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Impact of *Helicobacter Pylori* Treatment Failure On Long-Term Clinical Outcomes in Patients with Atrial Fibrillation

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&Author Contributions:

Kim SE, Park HS and these authors are contributed equally to this work.

1. Abstract

There was limited data about the association between the *Helicobacter pylori(H.pylori)* and AF in the long-term follow up. We evaluated the impact of *H.pylori* treatment failure on long-term clinical outcomes with AF. The echocardiography, electrocardiogram and *H.pylori* database were reviewed from 2017-19 to identify patients with AF and *H. pylori*. Among 701 patients with AF, 322(45.9%) patients had *H.pylori* infection. Finally 123 consecutive AF patients(mean age;59.6±10.9 years;mean 25.2±0.6 months followed-up) who underwent *H.pylori* eradication were enrolled and divided into two groups according to *H.pylori* treatment failure. There was no difference of total any events in both groups. However, arrhythmic events are lower in AF patients with *H.pylori* treatment failure compared with those without *H.pylori* treatment failure (P=0.034). In univariate analysis, hypertension, smoke, *H.pylori* treatment failure, age, E/E'(peak mitral flow velocity of the early rapid filling wave/early diastolic mitral annulus velocity), and CHA_2DS_2VASc score were significantly associated with neurologic events including stroke, transient ischemic attack. In multivariate analysis, *H.pylori* treatment failure was independent risk factors for neurologic events (P=0.018) at the long-term follow-up. *H.pylori* treatment failure was associated with higher incidence of arrhythmic and neurologic events in patients with AF, suggesting more intensive medical therapy with close clinical follow-up will be required. And the reason of higher incidence of neurologic events in *H.pylori* treatment failure group requires further study.

2. Introduction

Atrial Fibrillation (AF) is the most common clinically significant arrhythmia in clinical practice. AF is associated with increased morbidity and mortality that primarily occur as a result of complications, such as thromboembolic events and heart failure [1].

AF is often associated with other cardiovascular diseases (CVDs), including diabetes mellitus, hypertension, congestive heart failure, ischemic heart disease, valvular heart diseases and other cardiomyopathies [2, 3]. However, in 10–15% of the cases, AF occurs in the absence of any such comorbidities and is determined as lone AF [4].

There is an increasing body of evidence linking inflammation to broad spectrum of cardiovascular condition, such as coronary artery disease. In addition, there are emerging data to support the association between inflammation and AF [5, 6]. In recent studies, other factors playing a role in the genesis of AF have gained attention including obesity, sleep apnea, alcohol abuse and other intoxications, exercise, latent hypertension, genetic factors, acid reflux disease, and local or systemic inflammation [4-6]. Recently C reactive protein (CRP) concentration, a sensitive marker of systemic inflammation,

was found to be twice as high in patients with AF as in a control group with no history of atrial arrhythmia [7].

A study showed that the *Helicobacter pylori* (*H.pylori*) infection rate was as high as 50% in Chinese adults, and *H.pylori* was not only an important pathogenic reason for chronic gastritis and stomach cancer but also closely related to the occurrence of non-gastrointestinal diseases [8]. A potential non-cardiovascular disease that predisposes to AF may be chronic gastritis caused by chronic *H.pylori* infection. Thus, we hypothesized that *H.pylori* infection and *H.pylori* treatment failure, suggestive of uncontrolled local chronic inflammation may be involved in the atrial inflammation resulting in AF. Some studies showed that chronic *H.pylori* infection was involved in AF and it played an important role in the development of AF [9, 10].

However, there was limited data about the association between *H.pylori* treatment failure and AF in the long-term follow up. The aim of this study was to evaluate the impact of *H.pylori* treatment failure on long-term clinical outcomes with AF.

3. Material and Methods

3.1. Study Populations

We retrospectively reviewed the medical records of 701 patients with non-valvular AF patients (mean age; 61.5±10.8 years, 70.3% male) at Kosin university gospel hospital from January, 2017 to November, 2019.

Inclusion criteria included AF patients with *H.pylori* infection. Patients with a history of AF documented by a standard electrocardiogram (ECG) or Holter-ECG were enrolled. Exclusion criteria included the patients did not do *H.pylori* eradication and could not be followed-up; age >80 years old; a history of structural heart disease; hepatic or renal disease; an acute cardiovascular or cerebrovascular event within the preceding 3 months; any major trauma or surgery within the preceding 3 months; hyperthyroidism; uncontrolled hypertension; malignancy; connective tissue disease; or any acute or chronic inflammatory disease. We used the following disease-specific exclusion criteria for gastric disease: previous gastric surgery, gastro-intestinal symptoms caused by conditions other than *H.pylori* infection.

