority of our patients underwent H. pylori eradication. We, therefore, think that H. pylori eradication is at least safe from a cardiovascular perspective and warranted from gastrointestinal standpoint.

Bernhard Wernly and Christian Datz contributed equally.

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1 | INTRODUCTION

Infection with Helicobacter pylori (H. pylori) varies regionally and socioeconomically but is generally frequent in humans. In total, about 4.4 billion people worldwide are estimated to be infected with H. pylori. Helicobacter pylori positivity (H. pylori positive) can be detected by urease breath test, stool antigen test, and histological diagnosis during endoscopy. In addition to gastroenterological diagnoses such as peptic ulcer disease, gastroesophageal reflux disease, or unexplained iron deficiency, also cardiological patients requiring chronic treatment with an antiplatelet agent are among the indications for testing for the presence of H. pylori and its treatment. However, since H. pylori can also be classified as at least an optional carcinogen, treatment and eradication of H. pylori are recommended in many clinical scenarios.

Cardiovascular (CV) disease (CVD) is one of the leading causes of death, especially in Western countries. In addition to mortality, CVD causes significant morbidity and challenges health care systems. The development of atherosclerosis and associated vascular complications is complex, involves metabolic changes, disturbances in lipid metabolism, and is associated with systemic low-grade inflammation. In addition to the acute treatment of cardiovascular complications, the mitigation of cardiovascular risk is a priority to improve the outcome of patients. To improve risk estimation, scores have been developed by international societies to assess individual cardiovascular risk—recently, the SCORE2 was developed and presented by the European Society of Cardiology.

Among other pathophysiological considerations, subclinical inflammation represents a possible link between infection with H. pylori and the development and progression of atherosclerosis. For example, an association between H. pylori positive and intima media thickness has been demonstrated. In addition to studies on the association of H. pylori with intima media thickness, there are also studies suggesting a positive association of H. pylori positive with coronary calcification.

Nota bene, however, there are definitely signals for a sex-, age-, and especially ethnicity-specific relationship between H. pylori positive and cardiovascular risk or cardiovascular surrogate parameters in all studies. In a European population-based cohort study by Schöttker et al. infection with H. pylori was even associated with a lower risk of cardiovascular events. The different methods for the detection of H. pylori in the previous literature also represent a relevant uncertainty. Therefore, the aim of our study was to investigate the association between H. pylori and cardiovascular risk in a contemporary European screening population using histologic diagnosis of H. pylori.

2 | METHODS

2.1 | Subjects

We included participants from the Salzburg Colon Cancer Prevention Initiative (Sakkopi), which is a cohort of asymptomatic patients screened for colorectal cancer between January 2007 and March 2020 at a single center in Austria. The total cohort consisted of 5977 consecutive patients. All subjects undergoing colonoscopy were offered esophagogastroduodenoscopy (EGD). Of these, 272 refused to undergo concurrent EGD and were excluded from this analysis. We further excluded 694 patients with known CV disease, as the SCORE2 is not applicable in those patients. Due to missing laboratory values, we could, therefore, calculate the SCORE2 for 3284 patients who were included in the present analysis.

Clinical as well as laboratory parameters were obtained in all participating subjects. Also, patients completed a questionnaire about their family and medical history, and body mass index (BMI), arterial hypertension, smoking status, dyslipidemia, as well as metabolic syndrome were defined according to current guidelines.

Data on death and ICD-10 coded causes of death were retrieved on June 25, 2021, from the Austrian "Sterberegister" based on the individual social security number of each Austrian individual. The presence of H. pylori was evaluated by histology from biopsies obtained during EGD. We advised our H. pylori positive patients to undergo H. pylori eradication. However, this was performed by the treating primary care physicians, and we do not have data on eradication and especially on success of eradication.

