

# World Journal of *Gastroenterology*

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**OPINION REVIEW**

- 2699** Which factors determine exocrine pancreatic dysfunction in diabetes mellitus?  
*Altay M*

**REVIEW**

- 2706** Proton pump inhibitors and dysbiosis: Current knowledge and aspects to be clarified  
*Bruno G, Zaccari P, Rocco G, Scalese G, Panetta C, Porowska B, Pontone S, Severi C*
- 2720** Diagnosis and therapeutic strategies for small bowel vascular lesions  
*Sakai E, Ohata K, Nakajima A, Matsuhashi N*

**MINIREVIEWS**

- 2734** Advanced diagnostics for pancreatic cysts: Confocal endomicroscopy and molecular analysis  
*Durkin C, Krishna SG*
- 2743** Long-lasting discussion: Adverse effects of intraoperative blood loss and allogeneic transfusion on prognosis of patients with gastric cancer  
*Nakanishi K, Kanda M, Kodera Y*

**ORIGINAL ARTICLE****Basic Study**

- 2752** MiR-34a overexpression enhances the inhibitory effect of doxorubicin on HepG2 cells  
*Zheng SZ, Sun P, Wang JP, Liu Y, Gong W, Liu J*
- 2763** Long noncoding RNA HOXA11-AS promotes gastric cancer cell proliferation and invasion *via* SRSF1 and functions as a biomarker in gastric cancer  
*Liu Y, Zhang YM, Ma FB, Pan SR, Liu BZ*
- 2776** Sp1 contributes to overexpression of stanniocalcin 2 through regulation of promoter activity in colon adenocarcinoma  
*Li JB, Liu ZX, Zhang R, Ma SP, Lin T, Li YX, Yang SH, Zhang WC, Wang YP*

**Retrospective Study**

- 2788** Increased risk of atrial fibrillation in patients with inflammatory bowel disease: A nationwide population-based study  
*Choi YJ, Choi EK, Han KD, Park J, Moon I, Lee E, Choe WS, Lee SR, Cha MJ, Lim WH, Oh S*

**Clinical Trials Study**

- 2799** Effects of early enteral nutrition on Th17/Treg cells and IL-23/IL-17 in septic patients  
*Sun JK, Zhang WH, Chen WX, Wang X, Mu XW*

**SYSTEMATIC REVIEWS**

- 2809** Autoimmune hepatitis treatment in the elderly: A systematic review  
*Durazzo M, Lupi G, Scandella M, Ferro A, Gruden G*

**META-ANALYSIS**

- 2819** Mini-invasive *vs* open resection of colorectal cancer and liver metastases: A meta-analysis  
*Ye SP, Qiu H, Liao SJ, Ai JH, Shi J*

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## Retrospective Study

# Increased risk of atrial fibrillation in patients with inflammatory bowel disease: A nationwide population-based study

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## Abstract

### BACKGROUND

Inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal tract, could play a role in the pathophysiology of atrial fibrillation (AF).

### AIM

To investigate the association between IBD and AF development.

### METHODS

We performed a population-based cohort study using records in the Korean National Health Insurance Services database between 2010 and 2014. A total of 37696 patients with IBD (12349 with Crohn's disease and 25397 with ulcerative colitis) were identified. The incidence rate of newly diagnosed AF in patients with IBD was compared with that in a 3 times larger cohort of 113088 age- and sex-matched controls without IBD.

### RESULTS

During  $4.9 \pm 1.3$  years of follow-up, 1120 patients newly diagnosed with AF (348 in the IBD group and 772 in controls) were identified. After adjustments using multivariable Cox proportional hazards, patients with IBD were at a 36% [95% confidence interval (CI) 20%-54%] higher risk of AF than controls. The association between IBD and the development of AF was stronger in younger than in older

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patients. Patients without cardiovascular risk factors showed a higher risk of AF primarily. Additionally, patients receiving immunomodulators [Hazard ratio (HR) 1.46, 95%CI 1.31-1.89], systemic corticosteroids (HR 1.37, 95%CI 1.10-1.71), or biologics agents (HR 2.38, 95%CI 1.51-3.75) were at higher risk of AF than patients without them.

## CONCLUSION

IBD significantly increased the risk of AF, and the impact of IBD on developing AF was in patients with moderate to severe disease.

**Key words:** Atrial fibrillation; Inflammatory bowel disease; Colitis, Ulcerative; Crohn's disease

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**Core tip:** Inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal tract, was strongly associated with an increased risk of atrial fibrillation (AF). Both Crohn's disease (CD) and ulcerative colitis (UC) increase the risk of AF, with a higher risk in patients with CD than UC. And the impact of IBD on developing AF was stronger in patients receiving immunomodulators, systemic corticosteroids or biologics agents, which are prescribed for moderate-to-severe disease than patients without them. Therefore, physicians need to consider screening for AF in patients with IBD, particularly those who use more potent therapies.

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## INTRODUCTION

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic progressive inflammatory disease that can affect the mucosa in any part of the gastrointestinal tract<sup>[1]</sup>. IBD is associated with an increased risk of cardiovascular diseases such as stroke, myocardial infarction, and early atherosclerosis with increased intimal thickness of the common carotid artery<sup>[2,3]</sup>. High levels of C-reactive protein (CRP), a major marker reflecting activity and severity of inflammation in IBD, are also associated with atherogenesis and atherosclerotic cardiovascular disease<sup>[4-6]</sup>.

Atrial fibrillation (AF) is the most common arrhythmia observed in clinical practice. Recently, inflammation is being recognized as a pathogenic contributor to the development of AF<sup>[7]</sup>. Previous research has shown a significant association between serum inflammatory mediators such as CRP, tumor necrosis factor- $\alpha$ , interleukin (IL)-2, IL-6, and IL-8, and the development and persistence of AF<sup>[8,9]</sup>. Several cardiovascular disorders, notably coronary atherosclerosis, are associated with inflammation, and cytokines are known to affect plaque rupture and thrombus formation resulting in myocardial infarction<sup>[10]</sup>. However, it is unclear whether autoimmune-mediated inflammation contributes to the development and persistence of AF.

