Effects of *Helicobacter pylori* Eradication on Platelet Activation and Disease Recurrence in Patients with Acute Coronary Syndromes

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ABSTRACT

Background. Platelet activation is consistently observed in animal models of *Helicobacter pylori* infection and could help to explain the alleged epidemiological association between *H. pylori* and coronary heart disease.

Materials and Methods. Ninety-two patients with recent acute coronary syndromes were enrolled. *Helicobacter pylori*-positive patients were randomized to receive a 7-day course of omeprazole, amoxycillin and metronidazole or placebos. Two months later, *H. pylori* status was reassessed and baseline parameters, including soluble P-selectin and platelet surface expression of CD62P, CD63 and CD41, were measured again. Patients were followed-up for 1 year or until death or readmission.

Results. No baseline differences were observed between *H. pylori*-positive and -negative cases. Among *H. pylori*-positive patients, 18 received placebo and 31 received active medication resulting in eradication in 21 cases. No differences were observed in inflammatory parameters or platelet activation markers between patients with persistent or resolved *H. pylori* infection. However, coronary events recurred at 6 and 12 months, respectively, in 35% and 55% of patients with persisting *H. pylori* infection compared with 10% and 25% of patients in whom *H. pylori* was either absent or eradicated ($p = .01$). Only final *H. pylori* status [RR 3.07 (95% CI 1.35–98)] and number of coronary risk factors [RR 2.58 (95% CI 1.51–4.41)] were independent predictors of recurrence.

Conclusions. Infection with *H. pylori* does not induce significant platelet activation in patients treated for coronary disease. *Helicobacter pylori*-infected patients, however, may have an increased risk of recurrence of coronary events.

Keywords. Atherosclerosis, coronary disease, infection, platelets.

Coronary atherosclerosis is a chronic inflammatory disorder, initiated and driven on by the recruitment and activation of inflammatory cells in the vascular intima [1], but only recently has it been linked with persistent viral and bacterial infections [2]. Epidemiological studies have shown increased prevalence of cardiovascular disease in patients with serological evidence of infection by intracellular pathogens such as cytomegalovirus, herpes simplex virus, *Chlamydia pneumoniae* and *Helicobacter pylori*, among other pathogens [2]. However, the underlying pathophysiological mechanisms supporting such associations remain poorly known.

Platelets play a pivotal role in the pathogenesis of both initiation and acute complications of atherosclerosis by adhering to dysfunctional endothelium or collagen and releasing their granular contents upon activation [1]. In fact, increased platelet reactivity adversely affects the survival of patients with myocardial infarction or percutaneous coronary interventions [3,4]. Interestingly, several groups of investigators have documented a distinctive role of platelets in the inflammatory response elicited by *H. pylori* in animal models [5–7]. Both chronic infection and acute exposure

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to *H. pylori* water extracts induce the formation of circulating leukocyte–platelet aggregates and an increase in platelet P-selectin surface expression. This platelet-activating effect of *H. pylori* has also been documented in human studies [6,8], but no data regarding the effects of this chronic infection on platelet activation markers in patients with coronary heart disease are yet available.

The present study was therefore aimed at examining the effects of *H. pylori* infection and eradication on platelet activation markers and recurrent acute coronary events (coronary death, myocardial infarction, unstable angina or need of revascularization) during the follow-up in subjects with recent acute coronary syndromes.

Methods

Study Population

Patients qualified for the study if they had survived an acute coronary syndrome (myocardial infarction or unstable angina) in the previous 2 weeks, were > 18 years old, had a life expectancy of > 2 years, and gave written informed consent. Exclusion criteria included the following: previous or planned coronary bypass surgery, New York Heart Association functional class III or IV or left ventricular ejection fraction < 25%, females capable of child bearing without adequate birth control, significant comorbid illnesses (including malignancy and known peptic ulcer disease), drug or alcohol abuse, renal failure (serum creatinine > 2 mg/dl) or liver failure, known hypersensitivity to any of the study medications, recent or chronic antibiotic treatment, or having been previously (within 6 months) included in any interventional trial. The study was approved by the ethics committee of the Hospital Clinic of Barcelona and by the Spanish health authorities (Agencia del Medicamento, Ministerio de Sanidad y Consumo).

