Received: 10 July 2022 | Revised: 14 August 2022 | Accepted: 18 August 2022

DOI: 10.1111/hel.12928

Helicobacter WILEY

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.

KEYWORDS
cardio-vascular risk factor, *Helicobacter pylori*, *Helicobacter pylori* infection

1 | INTRODUCTION

Infection with *Helicobacter pylori* (*H. pylori*) varies regionally[1,2] and socioeconomically[3] but is generally frequent in humans. In total, about 4.4 billion people worldwide are estimated to be infected with *H. pylori*.[4] *Helicobacter pylori* positivity (*H. pylori* positive) can be detected by urease breath test, stool antigen test, and histological diagnosis during endoscopy.[5,6] 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.[7] However, since *H. pylori* can also be classified as at least an optional carcinogen,[8] treatment and eradication of *H. pylori* are recommended in many clinical scenarios.[5,9]

Cardiovascular (CV) disease (CVD) is one of the leading causes of death, especially in Western countries.[10] In addition to mortality, CVD causes significant morbidity and challenges health care systems.[11] 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.[12] 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[10] to assess individual cardiovascular risk—recently, the SCORE2[13] 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.[4,14] 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.[15]

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.[4,14] In a European population-based cohort study by Schöttker et al[16] 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.[17,18] 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.[19,20] 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.[13] 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.[13] We fitted models for the dependent binary variable *H. pylori* positive using multilevel logistic 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).

We further fitted multivariable multilevel linear or logistic regression models using the year of inclusion as a random effect, the *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 (*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 *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 *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.

3 | RESULTS

In total, 2659 patients were *H. pylori* negative and 625 *H. pylori* positive. *Helicobacter pylori* positive were more often male and older and evidenced more often a 10-year CV risk >10% (23% vs. 18%; $p < .001$; Table 1). *Helicobacter pylori* positive patients evidenced higher BMI (28 ± 5 vs. $27 \pm 5\,kg/m^2$; $p < .001$) and lower HDL (56 ± 15 vs. $58 \pm 16\,mg/dl$; $p < .001$) 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 *H. pylori* (Table 1). Still, in multilevel linear regression analysis, *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

	HP−	HP+	
	N = 2659	*N* = 625	*p*-Value
Age (years)	56 (7)	56 (7)	.090
Age < 45 years	4% (106)	3% (20)	.61
Age 45–54 years	42% (1110)	40% (251)	
Age 55–64 years	41% (1091)	42% (264)	
Age 65–74 years	13% (352)	14% (90)	
Male sex	53% (1412)	56% (349)	.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)	
Pre-obesity	40% (1054)	45% (284)	
Obesity	22% (580)	25% (158)	
Systolic BP (mmHg)	132 (18)	133 (19)	.15
Diastolic RR (mmHBP)	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)	
SCORE2 ≥ 10%	18% (468)	23% (142)	
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)	
WHO CVD Risk <20%	24% (640)	24% (151)	
WHO CVD Risk <30%	4% (118)	6% (39)	
WHO CVD Risk ≥30%	1% (24)	2% (10)	
Smoking status			
Never smoker	34% (891)	32% (200)	.73
Ex-smoker	40% (1060)	41% (255)	
Active smoker	26% (698)	27% (170)	

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,[13] 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 *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 *H. pylori* positive (aOR 1.02 95% CI 1.01–1.04; $p < .001$) and remained so after multivariable adjustment for age and sex (aOR 1.03 95% CI 1.01–1.05; $p = .01$) as well after additional adjustment for the concomitant diagnosis of metabolic syndrome (aOR 1.03 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 *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 *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%) *H. pylori* was low and similar ($p = .51$). Similarly, all cause mortality was similar (3.3% vs. 4.0%; $p = .39$) in patients with and without *H. pylori*. In Cox regression, *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 *H. pylori* positive and SCORE2, which is a surrogate parameter for CV risk. In our cohort, *H. pylori* positive patients had a higher cardiovascular risk and vice versa, patients with higher CV risk had a higher probability of *H. pylori* infection. We also demonstrated this association of higher CV risk and *H. pylori* positive in sensitivity analyses in all subgroups evaluated. Nevertheless, overall, the absolute numerical effects were small (1% 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 *H. pylori* in our cohort.

There are data, especially from meta-analyses and nested analyses,[14,15,21,22] suggesting a positive association of *H. pylori* and CV risk. On the contrary, cohort studies[23–25] in high-impact journals could not demonstrate an independent association of *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 *H. pylori* and CVD. First, *H. pylori* and CVD are both traditionally associated with a cardiometabolic phenotype.[26] These common co-associations may therefore contribute to the robust association of *H. pylori* and CVD observed in some studies.[14,15] Interestingly, although in our study calculated CV risk by SCORE2 was higher in *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[13] 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 *H. pylori* could contribute to the progression of CVD, which is also characterized by a proinflammatory state.[12] 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 *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.[16] In this study, detection of the *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 *H. pylori*, whereas our study demonstrated active *H. pylori* infection by histological detection. Thus, in our study, *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 *H. pylori* and without *H. pylori*. It is also important to note that by far the majority of patients who were *H. pylori* positive in our study underwent eradication. Therefore, eradication of *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 eradications and the success of *H. pylori* eradication. Another limitation is our lack of knowledge about the exact *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[27] and basic science[28–30] studies.