322 patients (45.9%) with AF had *H.pylori* infection. And finally, we could enroll 123 consecutive AF patients (mean age; 59.6±10.9 years) who underwent *H.pylori* eradication because of *H.pylori* infection (Figure 1). All patients were monitored to evaluate total any event rates including thromboembolic events, bleeding events, GI symptoms, arrhythmic events, re-hospitalizations and mortality according to *H.pylori* treatment failure during follow-up. The baseline characteristics of the patients are presented in (Table 1).

Table 1: Baseline clinical characteristics in AF patients with *Helicobacter pylori* infection according to *Helicobacter pylori* treatment failure

Variables	H.pylori treatment failure group (n=26)	Successful H.pylori treatment group (n=97)	P-value
Age (years)	71.2±9.3	68.7±8.6	0.092
Male (%)	16 (61.5)	68 (70.1)	0.478
CHF (%)	8 (30.8)	21 (21.6)	0.435
DM (%)	6 (23.1)	24 (24.7)	1.000
HTN (%)	12 (46.2)	47 (48.5)	1.000
CVA (%)	2 (7.7)	24 (24.7)	0.064
TIA (%)	5 (19.2)	21 (21.6)	1.000
CAD (%)	4 (15.4)	35 (36.1)	0.057
CMP	0 (0)	7 (7.2)	0.343
HCMP (%)	0 (0)	6 (6.2)	
DCMP (%)	0 (0)	1 (1.0)	
COPD (%)	0 (0)	6 (6.2)	0.341
Alcohol (%)	2 (7.7)	9 (9.3)	1.000
Smoking (%)	1 (3.8)	12 (12.4)	0.297
CRF	5 (19.2)	10 (10.3)	0.308
CHA2DS2 VASc score	2.9±1.3	3.0±1.6	0.687
HAS BLED score	1.6±1.0	1.3±1.0	0.207
Medication			
PPI before eradication	17 (65.4)	60 (61.9)	0.608
Pantoprazole	5 (19.2)	14 (14.4)	
Omeprazole	4 (15.4)	23 (23.7)	
H. pylori eradiation			
3 medications	25 (96.1)	94 (96.9)	1.000
4 medications	1 (3.9)	3 (3.1)	0.583
Beta blocker	20 (76.9)	63 (64.9)	0.346
CCB	11 (42.3)	32 (33.0)	0.488
ARB & ACEi	5 (19.2)	20 (20.6)	1.000
Statin	15 (57.7)	51 (52.6)	0.665
Aspirin	10 (38.5)	26 (26.8)	0.331
NOAC	4 (15.4)	15 (15.5)	1.000
VKA	7 (26.9)	32 (33.0)	0.640

Note: Values are mean ± SD (range). DM indicates diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; DM, diabetes mellitus; HTN, essential hypertension; CVA, cerebrovascular accident; TIA, transient ischemic attack; CAD, coronary artery disease; CMP, cardiomyopathy; HCMP, hypertrophic cardiomyopathy; DCMP, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PPI, proton pump inhibitor; H.pylori, Helicobacter pylori; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor; NOAC, new oral anticoagulants; VKA, vitamin K antagonist.

3.2. Data Collection

After ECG and chest X-ray, cardiovascular status was evaluated for each patient using echocardiography, an exercise test, 24-h Holter recordings, and blood laboratory data from the initial visit, as determined by the attending physicians. From the database, the following information was collected: (1) patient data, including sex, age, height, and weight; (2) cardiovascular risk factors, including hypertension (use of antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure 90 mmHg on admission) and diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin ≥6.5%); (3) cardiovascular disease status, including structural heart disease, congestive heart failure, or a history of a disabling cerebral infarction or transient ischemic attack (TIA); and (4) use of medication. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

3.3. Esophagogastroduodenoscopy and Rapid Urease Test

All participants were asked to refrain from food and water intake for more than eight hours before esophagogastroduodenoscopy. We classified endoscopic findings as follows: gastric ulcers, duodenal ulcers, gastric and duodenal ulcers and others containing nodular gastritis, gastric erosion, and gastric polyp.