Study Flow

At hospital discharge, patients who met all the study criteria and gave informed consent were screened for *H. pylori* infection using a [^{13}C]urea breath test, a highly accurate, noninvasive technique, to detect current infection [9], generously provided by Isomed S.L. (Madrid, Spain). Two weeks later, blood was drawn for laboratory testing and *H. pylori*-positive patients were randomized (ratio 3 : 2) to one of the two treatment groups (omeprazole + amoxycillin + metronidazole or their corresponding placebos) using opaque, sealed envelopes which contained correlative numbers. The randomization list, previously computer-generated in blocks of five to avoid major deviations from the calculated number of patients to treat, was kept in the Pharmacy Department until completion of the study. Randomized patients were instructed to take the study medications twice a day for 7 days. Two months later, recruited patients returned for a review of their clinical status, blood sampling and, for *H. pylori*-positive cases only, drug compliance (pill count) and [^{13}C]urea breath testing. The results of the 2-month [^{13}C]urea breath test were only disclosed to the investigators involved in laboratory analysis and clinical follow-up after study completion. Further follow-up clinical controls, either in-office or telephone-based, were scheduled at both 6 and 12 months. Infarction was defined by the presence of two of the three following signs: the investigator's assessment of clinical signs and symptoms of ischemia, an elevation in levels of cardiac markers [creatine kinase (CK) more than twice the upper limit of normal; myocardial band (MB) fraction at least 3%; troponin I more than twice the upper limit of normal] or new, diagnostic Q-waves in two contiguous leads. Unstable angina was defined as exacerbation of the patient's usual symptoms that resulted in urgent hospitalization, supported by either electrocardiographic evidence of ischemia or an elevated level of a cardiac marker (troponin I, CK, or CK-MB) greater than normal but not diagnostic for myocardial infarction.

An end-point committee, blinded as to *H. pylori* status and treatment groups, evaluated clinical outcomes and censored patients when appropriate.

Study Drugs

Omeprazole (20-mg capsules) and its placebo were kindly provided by Astra España. Amoxycillin (500 mg capsules), metronidazole (500 mg capsules) and their corresponding placebos were manufactured, labeled with the randomization number, and supplied by the Pharmacy Department of the Hospital Clinic.

Laboratory Testing

Platelet activation was studied in whole blood using flow-cytometric dual-color analysis as

previously described [6]. Monoclonal antibodies (mAb) conjugated with fluorescein-5-isothiocyanate (FITC) and phycoerytrin were purchased from Immunotech (Marseille, France). Platelet alpha-granule secretion was assessed using an anti-P-selectin mAb (clone CLB-Thromb/6) and platelet lysosome degranulation was measured using an anti-CD63 mAb (clone CLB-gran12), both conjugated with FITC. Platelet membrane glycoprotein IIb/IIIa was detected with an anti-CD41a mAb conjugated with phycoerythrin (clone P2). A FITC-labeled anti-immunoglobulin G1 (IgG1) mAb (clone 679.1Mc7) was used as a negative control. Results regarding glycoprotein IIb/IIIa expression are given as mean fluorescence intensity (arbitrary units). For P-selectin and CD63, the data are expressed as the percentage of positive platelets relative to negative control staining.

Quantitative plasma levels of soluble P-selectin (ng/ml) were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R & D Systems Inc., Minneapolis, MN, USA) following the manufacturer's instructions. High-sensitivity C-reactive protein was measured by an established in-house high-sensitivity ELISA [10]. Antibodies against *C. pneumoniae* were detected with an indirect microimmunofluorescence test (*C. pneumoniae* IgG/IgM Micro-IF Test kit, ThermoLabsystems, Vantaa, Finland). The remaining laboratory parameters, including plasma fibrinogen levels, leukocyte count and lipid levels, were determined by standard methods.

Statistical Analysis

The main hypothesis was that *H. pylori* eradication would induce a reduction in the surface expression of platelet P-selectin (CD62P). Additional platelet activation markers such as CD63 and glycoprotein IIb/IIIa (CD41/CD61 complex) surface expression, and soluble P-selectin plasma concentration were also assessed, as well as fibrinogen and C-reactive protein plasma levels. Regarding clinical objectives, we tested whether *H. pylori* status exerted any influence on the incidence of recurrent acute coronary events (coronary death, myocardial infarction, unstable angina, or need for revascularization).

