**Name of journal: *World Journal of Cardiology***

**ESPS Manuscript NO: 14646**

**Columns: REVIEW**

***Helicobacter pylori*: Does it add to risk of coronary artery disease**

Sharma V *et al.* CAD and *Helicobacter pylori*

Vishal Sharma, Amitesh Aggarwal

**Vishal Sharma,** Department of Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

**Amitesh Aggarwal,** Department of Medicine, University College of Medical Sciences and GTB Hospital, Delhi 110095, India

**Author contributions:** Sharma V and Aggarwal A solely contributed to this paper.

**Conflict-of-interest:** No conflicts.

**Open-Access:** This article is an open-access article which selected by an in-house editor and fully peer-reviewed by external reviewers. It distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Amitesh Aggarwal, Assistant Professor,** Department of Medicine, University College of Medical Sciences and GTB Hospital, Dilshad Garden, New Delhi, Delhi 110095 India. [dramitesh@gmail.com](mailto:dramitesh@gmail.com)

**Telephone:** +91-98-11060025

**Received:** October 17, 2014

**Peer-review started:** October 20, 2014

**First decision:** November 27, 2014

**Revised:** December 14, 2014

**Accepted:** December 29, 2014

**Article in press:**

**Published online:**

**Abstract**

*Helicobacter pylori* (*H. pylori)* is a known pathogen implicated in genesis of gastritis, peptic ulcer disease, gastric carcinoma and gastric lymphoma. Beyond the stomach, the organism has also been implicated in the causation of immune thrombocytopenia and iron deficiency anemia. Although an area of active clinical research, the role of this gram negative organism in causation of atherosclerosis and coronary artery disease remains enigmatic. Coronary artery disease (CAD) is a multifactorial disease which results from the atherosclerosis involving coronary arteries. The major risk factors include age, diabetes mellitus, smoking, hypertension and dyslipidemia. The risk of coronary artery disease is believed to increase with chronic inflammation. Various organisms like Chlamydia and Helicobacter have been suspected to have a role in genesis of atherosclerosis *via* causation of chronic inflammation. This paper focuses on available evidence to ascertain if the role of *H. pylori* in CAD causation has been proven beyond doubt and if eradication may reduce the risk of CAD or improve outcomes in these patients.

**Key words:** Extra gastric; Coronary artery disease; *Helicobacter pylori*; Atherosclerosis; Inflammation

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Coronary artery disease is a multifactorial disease and inflammation plays an important role in Atherogenesis. *Helicobacter pylori* (*H. pylori)* is speculated to be one organism which may incite the inflammatory response thereby predisposing infected individuals to coronary artery disease. This paper looks at clinical evidence in relation to *H. pylori* infection and CAD and also examines the evidence of effects of eradication of *H. pylori* on CAD and its risk factors.

Sharma V, Aggarwal A. *Helicobacter pylori*: Does it add to risk of coronary artery disease. *World J Cardiol* 2015; In press

**INTRODUCTION**

*Helicobacter pylori (H. pylori)*, first identified by Marshall and Warren in 1982, is a ubiquitous gram negative bacterium. A mixture of serendipity and diligent research lifted the veil off this enigmatic organism which was first thought to be Campylobacter like. The Easter holidays of 1982 had ensured that the culture plates were not destroyed after 48 h of absence of growth and led on to the discovery of *H. pylori*[1]. However, it was after much perusal that the scientific community accepted the bacterium-ulcer-cancer dogma eventually culminating in the 2005 Nobel Prize[2]. Over years it has become clear that this bacterium is responsible for many disease other than the gastric diseases. In the stomach *H. pylori* is implicated in the causation of chronic gastritis, peptic ulcer (gastro-duodenal), gastric MALTOMA (mucosa associated lymphoid tissue lymphoma) and gastric adenocarcinoma. It is also associated with certain extra-gastric disorders like immune thrombocytopenia and iron deficiency anaemia[3,4]. Although the role of these in causation of gastric injury has emerged in recent times, the role of *H. pylori* and its virulence factors in causation of atherosclerosis and coronary artery disease is not entirely clear as yet. The present review will focus on the relationship between this bacterium and the coronary artery disease

**THE BACTERIUM**

*H. pylori* have an inherent ability to survive in the gastric epithelium where they reside in the mucous layer and remain protected from the gastric acid. Urease, an enzyme abundantly present in this flagellate organism, helps create an alkaline environment to help in survival in the otherwise acidic environment. While most infected individuals remain unaffected, others develop a myriad of clinical manifestations ranging from gastritis to gastric cancer. What fuels and drives the pathogenesis of these varied clinical spectrums is not completely understood. While it is estimated that around half the world’s population harbours infection with *H. pylori*, only a fraction of the infected manifest with the implicated diseases. The various factors implicated in disease causation following infection by *H. pylori* include both the bacterial virulence factors and the host response to the infection. The bacterial virulence factors include BabA (bacterial binding and inflammation), lipopolysaccharide (interaction with toll-like receptors and mediation of inflammation), cag pathogenicity island (heightened inflammatory response to infection) and vacA toxin (impaired host responses). The host responses which affect the outcome of infection include IL-1β (certain polymorphisms associated with carcinogenesis), activation of NF-κB, IL-8 levels, recruitment of neutrophils, macrophages and oxidative injury and TH1 cell response may all mediate tissue injury and reaction to *H. pylori* infection.