The presence of *H.pylori* infection was detected by the positivity of the rapid urease test (CLOtest®, Delta West, Bentley, WA, Australia) done during endoscopy. The antrum and corpus were the site of the gastric mucosal biopsy, and normal or near-normal gastric mucosa with little atrophy or intestinal metaplasia was acquired. The tissue samples were immersed in the rapid urea reagent. The rapid urease test was defined as positive when the reagent colour changed from yellow to red at least 12 hours later.

3.4. Definitions of H.pylori Treatment Failure

In our study, we defined *H.pylori* treatment failure with urea breath test (UBT) after initial treatment or endoscopic biopsy as follows:

1) Initial clarithromycin-based triple therapy failure

2) Change treatment regimen into 2nd or 3rd treatment including levofloxacin-based, metronidazole-based triple treatment or bismuth-based quadruple treatment.

3.5. Definitions of Atrial and Ventricular Arrhythmia

In the present study, paroxysmal AF at the initial visit was defined as sinus rhythm on ECG and previous diagnosis of paroxysmal AF by referring physicians. Patients whose AF was estimated to continue for ≥7 days after the initial visit were considered to have persistent AF originally and were excluded from the analysis. During the follow-up period, the onset of persistent AF was defined as the first time in which all ECGs indicated AF after ≥3 consecutive ECGs at intervals of ≥1 week after the initial examination, and chronic AF was defined as AF that was present for at least 6 months without intervening spontaneous episodes of sinus rhythm for which cardioversion was unsuccessful and subsequently not attempted [11]. When an ECG could not be obtained thrice during the period, the physicians made a clinical judgment regarding the onset time of AF progression. Atrial arrhythmia during follow-up was defined as atrial premature complex, atrial tachycardia, atrial flutter. Ventricular arrhythmia during follow-up was defined as ventricular premature complex, ventricular tachycardia, and ventricular fibrillation.

3.6. Clinical Endpoints

The primary end points were to evaluate the impact of *H.pylori* treatment failure on arrhythmic events including atrial and ventricular arrhythmias in patients with AF in the long-term follow-up. And *the secondary endpoint* was to evaluate the impact of neurologic events including painless weakness, hemiparesis, hemiplegia, disability of understanding, loss of vision, dysarthria according to *H.pylori* treatment failure in patients with AF during follow-up.

3.7. Transthoracic Echocardiography

All enrolled subjects underwent 2-dimensional transthoracic echocardiography (TTE). All examinations were performed using a commercially available Vivid 7™ (GE Medical System, Vingmed, Horten, Norway) ultrasound system. All recorded echocardiograms were measured and interpreted with clinical information blinded using a computerized off-line analysis station (Echopac™ 6.3.4; GE Medical System). All measurements were derived from 3 consecutive cardiac cycles and averaged. The Left Ventricular (LV) dimensions, wall thicknesses and left atrial dimensions (LAD) were determined in the parasternal long-axis view with the M-mode cursor positioned just beyond the mitral leaflet tips perpendicular to the long axis of the ventricle according to the recommendations of the American Society of Echocardiography [12]. The LV ejection fraction (LVEF) was obtained via the modified biplane Simpson method from the apical 4- and 2-chamber views.

3.8. Statistical Analysis

All continuous variables are expressed as either mean ± standard deviation (SD) or median (25th, 75th interquartile range), depending on the distribution. For continuous data, statistical differences were evaluated using Student's *t*-test or the Mann-Whitney *U* test, depending on the data distribution. Categorical variables are presented as frequencies (percent) and were analyzed using the chi-squared test. To determine whether any of the variables were independently related to arrhythmic and neurologic events, a multivariate analysis of variables with a *P*-value <0.05 in the univariate analysis was performed using linear logistic regression analysis. All correlations were calculated using Spearman's rank correlation test. All statistical analyses were conducted using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was set at $P < 0.05$ (two-sided).

3.9. Ethics Statement

This study was approved by the Institutional Review Board of Kosin University Gospel Hospital (IRB No. 2017-08-031).