2.2 | Statistical analysis

Most continuous variables were non-normally distributed. Continuous data are given as median ± inter-quartile range (IQR) and compared using Mann's Whitney U-Test or mean ± standard deviation (SD) and compared using Student’s T-test accordingly. Categorical data are given as numbers (percentage) and compared using the chi-square test. All tests were two-sided, and a p-value of <.05 was considered statistically significant.

The primary endpoint was the 10-year cardiovascular risk assessed by SCORE2. The primary exposure was the histologic diagnosis of H. pylori in the specimen obtained during EGD. We fitted models for the dependent continuous variable SCORE using multilevel linear regression with robust standard errors with the year of inclusion as a random effect and the diagnosis of H. pylori as a fixed effect (model-1).

The secondary endpoint was the histologic diagnosis of H. pylori in the specimen obtained during EGD and for this analysis, the
primary exposure was the 10-year cardiovascular risk assessed by SCORE2.\textsuperscript{13} We fitted models for the dependent binary variable \textit{H. pylori} positive using multilevel logistic regression with robust standard errors with the year of inclusion as a random effect and the diagnosis of \textit{H. pylori} as a fixed effect (model-1).

We further fitted multivariable multilevel linear or logistic regression models using the year of inclusion as a random effect, the \textit{H. pylori} status or as a binary variable or the SCORE2 as continuous variable, and the covariables age and sex as fixed effects (model-2). Model-3 adds the concomitant diagnosis of metabolic syndrome as a fixed effect.

For the linear regression, we obtained regression coefficients and respective 95% confidence intervals (95% CI). For the logistic regressions, we obtained odds ratios (OR) and respective 95% CI for the binary endpoints. The regression analyses were conducted using only robust estimators of the standard errors and not in the sense of robustness against violations of normality assumptions as for the robust methods (e.g. Mann–Whitney tests) used for the univariate analyses.

We performed sensitivity analyses stratifying the presence of the secondary endpoint (\textit{H. pylori} positive) according to the patient-specific baseline characteristics: We stratified for sex, age (in categories), BMI (in categories according to the World Health Organization), smoking status, the diagnosis of metabolic syndrome and positive family history. For the sensitivity analyses, we fitted model-B1 with \textit{H. pylori} status as a binary independent variable as a fixed effect and SCORE2 as the dependent variable in the strata. We plotted the OR and 95% CI of the sensitivity analyses in forest plots. Stata/IC 17 was used for all statistical analyses.

Further, we assessed the association between \textit{H. pylori} status and the mortality endpoints (cardiovascular and all-cause mortality) using proportional hazard Cox regression and obtained hazard ratios (HR) and respective 95% confidence intervals (95% CI).

We performed the study and all procedures according to the principles of the Declaration of Helsinki. The local ethics committee for the province Salzburg approved the study protocol (approval no. 415-E/1262). Written informed consent was obtained from every participant.

### RESULTS

In total, 2659 patients were \textit{H. pylori} negative and 625 \textit{H. pylori} positive. \textit{Helicobacter pylori} positive patients were more often male and older and evidenced more often a 10-year CV risk >10% (23% vs. 18%; \(p<.001\); Table 1). \textit{Helicobacter pylori} positive patients evidenced higher BMI (28.5±5 vs. 27.5±5kg/m\(^2\); \(p<.001\)) and lower HDL (56±15 vs. 58±16mg/dl; \(p<.001\)) concentrations. However, both systolic and diastolic blood pressure, as well as LDL concentration and also the Hba1c concentrations were similar between patients with and without \textit{H. pylori} (Table 1). Still, in multilevel linear regression analysis, \textit{H. pylori} positive was associated with SCORE2 (\(r=.64\); 95% CI 0.31–0.96; \(p<.001\)) and remained so after adjustment for age and