**CORONARY ARTERY DISEASE: A MULTIFACTORIAL DISEASE**

Coronary artery disease is a multifactorial disease manifesting in a number of clinical presentations including angina, myocardial infarction and heart failure. The CAD is primarily a result of coronary atherosclerosis for which a multitude of risk factors are implicated including hyperlipidemia, smoking, diabetes mellitus, lack of physical activity, male gender, increasing age, obesity amongst others[5]. There is a growing acknowledgement of inflammatory factors including C-reactive protein in prediction of increased risk of CAD[6]. *H. pylori* has also been implicated by some to have a role in predisposition to cardiac risk and causation of CAD. Indeed, in a polymerase chain reaction (PCR) based study for detection of *H. pylori* in the coronary plaques of patients who underwent coronary artery bypass grafting (CABG), 29.5% patients had a detectable *H. pylori* on PCR. Also there was serological evidence of infection in 53.3% of these 105 patients[7]. Therefore the infection by *H. pylori* may play a role in plaque rupture and causation of ischemic heart disease. Interestingly, CagA may also play a role in the pathogenesis of CAD as results of one study suggest that anti-CagA antibody titres were higher in patients with CAD vis-à-vis normal subjects. Also patients with anti-CagA positivity had more severe lesions of CAD[8].It is believed that the chronic inflammation associated with chronic infections may result in progressive atherosclerotic disease eventually manifesting as CAD[9].

**CORONARY ARTERY DISEASE AND *H. PYLORI***

***Epidemiological evidence***

A number of reports have evaluated the role of *H. pylori* in causation of CAD. In a report on 120 patients who underwent coronary angiography, the prevalence of serologically detectable evidence of *H. pylori* infection was more in patients with angiographically documented CAD (> 50% stenosis in atleast one coronary artery). The evidence of infection was found in 70% patients with single vessel disease, 76.3% patients with double vessel disease but only in 50% individuals with no CAD[10].Coronary artery calcium is believed to be a marker of atherosclerosis and its progression a predictor of CAD events. The correlation of CAC with various pathogens is conflicting. In a report on 201 asymptomatic subjects, the antibodies to heat shock protein 65 correlated with CAC score as also with evidence of *H. pylori* infection[11].Another large study from Korea which 2029 individuals for *H. pylori* antibody and coronary artery calcification score found that *H. pylori* seropositivity was different amongst those with and those without CAC[12]. This association was more evident in patients with early coronary atherosclerosis[12].However another report about presence of *H. pylori* infection in a large cohort of individuals who underwent repeat CAC assessment, the presence of *H. pylori* infection (IgG to *H. pylori*) did not correlate with development or progression of CAC[13].In a report comparing patients with CAD and healthy controls, sero-positivity for *H. pylori* infection was significantly higher in patients of CAD (59%) vis-à-vis the healthy controls (39%)[14].Similar reports from India also corroborate that *H. pylori* sero-positivity was much higher in patients with CAD when compared with asymptomatic controls[15-17].Few reports have indicated, to the contrary, that there is no significant association between *H. pylori* infection and CAD. In a report from Asian Indian families which evaluated role of multiple pathogens in causation of CAD, while CMV infection appeared to elevate the risk of CAD infection with *H. pylori* did not increase the risk[18]. In a large Japanese study to assess seroprevalence of *H. pylori* in CAD and asymptomatic controls no significant differences were detected between the two groups[19]. However when a subgroup of patients younger than 55 years was analysed the seroprevalence of *H. pylori* antibody was higher in cases than controls (58.7% and 43.3%, respectively)[19]. Another report about incidence of CAD in elderly individuals who were assessed for *H. pylori* infection at baseline and followed up for 10 years indicated that *H. pylori* positivity was not associated with increased incidence of CAD[20]. As described previously, PCR based studies of the coronary plaque have been done and have detected *H. pylori* DNA in them. In a controlled study of atheromatous plaques of 46 patients who underwent CABG, 22 (47.8%) showed *H. pylori* DNA while none of the controls who underwent coronary artery biopsy had PCR detectable *H. pylori*[21]. Aortic biopsies from areas free of atheromatous plaque have also been reported to be positive in a significant number of patients with CAD but none of the controls[22]. Table 1 summarises the recent studies reporting about association of *H. pylori* with CAD.

**CAG-A AND CAD**

As previously mentioned, role of cag-A has also been evaluated as a predisposing factor for occurrence of coronary artery disease[8]. In a study of cardiac peptides including Brain Natriuretic Peptide in 103 patients with non-ST elevation myocardial infarction and their relation with *H. pylori* infection, it was found that individuals infected with cag-A positive strains of *H. pylori* had higher levels of BNP in the serum[30].BNP is a marker of heart failure and may predict a more serious course of the disease thereby suggesting that *H. pylori* infection with cag-A positive strains may lead to an adverse outcome. Interestingly, IL-6 levels were also found to correlate with the cag-A status. This suggests that the inflammatory response to cag-A positive *H. pylori* may mediate atherogeneis in a subgroup of patients with CAD[30].However other reports indicate that cag-A positivity does not vary significantly between angiographically positive and negative group of individuals. In a report of 112 consecutive individuals who underwent coronary angiography, the cag-A positivity did not affect the severity of CAD[31].In a large study including 505 patients with CAD and 1025 matched controls, neither the prevalence of *H. pylori* infection was increased in the diseased subjects nor did the presence of cag-A positive strains predict higher likelihood of CAD[32].In a large population based report on 685 individuals, merely the presence of infection by *H. pylori* did not correlate with serum markers of inflammation. However those seropositive for cag-A positive strains had an increased values of common carotid artery intima-media thickness and the risk of atherosclerosis was enhanced by CRP positivity[33].Another report also indicated that cag-A positive strains appeared to raise the risk of CAD while merely the presence of *H. pylori* infection was not significantly different between cases and controls[34].An interesting study reported about sero-prevalence of anti-Cag A antibodies across a spectrum of presentations which included controls, stable and unstable angina and found that anti-Cag A titres were significantly higher in patients with unstable angina[35].