Table 2: Baseline laboratory and echocardiographic findings in AF patients with *Helicobacter pylori* infection according to *Helicobacter pylori* treatment failure

Variables	*H.pylori* treatment failure group (n=26)	Successful *H.pylori* treatment group (n=97)	*P*-value
Laboratory findings			
WBC (10^3/uL)	9.2±7.6	7.2±3.3	0.062
Neutrophil (%)	63.6±18.7	63.6±15.0	0.995
Lymphocyte (%)	24.9±17.5	24.4±11.8	0.878
NLR	7.95±3.3	4.4±1.1	0.051
Bilirubin (mg/dL)	0.9±0.4	0.9±0.4	0.413
AST (mg/dL)	32.5±22.8	32.7±14.2	0.423
ALT (mg/dL)	31.0±19.8	28.4±22.0	0.393
Glucose (mg/dL)	106.8±78.6	95.7±63.4	0.802
Total cholesterol (mg/dL)	158.7±50.1	166.6±51.2	0.519
LDL (mg/dL)	89.8±45.0	94.5±46.2	0.697
HDL (mg/dL)	37.1±14.7	39.8±16.7	0.913
Triglyceride (mg/dL)	121.4±82.0	124.6±75.8	0.355
Creatinine (mg/dL)	1.4±1.3	1.2±0.8	0.624
CRP (mg/dL)	45.0±12.0	44.7±18.0	0.355
Echo parameters			
LVEF (%)	61.0±8.4	62.2±9.1	0.576
LVIDs (mm)	32.8±5.7	31.1±7.2	0.321
LVIDd (mm)	48.9±6.3	47.8±6.4	0.468
IVSD (mm)	12.0±2.3	12.2±2.7	0.741
LVPWD (mm)	10.3±1.4	10.8±1.8	0.276
LAVI (mL/m^2)	43.4±5.6	56.8±26.7	0.353
E velocity (cm/sec)	0.9±0.2	0.8±0.3	0.132
A velocity (cm/sec)	0.5±0.4	0.6±0.2	0.118
E/A	1.6±0.6	1.0±0.6	0.045
E′	0.08±0.03	0.07±0.02	0.186
A′	0.1±0.03	0.1±0.02	0.162
E/E′	13.1±7.5	12.5±6.7	0.713

Note: Values are mean ± SD (range). H.pylori, indicates Helicobacter pylori; WBC, white blood cell; NLR, neutrophil/lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, lower density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; LVIDd, left ventricular diastolic diameter; LVIDs, left ventricular systolic diameter; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LAD, left atrial diameter; LAVI, left atrial volume index; E, the peak mitral flow velocity of the early rapid filling wave; A, peak velocity of the late filling wave due to atrial contraction; E', early diastolic mitral annulus velocity; A', late diastolic mitral annulus velocity.

4. Results

The baseline demographics for both groups are listed in Table 1. Among 701 patients with AF, 322 (45.9%) patients had *H.pylori* infection. Of those, this study consisted of 123 subjects who underwent *H.pylori* eradication and we analyzed those data according to *H.pylori* treatment failure (26 subjects with *H.pylori* treatment failure and 97 subjects without treatment failure). Baseline characteristics were not statistically different in both groups. For the history of medications, there was also no difference in both groups.

In baseline laboratory findings, there was no difference in both groups. And there was also no difference of the echocardiographic findings in both (Table 2).

The clinical outcomes in patients with AF according to *H.pylori* treatment failure at 24-month follow-up are shown in (Table 3). All patients were monitored to evaluate total any event rates including re-admission, mortality, coronary events, arrhythmic events, neurologic events, GI symptoms, and bleeding events during follow-up. Arrhythmic events (P=0.034), neurologic events (P=0.033) and GI symptoms (P=0.04) were higher in *H.pylori* treatment failure compared to those without *H.pylori* treatment failure.

We also compared the baseline characteristics and clinical outcomes according to *H.pylori infection* in patients with AF. There was no difference of baseline characteristics except that more PPIs were used in *H.pylori* infection group compared without those (Supplemental Table 1). And there was no difference of arrhythmic events and neurologic events according to *H.pylori* infection in patients with AF. However, *H.pylori* infection group had higher incidence of GI symptoms and trend of higher bleeding events (Supplemental Table 2).

In total patients with AF and H. pylori infection, hypertension, smoke, *H.pylori* treatment failure, age, E/E' (the peak mitral flow velocity of the early rapid filling wave/early diastolic mitral annulus velocity), and CHA_2DS_2 VASc score were significantly associated with neurologic events including stroke, transient ischemic attack at 24-month follow-up in univariate analysis. In multivariate analysis, *H.pylori* treatment failure was independent risk factors for neurologic events (P=0.018) at 24-month follow-up (Table 4).

Table 3: Clinical outcomes in AF patients with *Helicobacter pylori* infection according to *Helicobacter pylori* treatment failure at 24-month follow-up.