Sample size was estimated for the main endpoint based on the results of a previous pilot investigation conducted in patients without coronary disease showing a reduction in platelet P-selectin after *H. pylori* eradication [6]. Eighteen patients in whom *H. pylori* had been eradicated would be required to detect such a reduction with a 90% statistical power and an alpha risk of 0.01. Taking into account the fact that the expected overall efficacy of the *H. pylori*-eradicating regime selected for this study is ~70% [11] and it has a drop-out rate of 5%, we estimated that we needed to recruit 47 *H. pylori*-positive patients in the study. The unbalanced randomization for *H. pylori* eradication therapy (3 : 2) was aimed at obtaining similar numbers of patients in whom *H. pylori* was eradicated or not eradicated. This study was designed to assess the effects of the outcome of *H. pylori* infection and not those strictly derived from the treatment received. Therefore, the main analyses were neither performed on an intention-to-treat nor on a per-protocol basis, but according to the effects of therapy on *H. pylori* gastric colonization.

Data are expressed as mean (SD). Proportions were compared with the χ^2 test or Fisher's exact test, and quantitative data were compared using an analysis of variance (ANOVA), Student's *t*-test or Mann–Whitney *U*-test, depending on the data distribution. Kaplan–Meier curves were produced to describe event-free survival, and the difference between groups was analysed with the log-rank test. The independent contribution of the potential determinants of event-free survival was analysed with the Cox model, with the occurrence of an end point as the dependent variable and the treatment code, final *H. pylori* status and other potential determinants (age, sex, smoking, diabetes, hypertension, hypercholesterolemia, number of coronary risk factors, previous ischemic episodes, baseline high-density lipoprotein cholesterol concentration, in-hospital treatment received – i.e. angioplasty/stent vs. medical therapy only) as independent variables. Continuous variables were dichotomized by their median values. The risk ratios and their 95% confidence intervals (CI) were also obtained from the Cox model. All *p*-values were two-sided. A p-value $< .05$ indicated a significant difference. Calculations were made with the SPSS 10.0 statistical package.

Results

Baseline Characteristics of Patients

A total of 92 patients were recruited into the study between November 2000 and October 2001

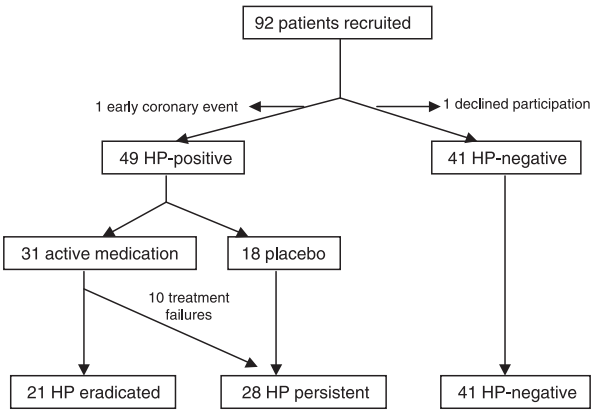

Figure 1 Flow of patients along the study.

(Fig. 1). One *H. pylori*-positive patient was readmitted early after discharge because of unstable angina before baseline blood sampling and randomization had taken place, and one *H. pylori*-negative patient declined further participation before the baseline parameters were obtained, 2 weeks after hospital discharge. Therefore, data from 90 patients were available for analysis. No significant differences between *H. pylori*-positive (n = 49) and *H. pylori*-negative (n = 41) patients were observed regarding demographic variables, prevalence of coronary risk factors, or severity of the index episode (data not shown). Management of coronary disease had included coronary angioplasty and/or stenting in 43% of *H. pylori*-positive patients and 40% of *H. pylori*-negative cases (p = ns). Lesions revealed by angiography (performed in 47 patients) were comparable in both groups, as was the noninvasive determination by ultrasonography of left ventricular ejection fraction [55 (12)% in *H. pylori*-negative vs. 59 (11)% in *H. pylori*-positive cases (p = ns)]. Serum lipid levels, inflammatory parameters (plasma fibrinogen, total leukocyte count, C-reactive protein) and platelet activation markers were also similar in both groups of patients (not shown). At discharge, the proportions of patients receiving aspirin (92 vs. 90%), clopidogrel (41 vs. 40%), beta-blockers (63 vs. 65%), angiotensin-converting enzyme inhibitors (29 vs. 30%), nitrates (33 vs. 37%) and hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (73 vs. 60%) were not different in *H. pylori*-positive vs. *H. pylori*-negative patients, respectively.