**MECHANISMS BEHIND ATHEROGENESIS**

One report has studied the association of atrophic gastritis with CAD. Atrophic gastritis is believed to be the end result of chronic gastric inflammation including that related to *H. pylori* infection. Decrease in serum pepsinogen I and a low Pepsinogen I/ II ratio points to the diagnosis of atrophic gastritis. In this intriguing report based on a population based study, Senamru *et al*[36] reported that prevalence of CAD was higher in the patients having atrophic gastritis (5.8%) when compared with individuals not having atrophic gastritis (2.8%). Atrophic gastritis may result in malabsorption of Vitamin B12 and Folate and result in increased homocysteine levels. Hyper-homocysteinemia is a recognised risk factor for CAD[37]. One report has also suggested structural homology between bacterial proteins and human tropomyosin and cardiac ATPases providing some insight into molecular mechanisms of role inflammatory response to *H. pylori* in initiating cardiac injury[30]. *H. pylori* has also been associated with dyslipidemia. In a Japanese study on 6289 subjects, infection with *H. pylori* was associated with low HDL and elevated LDL levels[38].Other reports have also provided similar evidence[39].Cag-A positive strains also exhibit elevated levels of highly sensitive CRP, oxidized LDL and apolipoprotein B all of which may participate in the pathogenesis of atherosclerosis[40].There is also a suggestion that *H. pylori* may have a prothrombotic role which may also increase the associated risk of atherosclerotic diseases. The bacterium may promote aggregation of platelets by binding to the von-Willibrand factor[41]. Infection with *H. pylori* may stimulate an inflammatory response against heat shock protein (hsp60) which may drive a helper T cell (TH1) response and increase the risk of atherosclerosis[42].The high degree of homology between bacterial and eukaryotic HSP may result in molecular mimicry and collateral immune damage from immune response primarily directed against infectious agents[43].The host reaction to the *H. pylori* lipopolysaccharide (LPS) may also be a risk factor for atherosclerosis[44].Figure 1 depicts the predominant mechanisms purported to play a role in geneis of *H. pylori*-related CAD.

**EFFECT OF ERADICATION**

The prognostic role of *H. pylori* infection has also been assessed in acute CAD. In 433 patients of acute coronary syndrome (ACS) the seroprevalence of *H. pylori* infection was determined using IgG and IgA serology. Those infected with *H. pylori* had an increased risk of short term adverse outcomes during the first month of follow-up[45].Another report which evaluated role of eight pathogens on occurrence future events in patients diagnosed to have angiographic evidence of CAD. Serological evidence of *H. pylori* infection predicted an increased risk of future events and mortality in these 1018 patients and increase in pathogen burden also affected long term outcome[46]. An interesting study evaluated the role of *H. pylori* eradication on coronary artery lumen reduction in patients who underwent percutaneous intervention for CAD. A higher loss of coronary lumen was noted in those patients who had serological evidence of *H. pylori* infection. Also, eradication of *H. pylori* attenuated this reduction in lumen of the coronary artery vis-à-vis the placebo group[47]. Another report by the same group provides similar findings but it is not clear if the report was based on different patients[48]. This small but elegant study opens debate about possible benefit of *H. pylori* eradication in attenuating further atherosclerotic process which is driven primarily by inflammatory mediators. In a study assessing the effect of *H. pylori* eradication on coronary risk factors in 48 patients, no differences were observed in pre and post-treatment fasting sugars, lipid profile and levels of tissue-plasminogen activator, fibrinogen, plasminogen activator inhibitor-1 and D-dimer levels[49]. However a larger study of 496 patients and reporting about pre and post- *H. pylori* eradication profile, the eradication of *H. pylori* seemed to increase HDL levels and reduce the levels of C reactive protein and those of fibrinogen. This suggests that attenuation of inflammatory response is likely after *H. pylori* eradication[50].In a report documenting the effects of *H. pylori* eradication on insulin resistance in 159 patients using homeostasis model assessment of insulin resistance, the insulin resistance measured six weeks post-eradication was lower than the baseline. The study also reported changes in lipid profile including an increase in HDL levels and a fall in LDL levels with *H. pylori* eradication[51].Another report also indicates that the *H. pylori* eradication may increase HDL levels and lead to reduction of CRP levels[52].Table 2 depicts various studies reporting about the effects of *H. pylori* eradication on CAD and its risk factors.

**ATHEROGENESIS BEYOND CORONARY ARTERIES**

In contrast to coronary artery disease, data is scarce on the relation between *H. pylori* infection and stroke. A meta-analysis found that *cag A*-positive *H. pylori* increases the risk of both ischemic stroke and coronary heart disease[53].

A case-control study of 150 patients by Yang *et al*[54] in 2011 does not reveal any strong association between chronic *H. pylori* infection and ischemic stroke.However, another study by Pan[55] suggested lowering of inflammatory markers and decrease in cerebral infarction readmission rates in patients of stroke with positive urease test treated with (conventional therapy + anti- *H. pylori* therapy. Wu *et al*[56] suggested role of increased expression of CD62p on platelets and increase in clotting indexes in pathogenesis of stroke in *H. pylori* positive patients.