Considering that pathogenesis of AF is being increasingly linked to systemic inflammation, IBD may a potential risk factor for AF. However, there is limited information regarding the association between the risk of development of AF and the presence of IBD. Therefore, we performed a nationwide population-based study to investigate the association between IBD and the development of AF, including in young individuals and those without cardiovascular risk factors.

## MATERIALS AND METHODS

### Data sources

Most Koreans (97.2%, approximately 50 million individuals) are enrolled in the mandatory National Health Insurance Service (NHIS) provided by the Korean government. This database includes all healthcare utilization-related information, including in-patient and outpatient services, diagnoses, and prescriptions recorded for reimbursement by the Health Insurance and Review Agency.

Additionally, a registration program for Rare Intractable Diseases (RID), a part of the NHIS, offers special support to patients with RID including IBD, since 2006. The diagnostic accuracy of IBD based on the RID registry was 95.5%-100% and 92.5%-95.5% in terms of sensitivity and specificity, respectively, as assessed by a previous epidemiological study<sup>[11]</sup>. This study used data from the NHIS and the RID program database, which stores diagnoses in the form of the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

### Study population

We identified patients diagnosed with IBD between January 1, 2010 and December 31, 2014 from the NHIS database (ICD-10-CM codes: K50.0-50.9 for CD and K51.0-51.9 for UC) and confirmed these diagnoses based on special codes (V130 for CD and V131 for UC) provided by the RID program. The special codes of the RID program are assigned to a patient with IBD who meets the following diagnostic criteria determined by certified physicians: (1) Diarrhea and abdominal pain lasting more than 16 wk; (2) Endoscopic features corresponding to IBD; and (3) Histopathological confirmation based on endoscopic biopsy. We excluded patients who had been diagnosed with AF prior to or within a month from the initial diagnosis of IBD.

### Endpoint

The primary endpoint was new-onset non-valvular AF, that occurred during the follow-up period. AF was defined using ICD-10-CM codes (I480-I484, I489), which were registered by the physicians responsible for diagnosis. To ensure diagnostic accuracy and exclude patients with transient AF, patients with AF were defined as those with AF, which have been diagnosed with discharge, or had been confirmed more than twice in an outpatient clinic. In addition, to include only non-valvular AF, patients diagnosed with mitral stenosis (I050, I052, I059) or those with mechanical heart valves (Z952-Z954) were and excluded from the analysis. The definition of AF was validated in previous nationwide studies<sup>[12-14]</sup>.

### Covariates

Baseline comorbidities and medication history were obtained from the medical claims data in the NHIS database by ICD-10-CM and prescription codes. We investigated the comorbidities of patients when they were first enrolled in the RID registry due to IBD. Baseline comorbidities included hypertension, diabetes mellitus (DM), dyslipidemia, ischemic heart disease, venous thromboembolism, end-stage renal disease (ESRD) and hyperthyroidism. Definitions of covariates were verified from previous papers and have been summarized in [S1 Table](#)<sup>[12,13]</sup>. Low income was defined as participation in the medical aid program or a monthly income corresponding to the lowest 25% of the total population. Cities with a population > 1 million were considered urban areas.

Of note, 5-aminosalicylic acid (5-ASA) is the preferred primary drug used to treat mild-to-moderate IBD in Asians, while drugs such as immunomodulators (azathioprine, methotrexate, cyclosporine, and tacrolimus) or biological agents (infliximab, adalimumab, and golimumab) are recommended as first- or second-line therapy for moderate-to-severe IBD<sup>[15]</sup>. Therefore, we estimated the severity of IBD based on a previous report of describing treatment of IBD; those receiving systemic corticosteroids in combination with 5-ASA, immunomodulators (azathioprine, methotrexate, cyclosporine, and tacrolimus) or biological agents (infliximab, adalimumab, and golimumab) were classified as having moderate-to-severe IBD in this study<sup>[16]</sup>.

### Statistical analysis

Demographic and baseline clinical characteristics are reported as means with standard deviation (SD) for normally distributed continuous variables and as numbers with percentages for categorical variables. The independent samples *t*-test was used for continuous variables and the chi-square test for categorical variables for intergroup comparisons.

The incidence rates (IR) of AF are presented per 1000 person-years and were calculated as the number of patients with AF divided by the total population for each year because the total population changes every year owing to death and emigration. The cumulative IR of AF in patients with IBD and matched control group were compared using Kaplan-Meier censoring estimates and the log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to evaluate

the association between IBD and the risk of development of AF. Adjusted hazard ratios (HR) have been presented with a 95% confidence interval (CI) and adjusted for known risk factors of AF and IBD, including age, sex, place, income, DM, hypertension, dyslipidemia, stroke, ischemic heart disease, venous thromboembolism, and ESRD. A two-sided  $P$  value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using the SAS software version 9.3 (SAS Institute, Cary, NC, United States) and the SPSS software version 23.0 (SPSS Inc., Chicago, IL, United States).

### **Ethical considerations**

The NHIS database is an open database with patient information anonymized to protect privacy. This information is accessible to all researchers whose study protocols have been approved by the official review committee. Our study was performed in accordance with the Declaration of Helsinki.

## **RESULTS**

### **Baseline characteristics**

We enrolled 37696 patients with IBD (12349 patients with CD and 25347 patients with UC). We selected a 3-fold larger group of age and sex-matched individuals without IBD (total 113088 patients: 37047 matched with patients with CD and 76041 matched with patients with UC) as the control group.

Baseline clinical characteristics of patients have been summarized in [Table 1](#). The percentage of patients with IBD was greater in urban than in rural areas (50.4 *vs* 46.8%, respectively,  $P < 0.001$ ). Additionally, the percentage of patients with IBD showed a higher income level (23.3 *vs* 19.8% respectively,  $P < 0.001$ ). Prevalence of DM, hypertension, and dyslipidemia was lower in patients with IBD than in the control group, whereas prevalence of ischemic heart disease, venous thromboembolism, ESRD, and hyperthyroidism was higher in those with IBD than in the control group ( $P < 0.001$  for all comparisons except dyslipidemia). Among patients with IBD, those with CD were younger than those with UC ( $30.4 \pm 14.2$  years *vs*  $43.8 \pm 15.6$  years), and the former group members more frequently received immunomodulators (55.8 *vs* 13.0%), systemic corticosteroid (58.64 *vs* 56.67%) and biological agents (13.3 *vs* 1.7%).