Variables	H.pylori treatment failure group (n=26)	Successful H.pylori treatment group (n=97)	P-value
Follow-up duration (months)	24.7±9.2	24.4±10.9	0.898
Total any Events (%)	26 (100)	93 (95.9)	0.578
Re-admission (%)	16 (61.5)	57 (58.8)	0.827
Mortality (%)	0 (0)	5 (5.2)	0.583
Cardiac death (%)	0 (0)	3 (60)	
Coronary Events (%)	2 (7.7)	23 (23.7)	0.099
Arrhythmic Events (%)	9 (4.5)	6 (2.8)	0.034
AF or ATach (%)	9 (100)	5 (83.3)	
VT or VF (%)	0 (0)	1 (16.7)	
Neurologic Events (%)	13 (50)	26 (26.8)	0.033
Painless weakness & Hemiparesis	9 (69.2)	20 (76.9)	
Hemiplegia	1 (7.7)	2 (7.7)	
Disability of understanding	2 (15.4)	1 (3.8)	
Loss of vision	1 (7.7)	1 (3.8)	
Disarthria	0 (0)	2 (7.7)	
GI symptoms (%)	11 (42.3)	20 (20.6)	0.04
Abdominal pain & discomfort	8 (72.7)	18 (90.0)	
Diarrhea or loose stool	2 (18.2)	1 (5.0)	
Dysphagia or dyspepsia	1 (9.1)	1 (5.0)	
Bleeding Events (%)	5 (19.2)	10 (10.3)	0.308
GI bleeding (%)	4 (80.0)	8 (80.0)	
Non-GI bleeding (%)	1 (20.0)	2 (20.0)	

Note: Values are mean ± SD (range). H.pylori indicates Helicobacter pylori; AF, atrial fibrillation; ATach, atrial tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; GI, gastrointestine.

Table 4: Univariate and multivariate Cox analyses for neurologic events in AF patients with *Helicobacter pylori* infection at 24-month follow-up

	Univariate analysis		**Multivariate analysis**	
Variable. N (%)	OR (95% CI)	*P*-Value	OR (95% C.I)	*P*-Value
Hypertension	2.500 (1.140 – 5.481)	0.022		
Smoke	6.333 (0.993 – 10.005)	0.062		
H.pylori treatment failure	2.731 (1.121 – 6.653)	0.027	3.287 (1.227 – 8.805)	0.018
Age	1.047 (1.001 – 1.096)	0.046		
E/E'	1.059 (0.997 – 1.125)	0.052		
CHA2DS2 VASs score	1.348 (1.004 – 1.809)	0.047	1.324 (0.987 – 1.776)	0.061

Note: OR indicates odd ratio; CI, confidence interval; *H.pylori, Helicobacter pylori*; E/E', the peak mitral flow velocity of the early rapid filling wave/early diastolic mitral annulus velocity.

Supplemental Table 1: Baseline clinical characteristics in AF patients according to *Helicobacter pylori* infection

Variables	*H.pylori* infection group (n=322)	Non-*H.pylori* infection group (n=379)	*P*-value
Age (years)	71.1±10.4	71.9±13.0	0.578
Male (%)	205 (63.7)	260 (69.0)	0.148
CHF (%)	49 (15.1)	54 (14.4)	0.435
DM (%)	63 (19.6)	56 (14.8)	0.106
HTN (%)	178 (55.3)	195 (51.4)	0.109
CVA or TIA (%)	43 (13.4)	40 (10.6)	0.064
CAD (%)	51 (15.9)	56 (15.0)	0.197
CMP	10 (3.1)	9 (2.7)	0.216
HCMP (%)	10 (100)	5 (55.5)	
DCMP (%)	0 (0)	4 (44.5)	
COPD (%)	11 (3.4)	9 (2.4)	0.497
Alcohol (%)	78 (24.2)	98 (26.0)	0.517
Smoking (%)	44 (13.7)	51 (13.5)	1.000
CRF	23 (7.1)	24 (6.1)	0.457
CHA2DS2 VASc score	2.7±1.6	2.5±1.5	0.925
HAS BLED score	1.5±1.1	1.6±1.0	0.635
Medication			
PPI	244 (75.4)	0 (0)	<0.001
Beta blocker	129 (40.1)	136 (36.0)	0.346
CCB	100 (31.1)	113 (30.0)	0.488
ARB & ACEi	62 (19.3)	76 (20.1)	0.64
Statin	100 (31.1)	120 (31.8)	0.665
Aspirin	120 (37.3)	152 (40.1)	0.484
Anticoagulation Treatment	127 (33.1)	146 (38.5)	0.096
NOAC	80 (24.8)	145 (38.3)	<0.001
VKA	27 (8.3)	1 (0.2)	<0.001