A meta-analysis of 13 studies including 4,041 participants indicated that positive anti-*H. pylori* IgG, anti-Cag A IgG and (13)C-urea breath test were significantly associated with increased risk of IS, respectively, and positive anti-Cag A IgG was more effective for predication of IS risk[57].

But a formal meta-analysis of ten prospective observational studies indicated no strong association between *H. pylori* infection and stroke, neither in those with cytotoxin-associated gene-A-positive infection[58].

All in all, the evidence supporting the role of *H. pylori* in causation of CAD is equivocal and interventions aimed at *H. pylori* eradication have not shown conclusive evidence of benefit in eradicating the organism vis-à-vis cardiovascular outcomes. Perhaps multicentre randomised trials comparing eradication of *H. pylori* in large populations at risk of CAD and then follow-up to deterimine risk of CAD may answer this question.

**REFERENCES**

1 Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; **1**: 1273-1275 [PMID: 6134060]

2 **Van Der Weyden MB**, Armstrong RM, Gregory AT. The 2005 Nobel Prize in physiology or medicine. *Med J Aust* 2005; **183**: 612-614 [PMID: 16336147]

3 **Tan HJ**, Goh KL. Extragastrointestinal manifestations of Helicobacter pylori infection: facts or myth? A critical review. *J Dig Dis* 2012; **13**: 342-349 [PMID: 22713083 DOI: 10.1111/j.1751-2980.2012.00599.x]

4 **Franceschi F**, Roccarina D, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Minerva Med* 2006; **97**: 39-45 [PMID: 16565697]

5 **Fruchart JC**, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. *Circulation* 2004; **109**: III15-III19 [PMID: 15198961 DOI: 10.1161/01.CIR.0000131513.33892.5b]

6 **Arroyo-Espliguero R**, Avanzas P, Cosín-Sales J, Aldama G, Pizzi C, Kaski JC. C-reactive protein elevation and disease activity in patients with coronary artery disease. *Eur Heart J* 2004; **25**: 401-408 [PMID: 15033252 DOI: 10.1016/j.ehj.2003.12.017]

7 **Izadi M**, Fazel M, Sharubandi SH, Saadat SH, Farahani MM, Nasseri MH, Dabiri H, SafiAryan R, Esfahani AA, Ahmadi A, Jonaidi Jafari N, Ranjbar R, Jamali-Moghaddam SR, Kazemi-Saleh D, Kalantar-Motamed MH, Taheri S. Helicobacter species in the atherosclerotic plaques of patients with coronary artery disease. *Cardiovasc Pathol* 2012; **21**: 307-311 [PMID: 22104005 DOI: 10.1016/j.carpath.2011.09.011]

8 **Niccoli G**, Franceschi F, Cosentino N, Giupponi B, De Marco G, Merra G, Conte M, Montone RA, Ferrante G, Bacà M, Gasbarrini A, Silveri NG, Crea F. Coronary atherosclerotic burden in patients with infection by CagA-positive strains of Helicobacter pylori. *Coron Artery Dis* 2010; **21**: 217-221 [PMID: 20389238 DOI: 10.1097/MCA.0b013e3283399f36]

9 **Kowalski M**, Pawlik M, Konturek JW, Konturek SJ. Helicobacter pylori infection in coronary artery disease. *J Physiol Pharmacol* 2006; **57** Suppl 3: 101-111 [PMID: 17033109]

10 **Vafaeimanesh J**, Hejazi SF, Damanpak V, Vahedian M, Sattari M, Seyyedmajidi M. Association of Helicobacter pylori infection with coronary artery disease: is Helicobacter pylori a risk factor? *ScientificWorldJournal* 2014; **2014**: 516354 [PMID: 24574896]

11 **Zhu J**, Katz RJ, Quyyumi AA, Canos DA, Rott D, Csako G, Zalles-Ganley A, Ogunmakinwa J, Wasserman AG, Epstein SE. Association of serum antibodies to heat-shock protein 65 with coronary calcification levels: suggestion of pathogen-triggered autoimmunity in early atherosclerosis. *Circulation* 2004; **109**: 36-41 [PMID: 14662717 DOI: 10.1161/01.CIR.0000105513.37677.B3]

12 **Park MJ**, Choi SH, Kim D, Kang SJ, Chung SJ, Choi SY, Yoon DH, Lim SH, Kim YS, Yim JY, Kim JS, Jung HC. Association between Helicobacter pylori Seropositivity and the Coronary Artery Calcium Score in a Screening Population. *Gut Liver* 2011; **5**: 321-327 [PMID: 21927661 DOI: 10.5009/gnl.2011.5.3.321]

13 **Laek B**, Szklo M, McClelland RL, Ding J, Tsai MY, Bluemke DA, Tracy R, Matsushita K. The prospective association of Chlamydia pneumoniae and four other pathogens with development of coronary artery calcium: the multi-ethnic study of atherosclerosis (MESA). *Atherosclerosis* 2013; **230**: 268-274 [PMID: 24075755 DOI: 10.1016/j.atherosclerosis.2013.07.053]

14 **Mendall MA**, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, Camm AJ, Northfield TC. Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994; **71**: 437-439 [PMID: 8011406 DOI: 10.1136/hrt.71.5.437]