### **Primary endpoint: New onset AF**

During the mean follow-up of  $4.87 \pm 1.28$  years, we identified 1120 cases of incident AF (IBD group: 348; control group: 772), with a crude IR of 1.90 per 1000 person-years in patients with IBD and 1.40 in matched controls. The incidence of AF was higher in the IBD group than in the control group ( $P < 0.001$  by the log-rank test, [Figure 1](#)). After adjustment for potential confounding factors, IBD was significantly associated with the incidence of AF (HR 1.36, 95%CI 1.20-1.55, [Table 2](#)). Within the IBD group, AF was significantly associated with both CD and UC compared to matched non-IBD subgroups (CD: HR 1.91, 95%CI 1.47-2.49; UC: HR 1.24, 95%CI 1.07-1.43, [Table 2](#)).

Additionally, patients who received medications (immunomodulators, systemic corticosteroid, and biological agents) for moderate-to-severe IBD showed a higher risk of AF than those who did not receive such medications ([Table 3](#)). The highest risk of AF was observed in the subgroup receiving biological agents (HR 2.37, 95%CI 1.50-3.74) compared with those receiving immunomodulators (HR 1.45, 95%CI 1.13-1.88) and systemic corticosteroids (HR 1.37, 95%CI 1.10-1.71).

### **Subgroup analysis performed to assess the risk of atrial fibrillation in patients with inflammatory bowel disease**

Both patients with UC and CD subgroups showed an increased risk of AF ([Figure 2](#)). Patients with IBD aged below 45 years showed a higher risk of AF than those belonging to the control group, and both UC and CD groups showed similar trend in age subgroups. In contrast, no significant difference was observed in those aged more than or equal to 45 years. Also, the risk of AF development was not significantly different between men and women. The association between IBD and AF was weaker in subgroups with well-known cardiovascular risk factors (hypertension, DM, and dyslipidemia) than in subgroups without such risk factors ( $P < 0.001$ ). These differences were statistically more significant in patients with CD ( $P < 0.001$ ) than in those with UC ( $P = 0.07$ ).

## **DISCUSSION**

**Table 1** Baseline characteristics of the study population

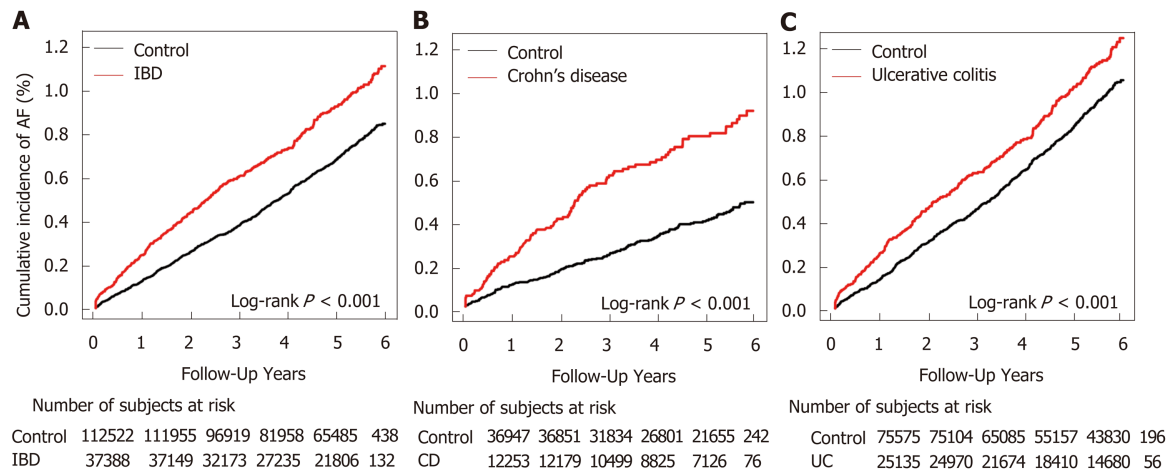
Variable, n (%)	IBD group	Control group	P value	CD group	Control group	P value	UC group	Control group	P value
Number	37696	113088		12349	37047		25347	76041	
Men	22985 (61.0)	68955 (61.0)	1	8679 (70.3)	26037 (70.3)	1	14306 (56.4)	42918 (56.4)	1
Age (mean $\pm$ SD, yr)	39.4 $\pm$ 16.4	39.42 $\pm$ 16.4	1	30.4 $\pm$ 14.2	30.36 $\pm$ 14.23	1	43.8 $\pm$ 15.6	43.8 $\pm$ 15.6	1
< 30	12184 (32.3)	36552 (32.3)	1	7080 (57.3)	21240 (57.3)	1	5104 (20.1)	15312 (20.1)	1
30-44	11459 (30.4)	34377 (30.4)		3354 (27.2)	10062 (27.2)		8105 (32.0)	24315 (32.0)	
45-59	9158 (24.3)	27474 (24.3)		1292 (10.5)	3876 (10.5)		7866 (31.0)	23598 (31.0)	
$\geq$ 60	4895 (13.0)	14685 (13.0)		623 (5.0)	1869 (5.0)		4272 (16.9)	12816 (16.9)	
Urban residence	19006 (50.4)	52913 (46.8)	< 0.001	6317 (51.2)	17416 (47.0)	< 0.001	12689 (50.1)	35497 (46.7)	< 0.001
Low income	7444 (19.8)	26338 (23.3)	< 0.001	2609 (21.1)	8535 (23.0)	< 0.001	4835 (19.1)	17803 (23.4)	< 0.001
Comorbidities									
Diabetes mellitus	1483 (3.9)	5306 (4.7)	< 0.001	260 (2.1)	782 (2.1)	0.97	1223 (4.8)	4524 (6.0)	< 0.001
Hypertension	4098 (10.9)	13732 (12.1)	< 0.001	595 (4.8)	2097 (5.7)	0.000	3503 (13.8)	11635 (15.3)	< 0.001
Dyslipidemia	2527 (6.7)	7929 (7.0)	0.042	361 (2.9)	1250 (3.4)	0.015	2166 (8.6)	6679 (8.8)	0.245
IHD	1557 (4.1)	3559 (3.2)	< 0.001	348 (2.8)	552 (1.5)	< 0.001	1209 (4.8)	3007 (4.0)	< 0.001
Thromboembolism	115 (0.3)	236 (0.2)	< 0.001	37 (0.3)	34 (0.1)	< 0.001	78 (0.3)	202 (0.3)	0.269
ESRD	107 (0.3)	180 (0.2)	< 0.001	48 (0.4)	40 (0.1)	< 0.001	59 (0.2)	140 (0.2)	0.130
Hyperthyroidism	750 (2.0)	1248 (1.1)	< 0.001	224 (1.8)	264 (0.7)	< 0.001	526 (2.1)	984 (1.3)	< 0.001
Medications									
Immunomodulators	10199 (27.1)	0	< 0.001	6895 (55.8)	0	< 0.001	3304 (13.0)	0	< 0.001
Steroids	21606 (57.3)	0	< 0.001	7241 (58.6)	0	< 0.001	14365 (56.7)	0	< 0.001
Biological agents	2075 (5.5)	0	< 0.001	1641 (13.3)	0	< 0.001	434 (1.7)	0	< 0.001
Follow-up duration (yr)	4.9 $\pm$ 1.3	4.9 $\pm$ 1.3		4.9 $\pm$ 1.3	4.8 $\pm$ 1.3		4.9 $\pm$ 1.3	4.9 $\pm$ 1.3	