![Table 1: Baseline characteristics of HP− and HP+ patients](image)

| Parameter                  | HP−       | HP+       | \(p\)-Value |
|----------------------------|-----------|-----------|-------------|
| Age (years)                | 56 (7)    | 56 (7)    | .90         |
| Age < 45 years             | 4% (106)  | 3% (20)   | .61         |
| Age 45–54 years            | 42% (1110)| 40% (251) | .21         |
| Age 55–64 years            | 41% (1091)| 42% (264) | .11         |
| Age 65–74 years            | 13% (352) | 14% (90)  |            |
| Male sex                   | 53% (1412)| 56% (149) | .22         |
| BMI (kg/m\(^2\))           | 27 (5)    | 28 (5)    | <.001       |
| BMI according to WHO        |           |           |             |
| Underweight                | 0% (13)   | 1% (4)    | <.001       |
| Normal weight              | 38% (1012)| 29% (179) | .15         |
| Pre-obesity                | 40% (1054)| 45% (284) | .089        |
| Obesity                    | 22% (580) | 25% (158) | .40         |
| Systolic BP (mmHg)          | 132 (18)  | 133 (19)  | .15         |
| Diastolic RR (mmHgP)        | 81 (10)   | 81 (10)   | .55         |
| Arterial hypertension      | 52% (1382)| 53% (331) | .66         |
| Cholesterol (mg/dl)         | 225 (43)  | 225 (41)  | .90         |
| LDL (mg/dl)                | 145 (40)  | 147 (39)  | .15         |
| HDL (mg/dl)                | 58 (16)   | 56 (15)   | .008        |
| Diabetes                   | 15% (405)| 18% (110) | .14         |
| HbA1c (%)                  | 5.5 (0.5)| 5.5 (0.5)| .14         |
| Metabolic syndrome         | 77% (2044)| 78% (490) | .41         |
| Creatinine (mg/dl)         | 0.9 (0.2)| 0.9 (0.1)| .39         |
| Haemoglobine (mg/dl)       | 14.7 (1.2)| 14.7 (1.2)| .88        |
| Thrombocytes (G/L)         | 239 (57)  | 237 (56)  | .43         |
| CRP (mg/dl)                | 0.3 (0.6)| 0.3 (0.8)| .65         |
| SCORE2 10-year CVD risk (%)| 6 (4)     | 7 (5)     | .003        |
| SCORE2 < 5%                | 46% (1218)| 41% (257) | .008        |
| SCORE2 < 10%               | 37% (973) | 36% (226) | .008        |
| SCORE2 ≥ 10%               | 18% (468)| 23% (142) | .008        |
| Region 10-year risk WHO-CVD (%) | 8 (6) | 9 (7) | .004 |
| WHO CVD Risk < 5%          | 39% (1026)| 35% (218) | .097        |
| WHO CVD Risk < 10%         | 32% (851) | 33% (207) | .66         |
| WHO CVD Risk < 20%         | 24% (640) | 24% (151) | .66         |
| WHO CVD Risk < 30%         | 4% (118)  | 6% (39)   | .39         |
| WHO CVD Risk ≥ 30%         | 1% (24)   | 2% (10)   | .39         |

Smoking status

- Never smoker: 34% (891) vs. 30% (200) \(p<.05\)
- Ex-smoker: 40% (1060) vs. 41% (255) \(p>.05\)
- Active smoker: 26% (698) vs. 27% (170) \(p>.05\)

Note: Most continuous variables were non-normally distributed. Continuous data are given as median ± inter-quartile range (IQR) and compared using Mann’s Whitney U-Test or mean ± standard deviation (SD) and compared using Student’s T-test accordingly. Categorical data are given as numbers (percentage) and compared using the chi-square test. All tests were two-sided, and a \(p\)-value of <.05 was considered statistically significant.
sex \( (r = .34\) 95% CI 0.10–0.58; \( p = .006\) \) as well as after adjustment for age, sex, and the diagnosis of metabolic syndrome \( (r = .33;\) 95% CI 0.09–0.57; \( p = .006\) \).