15 **Tewari R**, Nijhawan V, Mishra M, Dudeja P, Salopal T. Prevalence of Helicobacter pylori, cytomegalovirus, and Chlamydia pneumoniae immunoglobulin seropositivity in coronary artery disease patients and normal individuals in North Indian population. *Med J Armed Forces India* 2012; **68**: 53-57 [PMID: 24623916 DOI: 10.1016/S0377-1237(11)60121-4]

16 **Jha HC**, Prasad J, Mittal A. High immunoglobulin A seropositivity for combined Chlamydia pneumoniae, Helicobacter pylori infection, and high-sensitivity C-reactive protein in coronary artery disease patients in India can serve as atherosclerotic marker. *Heart Vessels* 2008; **23**: 390-396 [PMID: 19037586 DOI: 10.1007/s00380-008-1062-9]

17 **Tamer GS**, Tengiz I, Ercan E, Duman C, Alioglu E, Turk UO. Helicobacter pylori seropositivity in patients with acute coronary syndromes. *Dig Dis Sci* 2009; **54**: 1253-1256 [PMID: 18770033 DOI: 10.1007/s10620-008-0482-9]

18 **Mundkur LA**, Rao VS, Hebbagudi S, Shanker J, Shivanandan H, Nagaraj RK, Kakkar VV. Pathogen burden, cytomegalovirus infection and inflammatory markers in the risk of premature coronary artery disease in individuals of Indian origin. *Exp Clin Cardiol* 2012; **17**: 63-68 [PMID: 22826649]

19 **Kinjo K**, Sato H, Sato H, Shiotani I, Kurotobi T, Ohnishi Y, Hishida E, Nakatani D, Mizuno H, Sasaki T, Kohama A, Abe Y, Morita H, Kubo M, Takeda H, Hori M. Prevalence of Helicobacter pylori infection and its link to coronary risk factors in Japanese patients with acute myocardial infarction. *Circ J* 2002; **66**: 805-810 [PMID: 12224816 DOI: 10.1253/circj.66.805]

20 **Haider AW**, Wilson PW, Larson MG, Evans JC, Michelson EL, Wolf PA, O'Donnell CJ, Levy D. The association of seropositivity to Helicobacter pylori, Chlamydia pneumoniae, and cytomegalovirus with risk of cardiovascular disease: a prospective study. *J Am Coll Cardiol* 2002; **40**: 1408-1413 [PMID: 12392829 DOI: 10.1016/S0735-1097(02)02272-6]

21 **Kowalski M**, Rees W, Konturek PC, Grove R, Scheffold T, Meixner H, Brunec M, Franz N, Konturek JW, Pieniazek P, Hahn EG, Konturek SJ, Thale J, Warnecke H. Detection of Helicobacter pylori specific DNA in human atheromatous coronary arteries and its association to prior myocardial infarction and unstable angina. *Dig Liver Dis* 2002; **34**: 398-402 [PMID: 12132786 DOI: 10.1016/S1590-8658(02)80036-6]

22 **Iriz E**, Cirak MY, Engin ED, Zor MH, Erer D, Ozdogan ME, Turet S, Yener A. Detection of Helicobacter pylori DNA in aortic and left internal mammary artery biopsies. *Tex Heart Inst J* 2008; **35**: 130-135 [PMID: 18612444]

23 **Shmuely H**, Wattad M, Solodky A, Yahav J, Samra Z, Zafrir N. Association of Helicobacter pylori with coronary artery disease and myocardial infarction assessed by myocardial perfusion imaging. *Isr Med Assoc J* 2014; **16**: 341-346 [PMID: 25058994]

24 **Padmavati S**, Gupta U, Agarwal HK. Chronic infections & amp; coronary artery disease with special reference to Chalmydia pneumoniae. *Indian J Med Res* 2012; **135**: 228-232 [PMID: 22446866]

25 **Grdanoska T**, Zafirovska P, Jaglikovski B, Pavlovska I, Zafirova B, Tosheska-Trajkovska K, Trajkovska-Dokic E, Petrovska M, Cekovska Z, Kondova-Topuzovska I, Georgievska-Ismail L, Panovski N. Chlamydia pneumoniae and helicobacter pylori serology - importance in patients with coronary heart disease. *Mater Sociomed* 2012; **24**: 151-156 [PMID: 23922522 DOI: 10.5455/msm.2012.24.151-156]

26 **Grub C**, Brunborg C, Hasseltvedt V, Aukrust P, Førre O, Almdahl SM, Hollan I. Antibodies to common infectious agents in coronary artery disease patients with and without rheumatic conditions. *Rheumatology (Oxford)* 2012; **51**: 679-685 [PMID: 22157685 DOI: 10.1093/rheumatology/ker251]

27 **Al-Ghamdi A**, Jiman-Fatani AA, El-Banna H. Role of Chlamydia pneumoniae, helicobacter pylori and cytomegalovirus in coronary artery disease. *Pak J Pharm Sci* 2011; **24**: 95-101 [PMID: 21454155]

28 **Azarkar Z**, Jafarnejad M, Sharifzadeh G. The relationship between helicobacter pylori infection and myocardial infarction. *Caspian J Intern Med* 2011; **2**: 222-225 [PMID: 24024020]

29 **Khodaii Z**, Vakili H, Ghaderian SM, Najar RA, Panah AS. Association of Helicobacter pylori infection with acute myocardial infarction. *Coron Artery Dis* 2011; **22**: 6-11 [PMID: 20962628 DOI: 10.1097/MCA.0b013e3283402360]