Among *H. pylori*-positive patients, 18 were assigned to receive placebo and 31 to receive active medication. Again, no significant differences existed between the groups of patients regarding the aforementioned data at baseline (data not shown).

Table 1 Characteristics of *Helicobacter pylori*-positive patients according to the evolution of infection

	H. pylori eradicated (n = 21)	*H. pylori* persistent (n = 28)	*p*
Age (years)	63 (10)	61 (10)	.6
Sex (% males)	81	78	1.0
Coronary risk factors (%)			
hypertension	66	50	.4
dyslipidemia	76	75	1.0
smoking	52	64	.6
diabetes mellitus	29	21	.7
Number of risk factors	1.9 (0.7)	2.0 (0.9)	.8
Index coronary event (%)			.7
acute infarction	52	46	
unstable angina	48	54	
LVEF (%)	58 (12)	60 (9)	.5
Maximum CK (U/l)	714 (616)	827 (668)	.6
Maximum CK-MB (U/l)	99 (102)	100 (64)	1.0
Maximum troponin I (μg/l)	3.8 (6.5)	0.4 (0.9)	.1
Hospital stay (days)	7.2 (2.8)	7.5 (3.1)	.7
Total cholesterol (mmol/l)	4.30 (0.85)	4.40 (1.04)	.7
LDL cholesterol (mmol/l)	2.31 (0.75)	2.49 (0.83)	.4
HDL cholesterol (mmol/l)	1.32 (0.39)	1.19 (0.28)	.2
Triglycerides (mmol/l)	1.36 (0.45)	1.40 (0.63)	.8
C-reactive protein (mg/dl)	0.33 (0.27)	0.45 (0.58)	.4
Leukocyte count ($\times 10^9$/l)	7.1 (1.8)	7.7 (1.8)	.3
Fibrinogen (μmol/l)	2.0 (2.6)	1.8 (2.7)	.8
Event during follow-up (%)	19	43	.1

LVEF: left ventricular ejection fraction; CK, creatine kinase; CK-MB, creatine kinase myocardial band; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Effects of Eradication on Platelet Activation Markers

Two months after randomization, 21 actively treated *H. pylori*-positive patients had eliminated the bacterium, resulting in an eradication rate of 68%. No spontaneous eradication occurred within the placebo group and therefore the infection persisted in 28 patients. No significant adverse effects were reported in either group. No major differences between patients with resolved or persistent *H. pylori* infection were observed regarding demographic variables or the severity of the ischemic episode (Table 1). Inflammation-related variables, such as total leukocyte counts, plasma fibrinogen concentration, or serum C-reactive protein also exhibited similar behavior in both groups of patients (Table 1).

No significant changes in platelet activation markers after treatment were observed in either group of patients (Table 2). No anti-chlamydial IgM antibodies were detected in any patient throughout the study (titers < 1/8). A serologically significant decline in anti-chlamydial IgG titers (more than one dilution) was observed in

Table 2 Changes in platelet activation markers according to evolution of *Helicobacter pylori* infection

	Group	Baseline	2-month follow-up	Paired *t*-test	ANOVA
CD62P (%)	*H. pylori*-negative	3.99 (4.05)	4.68 (6.41)	0.6	
	H. pylori eradicated	3.62 (4.84)	5.15 (9.48)	0.4	0.3
	H. pylori persistent	5.29 (6.10)	3.57 (3.93)	0.2	
CD63 (%)	*H. pylori* negative	3.88 (3.94)	3.07 (2.48)	0.3	
	H. pylori eradicated	2.81 (2.63)	2.94 (3.15)	0.4	0.7
	H. pylori persistent	3.15 (2.08)	2.62 (1.69)	0.3	
CD41a (MFI)[a]	*H. pylori* negative	140 (36)	148 (46)	0.4	
	H. pylori eradicated	165 (33)	182 (44)	0.2	0.9
	H. pylori persistent	141 (39)	150 (38)	0.3	
Soluble P-selectin (ng/ml)	*H. pylori* negative	35.5 (22.1)	35.8 (19.3)	0.9	
	H. pylori eradicated	33.1 (23.9)	33.1 (22.3)	0.9	0.3
	H. pylori persistent	35.7 (32)	29.3 (15.5)	0.2	

[a]MFI = mean fluorescence intensity, arbitrary units.