In total, 1477 patients evidenced a SCORE2 ≤ 5% and 1807 a SCORE2 > 5% (Table 2). We chose this cut-off based on the recommendations of the ESC, but also because it was near the median SCORE2 of 5.5%. As anticipated, patients with higher SCORE2 were older and evidenced higher rates of traditional cardiovascular risk factors. Also, patients with SCORE2 > 5% evidenced higher rates of \textit{H. pylori} positive (20% vs. 17%; \( p = .04\)). In multilevel logistic regression, SCORE2 (as a continuous independent variable included as a fixed effect in the model) was associated with higher odds for \textit{H. pylori} positive \( (\text{aOR} 1.02 \text{ 95\% CI 1.01–1.04; } p < .001) \) and remained so after multivariable adjustment for age and sex \( (\text{aOR} 1.03 \text{ 95\% CI 1.01–1.05; } p = .01) \) as well as additional adjustment for the concomitant diagnosis of metabolic syndrome \( (\text{aOR} 1.03 \text{ 95\% CI 1.01–1.05; } p = .02) \).

For the sensitivity analyses, we fitted model-B1 with SCORE2 as a continuous independent variable as a fixed effect and \textit{H. pylori} positive as the dependent variable in the strata. We plotted the aOR and 95% CI in Figure 1. We found that a higher SCORE2 was associated with higher odds for \textit{H. pylori} positive across all strata at least in trend.

The cardiovascular mortality in both patients without \( (n = 14; 0.5\%) \) and with \( (n = 2; 0.3\%) \) \textit{H. pylori} was low and similar \( (p = .51) \). Similarly, all cause mortality was similar \( (3.3\% \text{ vs. } 4.0\%; \text{ } p = .39) \) in patients with and without \textit{H. pylori}. In Cox regression, \textit{H. pylori} positive was associated with neither CV (HR 0.60 95\% CI 0.14–2.63; \( p = .50 \)) nor all-cause (HR 1.20 95\% CI 0.77–1.87; \( p = .43 \)) mortality during a median follow-up of 9 years.

### 4 | DISCUSSION

In our study, we investigated the association of \textit{H. pylori} positive and SCORE2, which is a surrogate parameter for CV risk. In our cohort, \textit{H. pylori} positive patients had a higher cardiovascular risk and vice versa, patients with higher CV risk had a higher probability of \textit{H. pylori} infection. We also demonstrated this association of higher CV risk and \textit{H. pylori} positive in sensitivity analyses in all subgroups evaluated. Nevertheless, overall, the absolute numerical effects were small \( (1\% \text{ SCORE2 difference between patients with and without } H. pylori) \), and the clinical relevance of the independent two-way association, although statistically significant, remains unclear. This is particularly underlined by the nondifferential cardiovascular mortality between patients with and without \textit{H. pylori} in our cohort.

There are data, especially from meta-analyses and nested analyses, suggesting a positive association of \textit{H. pylori} and CV risk. On the contrary, cohort studies in high-impact journals could not demonstrate an independent association of \textit{H. pylori} with CV outcomes, so from a purely epidemiological and descriptive point of view, this question remains open.

There are multiple potential connections between \textit{H. pylori} and CVD. First, \textit{H. pylori} and CVD are both traditionally associated with a cardiometabolic phenotype. These common co-associations may therefore contribute to the robust association of \textit{H. pylori} and CVD observed in some studies. Interestingly, although in our study calculated CV risk by SCORE2 was higher in \textit{H. pylori} positive patients, traditional risk factors such as blood pressure, lipid status, and Hba1c were similar. At this point, it is necessary to state that formally SCORE2 should not be calculated for patients with diabetes—nevertheless, the diagnosis of diabetes enters into the calculation of SCORE2 in the Stata script to calculate SCORE2 provided by the authors, and we therefore decided to include these patients for pragmatic reasons.

Second, subclinical inflammation triggered by \textit{H. pylori} could contribute to the progression of CVD, which is also characterized by a proinflammatory state. Here, we have seen no evidence of differential concentration of CRP, although this is a suboptimal marker for low-grade inflammation.