30 **Figura N**, Palazzuoli A, Vaira D, Campagna M, Moretti E, Iacoponi F, Giordano N, Clemente S, Nuti R, Ponzetto A. Cross-sectional study: CagA-positive Helicobacter pylori infection, acute coronary artery disease and systemic levels of B-type natriuretic peptide. *J Clin Pathol* 2014; **67**: 251-257 [PMID: 24334757 DOI: 10.1136/jclinpath-2013-201743]

31 **Rogha M**, Dadkhah D, Pourmoghaddas Z, Shirneshan K, Nikvarz M, Pourmoghaddas M. Association of helicobacter pylori infection with severity of coronary heart disease. *ARYA Atheroscler* 2012; **7**: 138-141 [PMID: 23205045]

32 **Whincup P**, Danesh J, Walker M, Lennon L, Thomson A, Appleby P, Hawkey C, Atherton J. Prospective study of potentially virulent strains of Helicobacter pylori and coronary heart disease in middle-aged men. *Circulation* 2000; **101**: 1647-1652 [PMID: 10758045 DOI: 10.1161/01.CIR.101.14.1647]

33 **Mayr M**, Kiechl S, Mendall MA, Willeit J, Wick G, Xu Q. Increased risk of atherosclerosis is confined to CagA-positive Helicobacter pylori strains: prospective results from the Bruneck study. *Stroke* 2003; **34**: 610-615 [PMID: 12624280 DOI: 10.1161/01.STR.0000058481.82639.EF]

34 **Gunn M**, Stephens JC, Thompson JR, Rathbone BJ, Samani NJ. Significant association of cagA positive Helicobacter pylori strains with risk of premature myocardial infarction. *Heart* 2000; **84**: 267-271 [PMID: 10956287 DOI: 10.1136/heart.84.3.267]

35 **Franceschi F**, Niccoli G, Ferrante G, Gasbarrini A, Baldi A, Candelli M, Feroce F, Saulnier N, Conte M, Roccarina D, Lanza GA, Gasbarrini G, Gentiloni SN, Crea F. CagA antigen of Helicobacter pylori and coronary instability: insight from a clinico-pathological study and a meta-analysis of 4241 cases. *Atherosclerosis* 2009; **202**: 535-542 [PMID: 18599062 DOI: 10.1016/j.atherosclerosis.2008.04.051]

36 **Senmaru T**, Fukui M, Tanaka M, Kuroda M, Yamazaki M, Oda Y, Naito Y, Hasegawa G, Toda H, Yoshikawa T, Nakamura N. Atrophic gastritis is associated with coronary artery disease. *J Clin Biochem Nutr* 2012; **51**: 39-41 [PMID: 22798711 DOI: 10.3164/jcbn.11-106]

37 **Tamura A**, Fujioka T, Nasu M. Relation of Helicobacter pylori infection to plasma vitamin B12, folic acid, and homocysteine levels in patients who underwent diagnostic coronary arteriography. *Am J Gastroenterol* 2002; **97**: 861-866 [PMID: 12003420 DOI: 10.1111/j.1572-0241.2002.05601.x]

38 **Satoh H**, Saijo Y, Yoshioka E, Tsutsui H. Helicobacter Pylori infection is a significant risk for modified lipid profile in Japanese male subjects. *J Atheroscler Thromb* 2010; **17**: 1041-1048 [PMID: 20610892 DOI: 10.5551/jat.5157]

39 **Jia EZ**, Zhao FJ, Hao B, Zhu TB, Wang LS, Chen B, Cao KJ, Huang J, Ma WZ, Yang ZJ, Zhang G. Helicobacter pylori infection is associated with decreased serum levels of high density lipoprotein, but not with the severity of coronary atherosclerosis. *Lipids Health Dis* 2009; **8**: 59 [PMID: 20030806 DOI: 10.1186/1476-511X-8-59]

40 **Huang B**, Chen Y, Xie Q, Lin G, Wu Y, Feng Y, Li J, Zhuo Y, Zhang P. CagA-positive Helicobacter pylori strains enhanced coronary atherosclerosis by increasing serum OxLDL and HsCRP in patients with coronary heart disease. *Dig Dis Sci* 2011; **56**: 109-114 [PMID: 20503072 DOI: 10.1007/s10620-010-1274-6]

41 **Fagoonee S**, De Angelis C, Elia C, Silvano S, Oliaro E, Rizzetto M, Pellicano R. Potential link between Helicobacter pylori and ischemic heart disease: does the bacterium elicit thrombosis? *Minerva Med* 2010; **101**: 121-125 [PMID: 20467411]

42 **Ayada K**, Yokota K, Kobayashi K, Shoenfeld Y, Matsuura E, Oguma K. Chronic infections and atherosclerosis. *Clin Rev Allergy Immunol* 2009; **37**: 44-48 [PMID: 18985284 DOI: 10.1007/s12016-008-8097-7]

43 **Ayada K**, Yokota K, Kobayashi K, Shoenfeld Y, Matsuura E, Oguma K. Chronic infections and atherosclerosis. *Ann N Y Acad Sci* 2007; **1108**: 594-602 [PMID: 17894024 DOI: 10.1196/annals.1422.062]