35% of patients randomized to receive antibiotic therapy, a proportion similar to that obtained in cases that were assigned to placebo or were *H. pylori*-negative at baseline (33%; p = ns). This result confirms the low or null anti-chlamydial activity of the combination of antibiotics selected for this study [12]. No relationship was observed between anti-chlamydial serological response and *H. pylori* infection outcome because anti-chlamydial IgG titers decreased in 38% of patients who eradicated *H. pylori* vs. 30% of those in whom gastric *H. pylori* colonization persisted (p = ns).

Impact of H. pylori *Infection on Recurrent Coronary Events*

During a median follow-up of 343 days, 23 patients required readmission because of unstable angina (n = 22) or acute myocardial infarction (n = 1), and one patient experienced sudden deatH. Baseline characteristics of patients experiencing acute coronary events during follow-up were similar to those who had an uneventful evolution except for a higher prevalence of coronary risk factors [2.4 (0.7) vs. 1.8 (0.8); p = .001], higher soluble P-selectin plasma levels [49 (33) ng/ml vs. 29 (18) ng/ml; p = .02] and lower high-density lipoprotein serum concentrations [1.11 (0.21) mmol/l vs. 1.27 (0.33) mmol/l; p = 0.01] 2 weeks after discharge in the former group. The proportion of patients who received active *H. pylori* eradication therapy was also similar among those who experienced and those who did not suffer from acute coronary events during follow-up (37 vs. 30%, respectively). Interestingly, 50% of patients with recurrence of coronary events tested positive for *H. pylori* infection after treatment compared with 24% of event-free cases (p = .02). Figure 2 shows the cumulative probability of remaining free of coronary events after discharge according to *H. pylori* status. At 6 and 12 months, respectively, coronary events recurred in 35% and 55% of patients with persisting *H. pylori* infection compared with 10% and 25% of patients in whom *H. pylori* was either absent or eradicated (log-rank, p = .01; Breslow, p = .01). Then, differences could not be accounted for by changes in anti-chlamydial serology because patients who experienced a decline in anti-chlamydial IgG titers showed a nonsignificant trend towards a worse event-free cumulative survival (log-rank, p = .15) compared to those in whom IgG titers remained unchanged or increased. The number of coronary risk factors identified at baseline was also strongly associated with event-free survival (log rank, p = .001). Other variables such as age, sex, previously known coronary disease, type of index episode (myocardial infarction vs. angina),

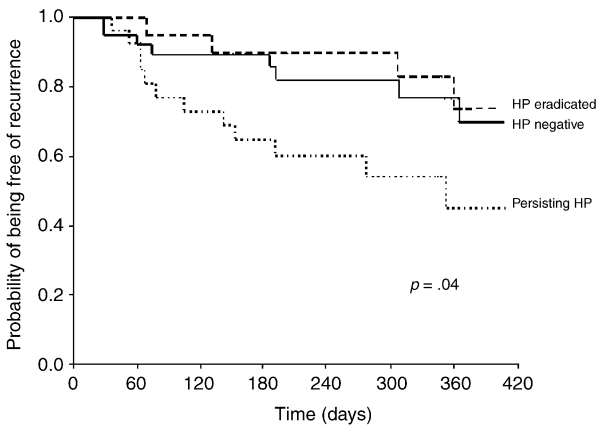

Figure 2 Kaplan–Meier estimates of probability of being free of recurrence of coronary events according to *Helicobacter pylori* (HP) status.