Values have been expressed as mean  $\pm$  SD or number of patients (%) as relevant. Follow-up duration is expressed in years. CD: Crohn's disease; ESRD: End-stage renal disease; IBD: Inflammatory bowel disease; IHD: Ischemic heart disease; SD: Standard deviation; UC: Ulcerative colitis.

This study is the first large population-based cohort study to investigate the association between IBD and the incidence of AF in Asians. The primary findings of our large population-based cohort study are: (1) IBD was associated with an increased risk of AF development; (2) both CD and UC increase the risk of AF, with a higher risk in patients with CD than UC; (3) patients receiving immunomodulators, systemic corticosteroids, and/or biological agents showed a higher risk of AF; and (4) the relative risk of IBD for the development of AF was particularly high in younger patients (aged below 45 years) and in those without cardiovascular risk factors.

Several previous studies have demonstrated the relationship between IBD and AF<sup>[17,18]</sup>. A small-scale study comprising 141 IBD cases showed that the prevalence of AF was higher across all age groups in patients with IBD than in the control group<sup>[17]</sup>. In a Danish nationwide study, 24499 patients with new-onset IBD were identified and compared with age- and sex-matched controls<sup>[18]</sup>. Overall IBD-associated risk of AF was increased by 26% (95%CI, 16%-36%). We observed that the risk of AF was higher in patients with IBD, which was in agreement with previous studies. Interestingly, the absolute risk of AF in patients with CD was higher than that in patients with UC (HR for CD and UC being 1.92 and 1.23, respectively).

There is a reasonable body of evidence to support the pathophysiological features between IBD and the development of AF. Systemic inflammation is known to be a significant contributor to the development of AF<sup>[7-9,19]</sup>. Recent studies performed in patients with IBD have demonstrated that atrial electromechanical conduction time is prolonged and that structural and electrophysiological changes occurring in atrial tissues affect left atrial electromechanical function<sup>[20,21]</sup>. Several previous studies have suggested that systemic inflammation is linked to various pathological processes such as oxidative stress, apoptosis, and fibrosis of cardiomyocytes, all of which lead to structural and electrical remodeling of the atria, promoting the development and persistence of AF<sup>[19,22,23]</sup>. Moreover, increases in the level of serum inflammatory markers, such as CRP and IL-6, were observed in patient with AF and IBD, especially CD<sup>[8,24]</sup>. Chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis are known to increase the risk of development of AF<sup>[25-27]</sup>.



**Figure 1** Kaplan–Meier survival curves for cumulative incidence of atrial fibrillation. Cumulative incidence was defined as the probability of new-onset atrial fibrillation during follow-up. A: Comparison between inflammatory bowel disease (IBD) group and control group; B: Comparison between Crohn's disease group and control group; C: Comparison between ulcerative colitis group and non-IBD group. CD: Crohn's disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; AF: Atrial fibrillation.

The positive relationship between the severity of IBD and the incidence of AF accounts for the association between the two diseases. In a Danish nationwide study, IBD was classified as flare-up, persistent disease, and remission based on disease activity, and the association between disease activity of IBD and the development of AF were evaluated<sup>[18]</sup>. Incidence of AF increased during IBD flare-ups and periods of persistent disease, but not during periods of remission<sup>[18]</sup>. Particular medication such as immunomodulators, systemic corticosteroid, and biological agents are recommended as first or second-line therapy for moderate-to-severe IBD, and 5-ASA is commonly used for the initial treatment of mild IBD<sup>[28–30]</sup>. Therefore, in large population-based studies with difficulty in obtaining clinical symptoms and sign, it is preferable to assess the severity of IBD using medical history instead of a clinical scoring system. In this study, patients with IBD who received these aforementioned agents may have a moderate-to-severe disease, and have shown a higher risk of AF. This suggests that patients with moderate-to-severe IBD have a higher risk of AF than those with mild IBD.

Advancing age is a well-known risk factor for AF<sup>[31]</sup>. Surprisingly, however, in our study, the association between IBD to the development of AF gradually weakened with increasing age. Additionally, the association between IBD and AF was more significant in patients without cardiovascular risk factors including DM, hypertension, and dyslipidemia.