44 **Grebowska A**, Rechciński T, Bak-Romaniszyn L, Czkwianianc E, Moran A, Druszczyńska M, Kowalewicz-Kulbat M, Owczarek A, Dziuba M, Krzemińska-Pakuła M, Płaneta-Małecka I, Rudnicka W, Chmiela M. Potential role of LPS in the outcome of Helicobacter pylori related diseases. *Pol J Microbiol* 2006; **55**: 25-30 [PMID: 16878600]

45 **Eskandarian R**, Ghorbani R, Shiyasi M, Momeni B, Hajifathalian K, Madani M. Prognostic role of Helicobacter pylori infection in acute coronary syndrome: a prospective cohort study. *Cardiovasc J Afr* 2012; **23**: 131-135 [PMID: 22555636 DOI: 10.5830/CVJA-2011-016]

46 **Rupprecht HJ**, Blankenberg S, Bickel C, Rippin G, Hafner G, Prellwitz W, Schlumberger W, Meyer J. Impact of viral and bacterial infectious burden on long-term prognosis in patients with coronary artery disease. *Circulation* 2001; **104**: 25-31 [PMID: 11435333 DOI: 10.1161/hc2601.091703]

47 **Kowalski M**. Helicobacter pylori (H. pylori) infection in coronary artery disease: influence of H. pylori eradication on coronary artery lumen after percutaneous transluminal coronary angioplasty. The detection of H. pylori specific DNA in human coronary atherosclerotic plaque. *J Physiol Pharmacol* 2001; **52**: 3-31 [PMID: 11795863]

48 **Kowalski M**, Konturek PC, Pieniazek P, Karczewska E, Kluczka A, Grove R, Kranig W, Nasseri R, Thale J, Hahn EG, Konturek SJ. Prevalence of Helicobacter pylori infection in coronary artery disease and effect of its eradication on coronary lumen reduction after percutaneous coronary angioplasty. *Dig Liver Dis* 2001; **33**: 222-229 [PMID: 11407666 DOI: 10.1016/S1590-8658(01)80711-8]

49 **Lu YH**, Yen HW, Lin TH, Huang CH, Lee KT, Wang WM, Wu DC, Voon WC, Lai WT, Sheu SH. Changes of coronary risk factors after eradication of Helicobacter pylori infection. *Kaohsiung J Med Sci* 2002; **18**: 266-272 [PMID: 12355926]

50 **Pellicano R**, Oliaro E, Fagoonee S, Astegiano M, Berrutti M, Saracco G, Smedile A, Repici A, Leone N, Castelli A, Luigiano C, Fadda M, Rizzetto M. Clinical and biochemical parameters related to cardiovascular disease after Helicobacter pylori eradication. *Int Angiol* 2009; **28**: 469-473 [PMID: 20087284]

51 **Gen R**, Demir M, Ataseven H. Effect of Helicobacter pylori eradication on insulin resistance, serum lipids and low-grade inflammation. *South Med J* 2010; **103**: 190-196 [PMID: 20134372 DOI: 10.1097/SMJ.0b013e3181cf373f]

52 **Kanbay M**, Gür G, Yücel M, Yilmaz U, Boyacioğlu S. Does eradication of Helicobacter pylori infection help normalize serum lipid and CRP levels? *Dig Dis Sci* 2005; **50**: 1228-1231 [PMID: 16047464 DOI: 10.1007/s10620-005-2764-9]

53 **Zhang S**, Guo Y, Ma Y, Teng Y. Cytotoxin-associated gene-A-seropositive virulent strains of Helicobacter pylori and atherosclerotic diseases: a systematic review. *Chin Med J (Engl)* 2008; **121**: 946-951 [PMID: 18706211]

54 **Yang X**, Gao Y, Zhao X, Tang Y, Su Y. Chronic Helicobacter pylori infection and ischemic stroke subtypes. *Neurol Res* 2011; **33**: 467-472 [PMID: 21669114 DOI: 10.1179/016164111X13007856083963]

55 **Pan G**. [Effect of anti-Helicobacter pylori on the prognosis in patients with acute cerebral infarction]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2011; **36**: 872-875 [PMID: 21946199]

56 **Wu HQ**, Tang Y, Zhang X, Wei XH, Wang HQ, Zhang WT, Zhang GL. [Effect of Helicobacter pylori infection on platelet activation and coagulation function in patients with acute cerebral infarction]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2012; **41**: 547-552 [PMID: 23086648]

57 **Wang ZW**, Li Y, Huang LY, Guan QK, Xu da W, Zhou WK, Zhang XZ. Helicobacter pylori infection contributes to high risk of ischemic stroke: evidence from a meta-analysis. *J Neurol* 2012; **259**: 2527-2537 [PMID: 22688569 DOI: 10.1007/s00415-012-6558-7]

58 **Yu M**, Zhang Y, Yang Z, Ding J, Xie C, Lu N. Association between Helicobacter pylori infection and stroke: a meta-analysis of prospective observational studies. *J Stroke Cerebrovasc Dis* 2014; **23**: 2233-2239 [PMID: 25263434 DOI: 10.1016/j.jstrokecerebrovasdis.2014.04.020]

**P-Reviewer:** Peteiro J, Schoenhagen P **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Recent reports on association of *Helicobacter pylori* infection with coronary artery disease**