Note: Values are mean ± SD (range). DM indicates diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; DM, diabetes mellitus; HTN, essential hypertension; CVA, cerebrovascular accident; TIA, transient ischemic attack; CAD, coronary artery disease; CMP, cardiomyopathy; HCMP, hypertrophic cardiomyopathy; DCMP, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; PPI, proton pump inhibitor; H.pylori, Helicobacter pylori; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin converting enzyme inhibitor; VKA, vitamin K antagonist; NOAC, new oral anticoagulants.

Supplemental Table 2: Clinical outcomes in AF patients according to *Helicobacter pylori* infection at 24-month follow-up

Variables	H.pylori infection group (n=322)	Non-H.pylori infection group (n=379)	P-value
Follow-up duration (months)	24.9±1.6	25.4±1.2	0.394
Re-admission (%)	100 (31.1)	111 (29.4)	0.278
Mortality (%)	7 (2.2)	5 (1.3)	0.401
Cardiac death (%)	3 (42.8)	3 (60)	
Coronary Events (%)	60 (18.6)	70 (18.5)	0.099
Arrhythmic Events (%)	42 (13.0)	47 (12.5)	0.079
AF or ATach (%)	41 (97.6)	40 (85.1)	
VT or VF (%)	1 (2.4)	7 (14.9)	
Neurologic Events (%)	53 (16.5)	57 (15.0)	0.068
Painless weakness & Hemiparesis	48 (90.6)	51 (89.4)	
Hemiplegia	2 (3.8)	2 (3.6)	
Disability of understanding	2 (3.8)	1 (1.7)	
Loss of vision	1 (1.8)	1 (1.7)	
Disarthria	0 (0)	2 (3.6)	
GI symptoms (%)	35 (10.9)	5 (1.3)	<0.001
Abdominal pain & discomfort	24 (70.2)	3 (60.0)	
Diarrhea or loose stool	10 (28.3)	1 (10.0)	
Dysphagia or dyspepsia	1 (1.5)	1 (10.0)	
Bleeding Events (%)	45 (14.0)	35 (9.3)	0.057
GI bleeding (%)	23 (51.0)	17 (48.0)	
Non-GI bleeding (%)	22 (49.0)	18 (52.0)	

Note: Values are mean ± SD (range). *H.pylori* indicates Helicobacter pylori; AF, atrial fibrillation; ATach, atrial tachycardia; VT, ventricular tachycardia; VF, ventricular fibrillation; GI, gastrointestine.

Kaplan-Meier analysis for event-free survivals from arrhythmic events including atrial fibrillation, atrial premature complex, atrial tachycardia, ventricular premature complex, and ventricular tachycardia according to *H.pylori* treatment failure (P=0.02; (Figure 2)) are lower in AF patients with *H.pylori* treatment failure compared with those without *H.pylori* treatment failure at 24-month follow-up.