Third, a specific cascade of \textit{H. pylori} infection, chronic atrophic gastritis, low vitamin B12 concentrations, and hyperhomocysteinemia has been postulated. However, this possible pathophysiological pathway could not be reproduced in a study by Schöttker et al. In this study, detection of the \textit{H. pylori} strain with cytotoxin-associated gene A, which is considered particularly virulent, was also not associated with increased CV mortality over five years. However, it must be mentioned here that the study by Schöttker et al. was based on serological detection of \textit{H. pylori}, whereas our study demonstrated active \textit{H. pylori} infection by histological detection. Thus, in our study, \textit{H. pylori} showed a robust and statistically independent association with the calculated CV risk, but not with the actual cardiovascular mortality observed. However, all-cause mortality was also the same comparing patients with \textit{H. pylori} and without \textit{H. pylori}. It is also important to note that by far the majority of patients who were \textit{H. pylori} positive in our study underwent eradication. Therefore, eradication of \textit{H. pylori} could result in a lower rate of cardiovascular events than originally thought. Here, our study has limitations because we do not know the number of eradication and the success of \textit{H. pylori} eradication. Another limitation is our lack of knowledge about the exact \textit{H. pylori} strain. In particular, strains carrying the virulence factor CagA (cytotoxin-associated gene A) have been associated with atherosclerosis in several studies. The robust relationship between CagA and atherosclerosis is based on both clinical and basic science studies.