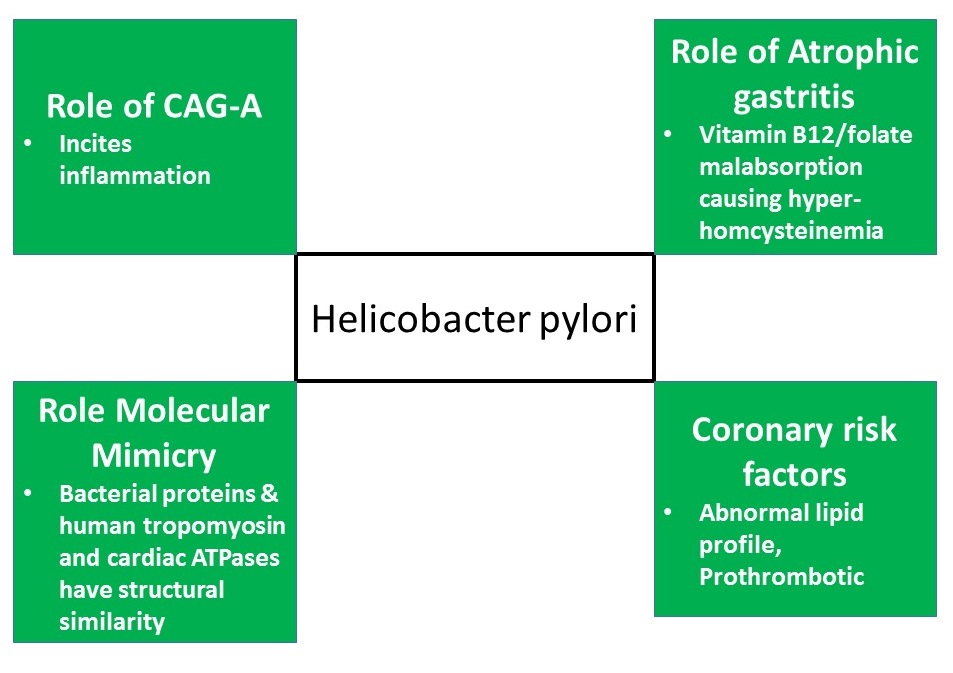
|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Population**  **(number of subjects)** | **Diagnosis of CAD** | **Association between *H. pylori* infection and CAD** |
| Shmuely *et al*[23]  (2014) | CAD (173) *vs* Controls (123) | Myocardial Perfusion imaging | Yes  No association with Cag-A |
| Vafaeimanesh *et al*[10]  (2014) | CAD (62) *vs* Controls (58) | Angiographic | Yes |
| Laek B *et al*[13]  (2013) | 5744 individuals, Age 45-84 years, Average follow-up of 2.4 years | Newly detectable Coronary artery calcium (CAC) | No correlation with CAC development |
| Mundkur *et al*[18]  (2012) | CAD and controls (433 each) from South Asians | Angiography | None |
| Padmavati *et al*[24]  (2012) | Acute Myocardial Infarction *vs* Controls | ECG, Enzymes | None |
| Tewari *et al*[15]  (2012) | 200 CAD cases and controls | ECG, treatment records | Yes |
| Grdanoska *et al*[25]  (2012) | Acute coronary syndromee (64), CAD (53), Controls (35) | ECG, Enzymes | Yes |
| Grub *et al*[26]  (2012) | Controls (30), CAD (52) and CAD with rheumatic diseases (67) | Patients referred for CABG | None |
| Park *et al*[12]  (2011) | 2029 subjects | Coronary artery calcium (CAC) | Yes |
| Al-Ghamdi *et al*[27]  (2011) | CAD (50) and controls (15) | ECG, Angiography | Yes |
| Azarkar *et al*[28]  (2011) | Controls (78) and Myocardial infarction (73) | ECG, Enzymes | Yes |
| Khodaii *et al*[29]  (2011) | Myocardial Infarction (500) and Controls (500) | ECG, Enzymes | Yes  Cag-A positivity also correlates with CAD |

CAD: Coronary artery disease; Cag-A: Cytotoxin associated gene A; ECG: Electrocardiography; CAC: Coronary artery calcium; CABG: Coronary artery bypass grafting; *H. pylori: Helicobacter pylori.*

**Table 2 Effect of Helicobacter pylori eradication on coronary artery disease**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Population** | **Intervention** | **Results** |
| Kowalski[47,48] | 40 patient with single vessel CAD and *H. pylori* infection | All underwent PTCA and 20 each received eradication or placebo | Attenuated reduction mean coronary artery lumen at 6 mo in those undergoing eradication |
| Lu *et al*[49] | *H. pylori* positive individuals | Testing of coronary risk factors before and after *H. pylori* eradication | No change in sugar, lipid and fibrinolytic parameters with eradication |
| Pellicano *et al*[50] | *H. pylori* positive individuals | Testing of coronary risk factors before and after *H. pylori* eradication | Improvement in HDL-C, reduction in CRP and fibrinogen levels. Elevation in BMI and diastolic blood pressure |
| Gen *et al*[51] | *H. pylori* positive individuals | Testing for insulin resistance, lipid profile and CRP before and after eradication | Improvement in insulin resistance, lipid abnormalities and CRP levels |
| Kanbay *et al*[52] | *H. pylori* positive individuals | Testing for lipid profile and CRP before and after eradication | Increase in HDL and reduction in CRP with successful eradication |

CAD: Coronary artery disease; CRP: C-reactive protein; HDL: High density lipoprotein; PTCA: Percutaneous transluminal coronary angioplasty; *H. pylori: Helicobacter pylori.*

****

**Figure 1 Postulated mechanisms of Atherogenesis in *Helicobacter pylori* infection.**