Several studies performed in Western population cohorts have reported a bimodal distribution of the incidence of IBD with a peak at a younger age (20–30 years) for CD, a later peak (30–40 years) for UC, and a lower second peak at an older age (60–70 years) for both diseases<sup>[32]</sup>. In contrast, in Asians including Koreans, the incidence of CD showed a peak in patients aged below 20 years and steadily decreased after that, whereas the incidence of UC was observed to plateau in patients aged 25–69 years<sup>[11]</sup>. In the present study, the prevalence of AF showed a peak at a younger age, and the association between IBD and the development of AF gradually became weaker with increasing age. These findings suggested that systemic inflammatory disease is one of the mechanisms contributing to the development of AF different from classic risk factors.

The incidence of IBD in Korea (2.9–3.6 per 100000 for CD and 4.2–5.1 per 100000 for UC) was the highest in East Asia, followed by that in Japan, China, and Hong Kong from 2006 to 2012<sup>[33,34]</sup>. The prevalence of IBD in Korea is steadily rising, and IBD-related healthcare costs are showing a significant increase<sup>[35]</sup>. This study is the first to demonstrate that IBD is an independent risk factor for the development of AF in Asians.

As well as having the increased IR with age, Asians have a generally higher incidence of AF-related risks of stroke and intracranial bleeding, compared with non-Asians<sup>[36,37]</sup>. The incidence rate ratio (IRR) of AF in patients with IBD in this Korean population-based cohort was not significantly different to that in patients with IBD in the previously described Danish population-based cohort (Korea: IRR 1.36, 95% CI

**Table 2 Risk of atrial fibrillation in patients with inflammatory bowel disease**

	IBD group <i>n</i> = 37696	Control group <i>n</i> = 113088	CD group <i>n</i> = 12349	Control group <i>n</i> = 37047	UC group <i>n</i> = 25347	Control group <i>n</i> = 76041
New-onset AF	348	772	95	145	253	627
Incidence rate <sup>1</sup>	1.90	1.40	1.59	0.80	2.05	1.69
Adjusted HR <sup>2</sup>	1.36	1 (reference)	1.91	1 (reference)	1.24	1 (reference)
95%CI	1.20–1.55		1.47–2.49		1.07–1.43	

<sup>1</sup>Incidence rates have been calculated per 1000 patient-years within a population aged > 20 years who had not previously been diagnosed with atrial fibrillation;

<sup>2</sup>Adjusted with respect to age, sex, place, income, diabetes mellitus, hypertension, dyslipidemia, previous history of stroke, ischemic heart disease, venous thromboembolism, and end-stage renal disease. AF: Atrial fibrillation; CI: Confidence interval; CD: Crohn's disease; HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

1.20–1.55; Denmark: IRR 1.26, 95%CI 1.16–1.36) after fully adjusting for risk factors of AF<sup>[18]</sup>. The lower prevalence of AF in Asians (approximately 1%) than that observed in non-Asians (approximately 2%) suggests that the risk of incident AF in patients with IBD is similar in Asians and non-Asians<sup>[12,38]</sup>. Our findings add new evidence that IBD, a systemic inflammatory disease, is associated with an increased prevalence of AF in Asians.

### Limitations

The primary limitation of this study is the observational population-based retrospective design, which does not permit specific determination of the severity of IBD. Therefore, detailed information regarding the severity, extent, location, and activity of the IBD, laboratory data, and duration of treatment modalities were not available in our study. Although we used certain prescriptions as a surrogate measure of moderate-to-severe IBD, there is still the limitation in discriminating between those with moderate-to-severe disease and those with remission.

Additionally, the role of confounders including general condition, presence of malnutrition, smoking, and other significant comorbidities such as cardiomyopathy, heart failure, and cancer could not be accurately evaluated in patients. However, this study used the certified database to identify patients diagnosed with IBD and to retrieve their medication history. The database of the RID program includes the complete medical history of patients, which is required to provide special financial support, thereby minimizing the possibility of inaccuracies in prescription data.

Secondly, the definitions of diseases were determined using ICD-10-CM codes of claims data from the NHIS database. Misclassification is a potential bias when using diagnostic codes. Also, when determining cases of IBD, the ascertainment bias could be induced depending on the patient's residences. Additionally, the detail information on AF subtypes such as paroxysmal, persistent, permanent, and perioperative AF could not be accurately identified in our database.

Moreover, we could not obtain accurate information regarding the time interval between the diagnosis of IBD and the onset of AF. However, patients were followed-up for more than 4 years, which is sufficient to detect AF caused by IBD. We excluded patients demonstrating new-onset AF within a year of being diagnosed with IBD to reduce the chance of coincidental occurrence of the disease.