Also, infection with \textit{H. pylori} could lead to unfavorable alteration of the gut microbiota and thus indirectly contribute to the progression of atherosclerosis. However, an evaluation in this regard is beyond our study. On the contrary, also \textit{H. pylori} eradication using broad spectrum antibiotics could also interfere with the gut microbiota. Furthermore, due to the side effects specific to some antibiotic preparations (such as QTc prolongation), direct negative cardiovascular effects from \textit{H. pylori} eradication are also conceivable. However, Shah et al did not find any signals for a negative effect on cardiovascular mortality due to \textit{H. pylori} eradication. We,
|                          | SCORE2 10-year CVD risk ≤5% | SCORE2 10-year CVD risk >5% | \( p \)-Value |
|--------------------------|-----------------------------|-----------------------------|--------------|
| **Age (years)**          |                            |                             |              |
| 52 (5)                  | 59 (6)                     |                             | <.001        |
| Age <45 years            | 8% (115)                   | 1% (11)                     | <.001        |
| Age 45–54 years          | 62% (923)                  | 24% (438)                   |              |
| Age 55–64 years          | 29% (424)                  | 52% (931)                   |              |
| Age 65–74 years          | 1% (15)                    | 24% (427)                   |              |
| **Male sex**             |                            |                             | <.001        |
| 66% (973)                | 30% (550)                  |                             |              |
| **BMI (kg/m²)**          |                            |                             | <.001        |
| 26 (4)                   | 28 (5)                     |                             |              |
| BMI according to WHO     |                            |                             | <.001        |
| 1% (14)                  | 0% (3)                     |                             |              |
| Underweight              | 50% (736)                  | 25% (455)                   |              |
| Normal weight            | 34% (502)                  | 46% (836)                   |              |
| Pre-obesity              | 15% (225)                  | 28% (513)                   |              |
| Obesity                  | 124 (14)                   | 139 (18)                    | <.001        |
| **Systolic BP (mmHg)**   |                            |                             | <.001        |
| 78 (9)                   | 83 (10)                    |                             |              |
| **Diastolic BP (mmHg)**  |                            |                             | <.001        |
| 32% (471)                | 69% (1242)                 |                             |              |
| **Arterial hypertension**|                            |                             | <.001        |
| 222 (39)                 | 227 (46)                   |                             |              |
| **Cholesterol (mg/dl)**  |                            |                             | <.001        |
| 140 (36)                 | 149 (41)                   |                             |              |
| LDL (mg/dl)              | 64 (17)                    | 53 (14)                     | <.001        |
| HDL (mg/dl)              | 3% (38)                    | 26% (477)                   | <.001        |
| **Diabetes**             |                            |                             | <.001        |
| 5.4 (0.4)                | 5.6 (0.6)                  |                             |              |
| **HbA1c (%)**            |                            |                             | <.001        |
| 64% (952)                | 88% (1582)                 |                             |              |
| **Metabolic syndrome**   |                            |                             | <.001        |
| 0.9 (0.3)                | 0.9 (0.1)                  |                             |              |
| **Creatinine (mg/dl)**   |                            |                             | <.001        |
| 14.3 (1.1)               | 15.0 (1.2)                 |                             |              |
| **Hemoglobin (mg/dl)**   |                            |                             | <.001        |
| 248 (57)                 | 231 (55)                   |                             |              |
| **Thrombocytes (G/L)**   |                            |                             | <.001        |
| 0.3 (0.7)                | 0.4 (0.7)                  |                             |              |
| **CRP (mg/dl)**          |                            |                             | <.001        |
| 0.3 (0.7)                | 0.4 (0.7)                  |                             |              |
| **SCORE2 10-year CVD risk (%)** |                     |                             | <.001        |
| 3 (1)                    | 9 (4)                      |                             |              |
| **SCORE2 <5%**           |                            |                             | <.001        |
| 100% (1475)              | 0% (0)                     |                             |              |
| **SCORE2 <10%**          |                            |                             | <.001        |
| 0%²                      | 66% (1197)                 |                             |              |
| **SCORE2 ≥10%**          |                            |                             |              |
| 0% (0)                   | 34% (610)                  |                             |              |
| **Region 10-year risk WHO-CVD (%)** |                   |                             | <.001        |
| 3 (2)                    | 12 (6)                     |                             |              |
| **WHO CVD Risk <5%**     |                            |                             | <.001        |
| 82% (1209)               | 2% (35)                    |                             |              |
| **WHO CVD Risk <10%**    |                            |                             | <.001        |
| 18% (267)                | 44% (791)                  |                             |              |
| **WHO CVD Risk <20%**    |                            |                             | <.001        |
| 0% (1)                   | 44% (790)                  |                             |              |
| **WHO CVD Risk <30%**    |                            |                             | <.001        |
| 0% (0)                   | 9% (157)                   |                             |              |
| **WHO CVD Risk ≥30%**    |                            |                             | <.001        |
| 0% (0)                   | 2% (34)                    |                             |              |
| **Smoking status**       |                            |                             |              |
| Never smoker             | 39% (575)                  | 29% (516)                   | <.001        |
| Ex-smoker                | 45% (662)                  | 36% (653)                   |              |
| Active smoker            | 16% (235)                  | 35% (633)                   |              |
| HP+                      | 17% (258)                  | 20% (367)                   | .039         |

**Note:** Most continuous variables were non-normally distributed. Continuous data are given as median ± inter-quartile range (IQR) and compared using Mann’s Whitney U-Test or mean ± standard deviation (SD) and compared using Student’s T-test accordingly. Categorical data are given as numbers (percentage) and compared using the chi-square test. All tests were two-sided, and a \( p \)-value of <.05 was considered statistically significant.
FIGURE 1 For the sensitivity analyses, we fitted model-B1 with SCORE2 as a continuous independent variable as a fixed effect and H. pylori positive as the dependent variable in the strata. We plotted the OR and 95% CI of the sensitivity analyses in forest plots.

therefore, think that H. pylori eradication is at least safe from a cardiovascular perspective.

5 | CONCLUSION

From a stringent scientific point of view, the relationship between CVD and H. pylori remains unclear. We could demonstrate a robust association of H. pylori with an established surrogate parameter for CV risk (SCORE2), but no association of H. pylori with actual CV mortality. However, reference must be made here primarily to the low absolute numerical differences of H. pylori infection worldwide: a systematic review of studies with national coverage. Dig Dis Sci. 2014;59:1698-1709. doi:10.1007/s10620-014-3063-0

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