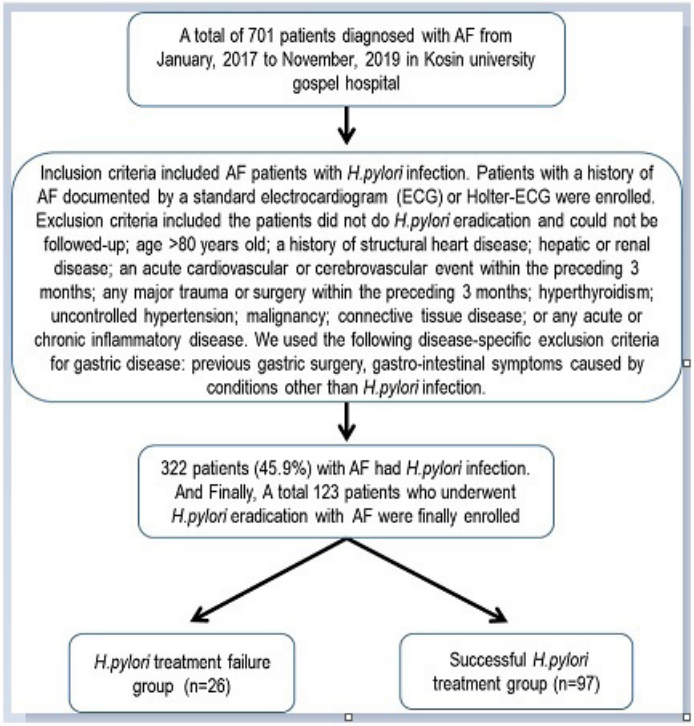

Figure 1: Scheme of Study

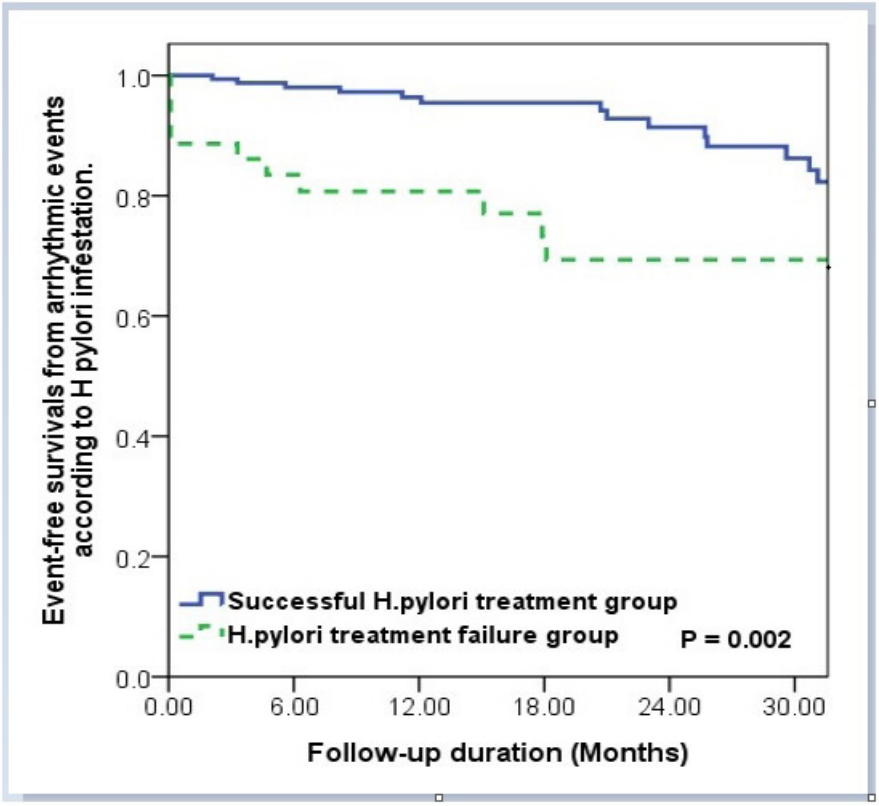

Figure 2: Kaplan-Meier analysis for event-free survivals from arrhythmic events including atrial fibrillation, atrial premature complex, atrial tachycardia, ventricular premature complex, and ventricular tachycardia according to *Helicobacter pylori* treatment failure

5. Discussion

The link between inflammation and CVDs is complex and many publications have provided support to the hypothesis of a causal association [13, 14]. And several studies have shown that there are many studies have indicated that inflammation might play a significant role in the initiation, maintenance, and perpetuation of AF Inflammation, although whether the inflammation is the inducement or the secondary outcome of AF has not been determined [15-18].

Previous study reported that periodontitis, as representative of chronic inflammation, induces a peripheral inflammatory and immune response, reflected in elevated C-reactive protein (CRP) [19]. Some researchers have shown that CRP is one of the independent risk factors of AF, baseline CRP level can predict the risk of AF in the future. And elevated inflammation cytokines contribute to the pathogenesis of AF. This may be due to genetic reasons and may also apply to chronic low grade infections [20]. And other study also reported that highly significant link between AF and *H.pylori* and confirmed that CRP is a good marker for the inflammatory process [7]. However, in our study, there was no difference of CRP level in both groups.

de Boer SP et al [21]. reported that once the tissue damage with bacterial infection is confirmed in the myocardium, it may be responsible for the substrate of arrhythmia. And if patients are infected with *H.pylori*, their bodies will produce H+/K+-ATP enzyme autoantibodies that bind to the H+/K+-ATP enzyme and then damage the atrial cell pump that makes the ion environment imbalanced and the depolarization delayed, which will trigger attack of AF [22]. And chronic inflammation and autonomic imbalance have been proposed as plausible pathophysiological mechanisms of AF [20, 23].