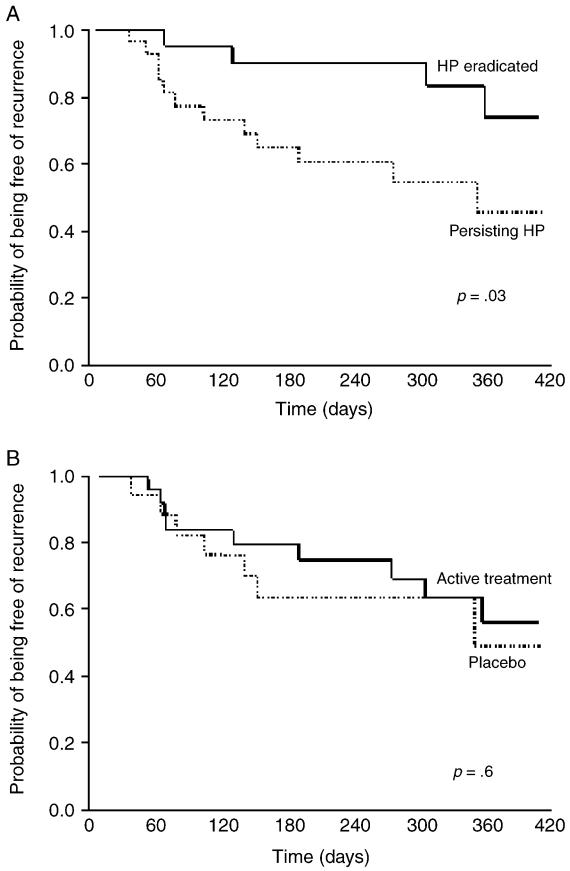

Figure 3 Kaplan–Meier estimates of probability of being free of recurrence of coronary events according to the evolution of *Helicobacter pylori* (HP) infection (A) or the randomization group irrespective of the outcome of infection (B) in baseline HP-infected patients.

in-hospital therapy received (medical treatment vs. angioplasty and/or stent), platelet P-selectin expression, C-reactive protein and soluble P-selectin levels did not significantly affect cumulative event-free survival. When only patients with baseline *H. pylori* infection were included in the analysis, differences in cumulative event-free survival were statistically significant when the patients were grouped according to the outcome of *H. pylori* infection (i.e. eradication vs. persistence of infection; log rank, $p = .03$; Breslow, $p = .03$), but not when groups were created according to the anti-*H. pylori* treatment received (i.e. active medication vs. placebo) irrespective of the outcome of the infection (Fig. 3).

Multivariate analysis identified the number of coronary risk factors present at baseline [RR 2.58 (95% CI 1.51–4.41); $p = .001$] and the final *H. pylori* status [RR 3.07 (95% CI 1.35–6.98); $p = .007$] as the only independent predictors of recurrence of acute coronary events during follow-up. Among the remaining variables included in the analysis, only female sex [RR 2.59 (95% CI 0.96–7.03); $p = .06$] was close to reaching statistical significance.

Discussion

The results of the present investigation clearly show that platelet activation status in patients with recent acute coronary syndromes is not affected by *H. pylori* infection. Neither baseline *H. pylori* infection nor *H. pylori* eradication in baseline *H. pylori*-infected cases was associated with any significant variations in platelet activation markers. Hence, our results do not support the hypothesis that platelet activation plays a major role in the increased risk of vascular events associated with chronic *H. pylori* infection, at least in the setting of patients with previous coronary events. Antiplatelet agents, probably the most prescribed drugs to patients with coronary disease, potently inhibit platelet activation and aggregation especially when used as combination therapies [13]. The fact that virtually all patients included in this study were being treated with one antiplatelet agent (and up to one-third were receiving both aspirin and clopidogrel) provides a likely explanation for the discrepancy between the results herein reported and previous data obtained in a series of patients without coronary disease [6]. Those results, together with the contributions of several groups of investigators reporting a prominent contribution of platelet activation in the inflammatory reactions elicited by *H. pylori* in diverse animal settings [14], suggest that *H. pylori*-induced platelet activation may play a role in the development and progression of atherosclerosis. In fact, recent investigations indicate that platelet activation and adhesion constitute key steps in the processes which take place at the initiation of atherosclerotic lesions [15,16]. Besides platelet activation, several other mechanisms through which *H. pylori* infection could negatively influence prognosis of coronary disease, namely proatherogenic changes of lipoproteins [17,18], fibrinogen [19], or homocysteine concentrations [20,21], have recently been ruled out. The recent identification of cross-reactivity of anti-CagA antibodies with arterial smooth muscle and endothelial cell antigens provides a rationale for the molecular mimicry theory [22]. This mechanism could also be involved in the endothelial dysfunction observed in humans

with serological evidence of several viral and bacterial infections, including *H. pylori* [23].