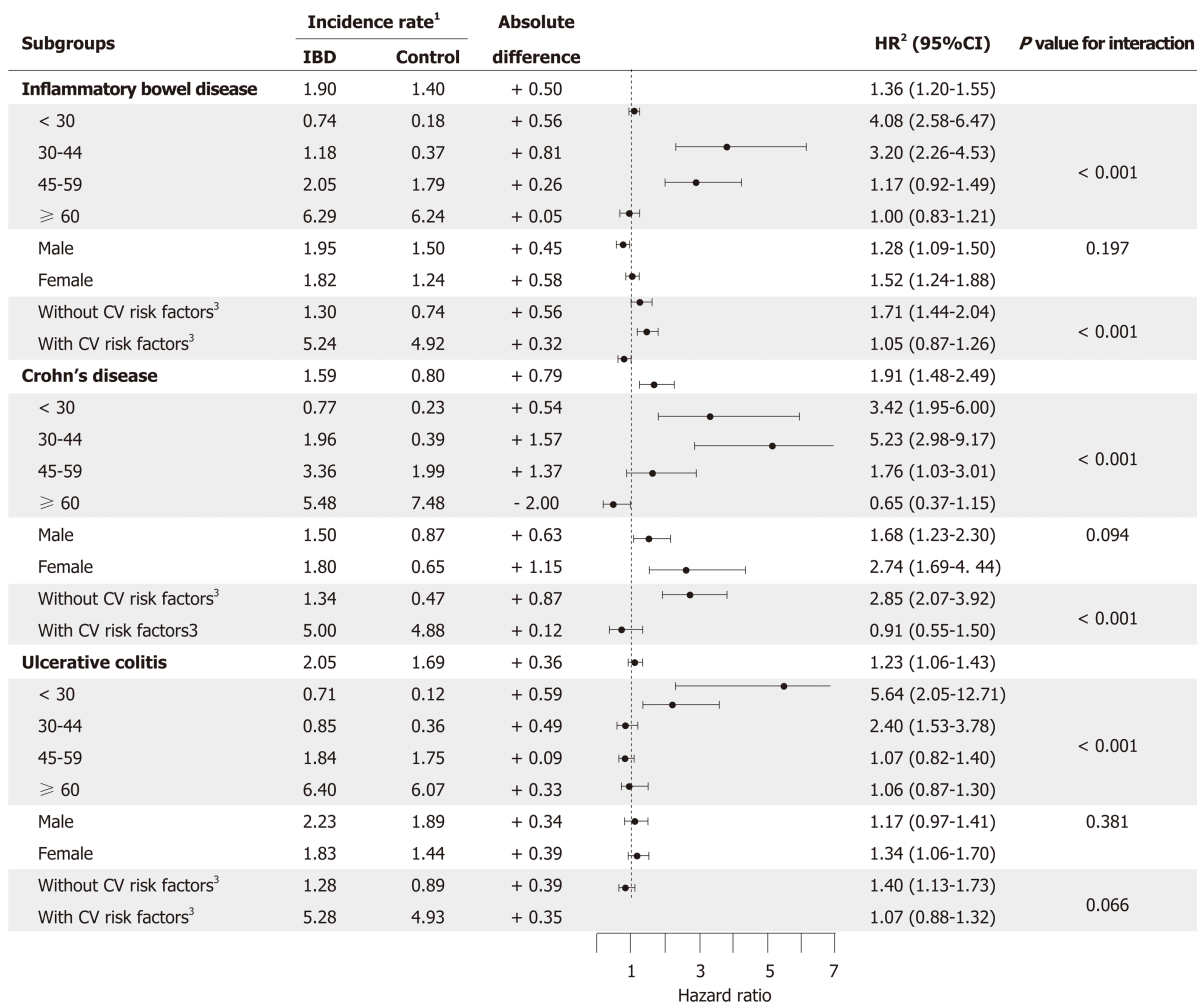
In conclusions, the key finding of our study is that IBD was associated with an increased risk of AF. Furthermore, IBD-associated AF was more common in younger patients with less comorbidities. Therefore, although IBD is a common disease in young people, we need to consider screening for AF, as timely intervention can reduce both morbidity and mortality secondary to the complications of AF.

**Table 3 Risk of atrial fibrillation in patients with inflammatory bowel disease according to medication**

Outcome	Immunomodulators		Systemic steroid		Biologic agents	
	Yes (n = 10199)	No (n = 27497)	Yes (n = 21606)	No (n = 16090)	Yes (n = 2075)	No (n = 35621)
Atrial fibrillation	85	263	227	121	21	327
Incidence rate <sup>1</sup>	1.72	1.97	2.21	1.50	2.16	1.89
Adjusted HR <sup>2</sup> (95%CI)	1.46 (1.13-1.89)	1 (reference)	1.37 (1.10-1.71)	1 (reference)	2.38 (1.51-3.75)	1 (reference)

<sup>1</sup>Incidence rates were calculated per 1000 patient-years, within the population who were over 20 years old and not previously diagnosed with atrial fibrillation;

<sup>2</sup>Adjusted with age, sex, place, income, diabetes mellitus, hypertension, dyslipidemia, previous history of stroke, ischemic heart disease, and end stage renal disease. HR: Hazard ratio; CI: Confidence interval.



**Figure 2 Subgroup analysis.** Subgroup analysis to assess the risk of atrial fibrillation in patients with inflammatory bowel disease (IBD) based on age (< 30, 30-44, 45-59, and ≥ 60 years), sex (men and women), and cardiovascular (CV) risk factors (those with and without CV risk factors). The association between IBD and the risk of development of atrial fibrillation was weaker in older individuals and in those with CV risk factors. <sup>1</sup>Incidence rates have been calculated per 1000 patient-years;

<sup>2</sup>Adjusted for age, sex, location, income, diabetes mellitus, hypertension, dyslipidemia, stroke, myocardial infarction, venous thromboembolism, and end-stage renal disease; <sup>3</sup>Hypertension, diabetes mellitus, or dyslipidemia. CI: Confidence interval; CV: Cardiovascular; HR: Hazard ratio; IBD: Inflammatory bowel disease.

## ARTICLE HIGHLIGHTS

### Research background

Systemic inflammatory disease is known to increase the risk of cardiovascular diseases such as stroke, myocardial infarction, and atherosclerosis. Also, it has recently emerged as a risk factor for atrial fibrillation (AF). Inflammatory bowel disease (IBD) is a chronic progressive inflammatory disease, which can affect the gastrointestinal tract. Considering that pathogenesis

of AF is linked to systemic inflammation, IBD might be a potential risk factor for AF development.

### Research motivation

Recently, the incidence and prevalence of IBD have increased in the young Asian population. The impact of IBD on cardiovascular disease is an important issue. Therefore, we need to clarify the relationship between IBD and AF development in the Asian population and young patients

### Research objectives

We aimed to investigate the association between IBD and AF development in Asians.

### Research methods

We performed a population-based cohort study using the certified claim database from the Korean National Health Insurance Services between 2010 and 2014. The special codes of the rare and intractable disease program were used to define the patient, which include the complete medical history of patients. A total of 37696 patients with IBD (12349 with Crohn's disease and 25397 with ulcerative colitis) were identified. The primary endpoint was new-onset AF, which occurred among IBD patients without a previous history of AF during the follow-up period. AF was defined using the International Classification of Disease, Tenth Revision, Clinical Modification codes (I480-I484, I489).