On the basis of the following facts, we hypothesized that *H.pylori* may be involved in the atrial inflammation resulting in AF. At first, *H. pylori* infection impairs endothelial function. And *H.pylori* treatment failure is associated with oxidative stress both locally and peripherally (serum). Endothelial dysfunction and oxidative stress are both involved in the pathophysiology of AF. CRP down-regulates endothelial nitric oxide (NO) synthase transcription in endothelial cells and destabilizes endothelial nitric oxide synthase messenger RNA, resulting in decreased NO release [24]. In our study, all the patients enrolled were AF patients and, we evaluated the impact of *H.pylori* treatment failure, suggestive of uncontrolled local chronic inflammation on clinical outcomes. And event-free survivals from arrhythmic events (P=0.02; Figure 2) are lower in patients with *H.pylori* treatment failure compared with those without *H.pylori* treatment failure.

However, unfortunately, there are no data currently on ways to risk-stratify these patients according to presence of *H.pylori* treatment failure in this study, because of small number of patients.

Based on the predictors of bleeding, using the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or

predisposition, labile International Normalized Ratio (INR), elderly (>65), drugs/alcohol concomitantly) score [25], there was trend of higher HAS-BLED score in *H.pylori* treatment failure group compared with those without treatment failure in our study. However, there was no difference of the incidences of bleeding events including GI and non-GI bleeding (P=0.308) according to *H.pylori* treatment failure at 24-month clinical follow-up.

In our study, it is of interest that although, there was no difference of the incidences of total any events including thromboembolic events, bleeding events, re-hospitalizations and mortality in both groups, the incidences of arrhythmic events (P<0.034) and neurologic events (P<0.033) were higher in AF patients with *H.pylori* treatment failure compared with those without *H.pylori* treatment failure.

This is the first study to evaluate the impact of *H.pylori* treatment failure on long-term clinical outcomes in patients with AF. There was no difference of the incidences of PeAF (P=0.563) in both groups. However, at 24-month follow-up, arrhythmic events (P=0.034) including atrial fibrillation, atrial tachycardia and atrial flutter were also higher in *H.pylori* treatment failure group, which is consistent with a previous study [26, 27] that both oxidants and inflammation play an important role in the initiation and maintenance of AF.

And, *H.pylori* treatment failure was associated with higher incidence of neurologic events (P=0.033) in the long-term follow-up. In our total patients with AF and *H. pylori* infection, various factors were associated with neurologic events, including hypertension, smoke, *H. pylori* treatment failure, age, E/E' on TTE, and CHA_2DS_2 VASc score. In multivariate analysis, *H. pylori* treatment failure and CHA_2DS_2 VASc score were independent predictors for neurologic events in AF patients with *H. pylori* infection at 24-month clinical follow-up (Table 4).

Further prospective studies are needed to determine if a true causal mechanism exists between *H.pylori* treatment failure and AF, as well as between *H.pylori* treatment failure and neurologic events. In addition, the response of AF related symptoms to *H.pylori* treatment and the potential for *H.pylori* treatment to reduce the development of AF and, to access whether the mechanisms is dependent on a specific subtype of AF merits further investigation.

There are some limitations to our study. First, this study was a single-center, retrospective small numbered study derived from real world practice with inherent limitations. Hence the results of our study should be considered as hypothesis generating, and future prospective studies are warranted to confirm our results. Second, asymptomatic episodes of AF may not have been recognized because AF recurrence was based on clinical symptoms and ambulatory monitoring for a short period. Third, patients with potentially reversible causes were excluded from the study. Therefore, the results of this study cannot be transferred to other patient populations with first detected PAF. Fourth, the patients with *H.pylori* treatment failure could not be treated continuously. Therefore, there was limitation to generate the direct correlation of *H.pylori* treatment failure and treatment with clinical outcomes. However, chronic inflammation and autonomic imbalance have been proposed as plausible pathophysiological mechanisms of AF. And this study has presents a new vision for the *H.pylori* treatment failure focusing on the arrhythmogenic and neurologic effects beyond local chronic inflammation.

6. Conclusion

The *H.pylori* treatment failure was associated with higher incidence of arrhythmic events and neurologic events in AF patients with *H. pylori* in the long-term follow-up, suggesting more intensive medical therapy with close clinical follow-up will be required. And the reason of higher incidence of neurologic events in *H.pylori* treatment failure group requires further study.

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