Also, infection with *H. pylori* could lead to unfavorable alteration of the gut microbiota and thus indirectly contribute to the progression of atherosclerosis.[31] However, an evaluation in this regard is beyond our study. On the contrary, also *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 *H. pylori* eradication are also conceivable. However, Shah et al[32] did not find any signals for a negative effect on cardiovascular mortality due to *H. pylori* eradication. We,

TABLE 2 Baseline characteristics of patients with SCORE2 0%–5% and SCORE2 > 5%

	SCORE2 10-year CVD risk ≤5%	SCORE2 10-year CVD risk >5%	
	N = 1477	*N* = 1807	*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	66% (973)	30% (550)	<.001
BMI (kg/m^2)	26 (4)	28 (5)	<.001
BMI according to WHO	1% (14)	0% (3)	<.001
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)	78 (9)	83 (10)	<.001
Diastolic BP (mmHg)	32% (471)	69% (1242)	<.001
Arterial hypertension	222 (39)	227 (46)	<.001
Cholesterol (mg/dl)	140 (36)	149 (41)	<.001
LDL (mg/dl)	64 (17)	53 (14)	<.001
HDL (mg/dl)	3% (38)	26% (477)	<.001
Diabetes	5.4 (0.4)	5.6 (0.6)	<.001
HbA1c (%)	64% (952)	88% (1582)	<.001
Metabolic syndrome	0.9 (0.3)	0.9 (0.1)	<.001
Creatinine (mg/dl)	14.3 (1.1)	15.0 (1.2)	<.001
Hemoglobin (mg/dl)	248 (57)	231 (55)	<.001
Thrombocytes (G/L)	0.3 (0.7)	0.4 (0.7)	<.001
CRP (mg/dl)	0.3 (0.7)	0.4 (0.7)	<.001
SCORE2 10-year CVD risk (%)	3 (1)	9 (4)	<.001
SCORE2 < 5%	100% (1475)	0% (0)	<.001
SCORE2 < 10%	0%[2]	66% (1197)	
SCORE2 ≥ 10%	0% (0)	34% (610)	
Region 10-year risk WHO-CVD (%)	3 (2)	12 (6)	<.001
WHO CVD Risk <5%	82% (1209)	2% (35)	<.001
WHO CVD Risk <10%	18% (267)	44% (791)	
WHO CVD Risk <20%	0% (1)	44% (790)	
WHO CVD Risk <30%	0% (0)	9% (157)	
WHO CVD Risk ≥30%	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.

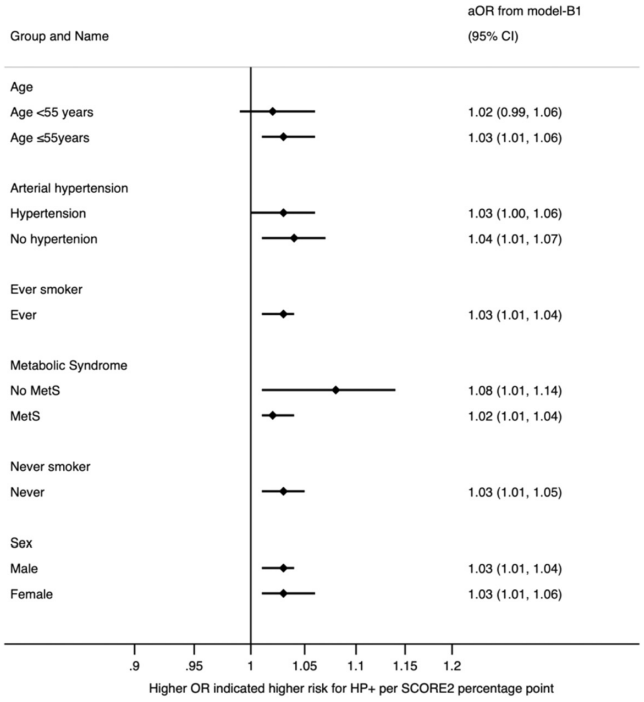

FIGURE 1 For the sensitivity analyses, we fitted model-B1 with SCORE2 as a continuous independent variable as a fixed effect and *H. pylori* positive as the dependent variable in the strata. We plotted the OR and 95% CI of the sensitivity analyses in forest plots.

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 mortality in our collective of asymptomatic patients who underwent screening for colorectal cancer. Another important point is that *H. pylori* was eradicated in most of our patients, although we do not have exact data for this. Eradication treatment may therefore have brought the risk of patients with *H. pylori* closer to that without *H. pylori*. As a limitation, it must also be mentioned that we only have mortality data but no information on cardiovascular events.

Based on our clinical assessment, the relationship of *H. pylori* and CVD may nevertheless be relevant. First, dyspeptic complaints are not always easy to distinguish from angina. Our data suggest that patients at higher CV risk are also more likely to have *H. pylori*, and it is worthwhile to clarify both entities in clinical practice. Whether *H. pylori* "test and treat" is justified purely on the rationale of cardiovascular risk mitigation remains unclear, or rather unlikely considering the low absolute numerical differences of *H. pylori* positive of patients with low (SCORE2 < 5%) and higher (SCORE > 5%). Here, an individualized approach could be helpful and contribute to the optimization of the outcomes of our patients. *Helicobacter pylori* eradication may also have led to a reduction in actual CV risk. In this respect, we think that our data support the notion that only a dead *H. pylori* is a good *H. pylori*.

AUTHOR CONTRIBUTIONS

SW, BW, and CD conceived the presented idea. All authors contributed to the final version of the manuscript and approved the final version.

CONFLICT OF INTEREST

CD is part of the scientific advisory board of SPAR Austria.

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How to cite this article: Wernly S, Semmler G, Völkerer A, et al. *Helicobacter pylori* and cardiovascular risk: Only a dead *Helicobacter* is a good *Helicobacter*? *Helicobacter*. 2022;27:e12928. doi: 10.1111/hel.12928