### Research results

During  $4.9 \pm 1.3$  years of follow-up, 1120 patients newly diagnosed with AF (348 in the IBD group and 772 in controls). IBD patients had a 36% (95% confidence interval 20%-54%) higher risk of AF than controls. The association between IBD and the development of AF was stronger in younger than in older patients, and in patients without cardiovascular risk factors. Additionally, moderate-severe IBD patients, who received immunomodulators, systemic corticosteroids, or biologics agents were at higher risk of AF. These findings supported that systemic inflammatory disease could be an independent risk factor for AF development. However, further studies on the impact of other systemic inflammation on AF need to be performed to provide conclusive evidence.

### Research conclusions

IBD, chronic systemic disease, significantly increase the risk of AF development in Asians, as similar to the Western population. Moreover, the impact of IBD on AF incident was higher in young patients and those without cardiovascular risk factors. Therefore, our findings supported that systemic inflammatory disease is an independent risk factor for AF, even in patients without classic cardiovascular risk factors.

### Research perspectives

It is necessary to pay attention to the occurrence of cardiovascular diseases such as AF in patients with IBD, even in young age. In particular, a patient receiving immunomodulators, systemic corticosteroids, or biologics agents for moderate-severe disease, had a higher risk of AF development than those without.

## REFERENCES

- 1 Thia KT, Loftus EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008; **103**: 3167-3182 [PMID: 19086963 DOI: 10.1111/j.1572-0241.2008.02158.x]
- 2 Papa A, Danese S, Urgesi R, Grillo A, Guglielmo S, Roberto I, Bonizzi M, Guidi L, De Vitis I, Santoliquido A, Fedeli G, Gasbarrini G, Gasbarrini A. Early atherosclerosis in patients with inflammatory bowel disease. *Eur Rev Med Pharmacol Sci* 2006; **10**: 7-11 [PMID: 16494104]
- 3 Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: A nationwide Danish cohort study. *Gut* 2013; **62**: 689-694 [PMID: 22961677 DOI: 10.1136/gutjnl-2012-303285]
- 4 Poullis AP, Zar S, Sundaram KK, Moodie SJ, Risley P, Theodossi A, Mendall MA. A new, highly sensitive assay for C-reactive protein can aid the differentiation of inflammatory bowel disorders from constipation- and diarrhoea-predominant functional bowel disorders. *Eur J Gastroenterol Hepatol* 2002; **14**: 409-412 [PMID: 11943955 DOI: 10.1097/00042737-200204000-00013]
- 5 Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. *Inflamm Bowel Dis* 2004; **10**: 661-665 [PMID: 15472532 DOI: 10.1097/00054725-200409000-00026]
- 6 Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107**: 499-511 [PMID: 12551878 DOI: 10.1161/01.CIR.0000052939.59093.45]
- 7 Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003; **108**: 3006-3010 [PMID: 14623805 DOI: 10.1161/01.CIR.0000103131.70301.4F]
- 8 Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 2005; **95**: 764-767 [PMID: 15757607 DOI: 10.1016/j.amjcard.2004.11.032]
- 9 Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. *J*