From the clinical point of view, our results indicate that the prognosis of acute coronary patients with persistent *H. pylori* infection may be impaired with respect to the clinical evolution experienced by *H. pylori*-negative patients. Moreover, prognosis of patients who underwent successful eradication was indistinguishable from event-free survival of uninfected cases. The main clinical benefit derived from *H. pylori* eradication was the reduction of recurrent episodes of unstable angina, because only a few cardiac deaths or myocardial infarctions were observed over the course of the year. We ruled out that these effects on survival depended on a possible impact of therapy on the degree of colonization by *C. pneumoniae*. Apart from selecting an antibiotic regime with little or no anti-chlamydial effect [12], serological controls ruled out unexpected effects of therapy on anti-chlamydial titers. The effects of *H. pylori* eradication therapy on survival could also be related to a putative immunomodulatory effect of metronidazole [24], or to the effects of antibiotics on oral and gut flora [25]. However, our analysis shows that the beneficial effects on survival derived from *H. pylori* eradication were not strictly dependent on the antibiotic therapy because survival curves were not significantly different when baseline *H. pylori*-positive patients were grouped according to the treatment received (triple therapy vs. placebo). In addition, multivariate analysis indicated that the variable independently predicting event-free survival in these cases was final *H. pylori* status, and not antibiotic therapy.

Regarding platelet activation markers, soluble P-selectin, perhaps a more reliable marker of *in vivo* platelet activation than surface expression of CD62P [26], was the only parameter associated with prognosis in univariate analysis. However, the association disappeared after adjustment for the number of coronary risk factors, in accordance with larger studies [27], suggesting that the degree of platelet activation in coronary patients depends on the presence of traditional risk factors or on the extent of the underlying atherosclerotic lesions [28].

The association between *H. pylori* infection and coronary disease is still controversial. Most serology-based epidemiological studies have found an association that usually weakens after adjusting for factors such as childhood socioeconomic circumstances [29]. It is not known how a poor social class during childhood increases the risk of coronary disease but the mechanism could be an enhanced susceptibility to *H. pylori* or other infectious agents. If that were the case, adjustments for socioeconomic status in epidemiological studies assessing the role of *H. pylori* in coronary disease would inappropriately mask any existing true association. A real impact of *H. pylori* infection on atherosclerosis is further reinforced by the existence of a stronger association of coronary atherosclerosis with more virulent *H. pylori* strains [30], and by its association with other conditions such as peripheral artery disease [21]. Regarding prospective, interventional trials, only limited and partial data are available, because most antibiotic-based studies performed in coronary patients have focused on *C. pneumoniae* infection [31–33]. However, in the STAMINA trial, patients treated with two different triple-therapy regimes (both active against *H. pylori*, but only one active against *C. pneumoniae*) exhibited virtually an identical improvement in 1-year cumulative event-free survival curves with respect to the placebo group [34]. Unfortunately, *H. pylori* status was only measured at baseline using serological techniques, and no attempts were made to assess *H. pylori* status after therapy. Such an analysis would have helped to clarify whether the benefits from antibiotics were related to their effects on *Chlamydia* sp., *H. pylori*, both, or neither, because additional bacteria, such as *Porphyromonas gingivalis*, the main microorganism responsible for adult periodontitis, has also been involved in experimental [35] and clinical atherosclerosis [36].

The present study was primarily designed and powered to detect *H. pylori*-induced differences in platelet activation markers in patients with recent acute coronary syndromes, and not to assess the impact of *H. pylori* infection and eradication on the rate of future coronary events. However, the clinical results observed in this series of patients, together with results obtained from recent studies [34], suggest that eradication therapy may improve the prognosis of *H. pylori*-positive patients with acute coronary syndromes. Whereas other authors conclude that this effect could be related to some general effects of antibiotics [34], our results suggest that getting rid of *H. pylori* is the essential goal. Irrespective of the mechanisms, larger, controlled trials are needed to translate these possible benefits of *H. pylori* eradication therapy to the bedside. Whether the culprit is *Helicobacter*, *Chlamydia*,

Porphyromonas, or a more global 'pathogen burden' [37], the clinical question that arises is whether the time will come to treat coronary disease with antibiotics.

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