- Cardiovasc Electrophysiol* 2010; **21**: 1064-1070 [PMID: 20455973 DOI: 10.1111/j.1540-8167.2010.01774.x]
- 10 Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004; **109**: II2-II0 [PMID: 15173056 DOI: 10.1161/01.CIR.0000129535.04194.38]
  - 11 Kim HJ, Hann HJ, Hong SN, Kim KH, Ahn IM, Song JY, Lee SH, Ahn HS. Incidence and natural course of inflammatory bowel disease in Korea, 2006-2012: A nationwide population-based study. *Inflamm Bowel Dis* 2015; **21**: 623-630 [PMID: 25647154 DOI: 10.1097/MIB.0000000000000313]
  - 12 Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score in the entire Korean population. *Int J Cardiol* 2017; **236**: 226-231 [PMID: 28233629 DOI: 10.1016/j.ijcard.2017.02.039]
  - 13 Kang SH, Choi EK, Han KD, Lee SR, Lim WH, Cha MJ, Cho Y, Oh IY, Oh S. Underweight is a risk factor for atrial fibrillation: A nationwide population-based study. *Int J Cardiol* 2016; **215**: 449-456 [PMID: 27131763 DOI: 10.1016/j.ijcard.2016.04.036]
  - 14 Lee SR, Choi EK, Rhee TM, Lee HJ, Lim WH, Kang SH, Han KD, Cha MJ, Cho Y, Oh IY, Oh S. Evaluation of the association between diabetic retinopathy and the incidence of atrial fibrillation: A nationwide population-based study. *Int J Cardiol* 2016; **223**: 953-957 [PMID: 27589043 DOI: 10.1016/j.ijcard.2016.08.296]
  - 15 Sung JJ, Kamm MA, Marteau P. Asian perspectives in the management of inflammatory bowel disease: Findings from a recent survey. *J Gastroenterol Hepatol* 2010; **25**: 183-193 [PMID: 19929931 DOI: 10.1111/j.1440-1746.2009.06024.x]
  - 16 Nakase H, Keum B, Ye BD, Park SJ, Koo HS, Eun CS. Treatment of inflammatory bowel disease in Asia: The results of a multinational web-based survey in the 2(nd) Asian Organization of Crohn's and Colitis (AOCC) meeting in Seoul. *Intest Res* 2016; **14**: 231-239 [PMID: 27433145 DOI: 10.5217/ir.2016.14.3.231]
  - 17 Pattanshetty DJ, Anna K, Gajulapalli RD, Sappati-Biyyani RR. Inflammatory bowel "Cardiac" disease: Point prevalence of atrial fibrillation in inflammatory bowel disease population. *Saudi J Gastroenterol* 2015; **21**: 325-329 [PMID: 26458861 DOI: 10.4103/1319-3767.166208]
  - 18 Kristensen SL, Lindhardsen J, Ahlehoff O, Erichsen R, Lamberts M, Khalid U, Torp-Pedersen C, Nielsen OH, Gislason GH, Hansen PR. Increased risk of atrial fibrillation and stroke during active stages of inflammatory bowel disease: A nationwide study. *Europace* 2014; **16**: 477-484 [PMID: 24108228 DOI: 10.1093/europace/eut312]
  - 19 Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. *J Am Coll Cardiol* 2012; **60**: 2263-2270 [PMID: 23194937 DOI: 10.1016/j.jacc.2012.04.063]
  - 20 Efe TH, Cimen T, Ertem AG, Coskun Y, Bilgin M, Sahan HF, Pamukcu HE, Yayla C, Sunman H, Yuksel I, Yeter E. Atrial Electromechanical Properties in Inflammatory Bowel Disease. *Echocardiography* 2016; **33**: 1309-1316 [PMID: 27158773 DOI: 10.1111/echo.13261]
  - 21 Nar G, Ergul B, Aksan G, Inci S. Assessment of Atrial Electromechanical Delay and Left Atrial Mechanical Functions in Patients with Ulcerative Colitis. *Echocardiography* 2016; **33**: 970-976 [PMID: 27009549 DOI: 10.1111/echo.13213]
  - 22 Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J* 2015; **79**: 495-502 [PMID: 25746525 DOI: 10.1253/circj.CJ-15-0138]
  - 23 Kourliouros A, Savelieva I, Kiotseoglou A, Jahangiri M, Camm J. Current concepts in the pathogenesis of atrial fibrillation. *Am Heart J* 2009; **157**: 243-252 [PMID: 19185630 DOI: 10.1016/j.ahj.2008.10.009]
  - 24 Saverymuttu SH, Hodgson HJ, Chadwick VS, Pepys MB. Differing acute phase responses in Crohn's disease and ulcerative colitis. *Gut* 1986; **27**: 809-813 [PMID: 3732890 DOI: 10.1136/gut.27.7.809]
  - 25 Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Svendsen JH, Torp-Pedersen C, Hansen PR. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012; **344**: e1257 [PMID: 22403267 DOI: 10.1136/bmj.e1257]
  - 26 Rhee TM, Lee JH, Choi EK, Han KD, Lee H, Park CS, Hwang D, Lee SR, Lim WH, Kang SH, Cha MJ, Cho Y, Oh IY, Oh S. Increased Risk of Atrial Fibrillation and Thromboembolism in Patients with Severe Psoriasis: A Nationwide Population-based Study. *Sci Rep* 2017; **7**: 9973 [PMID: 28855659 DOI: 10.1038/s41598-017-10556-y]
  - 27 Moon I, Choi EK, Jung JH, Han KD, Choi YJ, Park J, Cho JH, Lee E, Choe W, Lee SR, Cha MJ, Lim WH, Oh S. Ankylosing spondylitis: A novel risk factor for atrial fibrillation - A nationwide population-based study. *Int J Cardiol* 2019; **275**: 77-82 [PMID: 30360993 DOI: 10.1016/j.ijcard.2018.10.024]
  - 28 Ye BD, Yang SK, Shin SJ, Lee KM, Jang BI, Cheon JH, Choi CH, Kim YH, Lee H; IBD Study Group of the Korean Association for the Study of the Intestinal Diseases. [Guidelines for the management of Crohn's disease]. *Korean J Gastroenterol* 2012; **59**: 141-179 [PMID: 22387837 DOI: 10.2165/00128413-200112840-00001]
  - 29 Choi CH, Kim YH, Kim YS, Ye BD, Lee KM, Lee BI, Jung SA, Kim WH, Lee H; IBD Study Group of the Korean Association for the Study of Intestinal Diseases. [Guidelines for the management of ulcerative colitis]. *Korean J Gastroenterol* 2012; **59**: 118-140 [PMID: 22387836 DOI: 10.4166/kjg.2012.59.2.118]
  - 30 Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho GT, Satsangi J, Bloom S; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60**: 571-607 [PMID: 21464096 DOI: 10.1136/gut.2010.224154]
  - 31 Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995; **155**: 469-473 [PMID: 7864703 DOI: 10.1001/archinte.1995.00430050045005]
  - 32 Loftus EV, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 1-20 [PMID: 12122726 DOI: 10.1016/S0889-8553(01)00002-4]
  - 33 Ng WK, Wong SH, Ng SC. Changing epidemiological trends of inflammatory bowel disease in Asia. *Intest Res* 2016; **14**: 111-119 [PMID: 27175111 DOI: 10.5217/ir.2016.14.2.111]
  - 34 Yang SK, Yun S, Kim JH, Park JY, Kim HY, Kim YH, Chang DK, Kim JS, Song IS, Park JB, Park ER, Kim KJ, Moon G, Yang SH. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986-2005: A KASID study. *Inflamm Bowel Dis* 2008; **14**: 542-549 [PMID: 17941073 DOI: 10.1002/ibd.20310]
  - 35 Kim JW, Lee CK, Rhee SY, Oh CH, Shim JJ, Kim HJ. Trends in health-care costs and utilization for inflammatory bowel disease from 2010 to 2014 in Korea: A nationwide population-based study. *J Gastroenterol Hepatol* 2018; **33**: 847-854 [PMID: 29055148 DOI: 10.1111/jgh.14027]
  - 36 Li YG, Lee SR, Choi EK, Lip GY. Stroke Prevention in Atrial Fibrillation: Focus on Asian Patients.

- Korean Circ J* 2018; **48**: 665-684 [PMID: [30073805](#) DOI: [10.4070/kcj.2018.0190](#)]
- 37 **Son MK**, Lim NK, Cho MC, Park HY. Incidence and Risk Factors for Atrial Fibrillation in Korea: The National Health Insurance Service Database (2002-2010). *Korean Circ J* 2016; **46**: 515-521 [PMID: [27482260](#) DOI: [10.4070/kcj.2016.46.4.515](#)]
- 38 **Schnabel RB**, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: A cohort study. *Lancet* 2015; **386**: 154-162 [PMID: [25960110](#) DOI: [10.1016/S0140-6736\(14\)61774-8](#)]



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