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*Published in:*
European Heart Journal

*DOI (link to publication from Publisher):*
10.1093/eurheartj/ehab315

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*Publication date:*
2021

*Document Version*
Publisher's PDF, also known as Version of record

*Link to publication from Aalborg University*

*Citation for published version (APA):*
Lower risk of stroke after alcohol abstinence in patients with incident atrial fibrillation: a nationwide population-based cohort study

So-Ryoung Lee¹, Eue-Keun Choi¹,²*, Jin-Hyung Jung³, Kyung-Do Han⁴, Seil Oh¹,², and Gregory Y.H. Lip²,⁵,⁶

¹Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea; ²Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea; ³Department of Medical Statistics, College of Medicine, Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea; ⁴Statistics and Actuarial Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Republic of Korea; ⁵Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Chest and Heart Hospital, Thomas Dr, Liverpool L14 3PE, UK; and ⁶Department of Clinical Medicine, Aalborg University, Aalborg 9000, Denmark

Received 27 August 2020; revised 21 November 2020; editorial decision 4 May 2021; accepted 14 May 2021; online publish-ahead-of-print 7 June 2021

See page 4769 for the editorial comment for this article ‘Alcohol intake and risk of stroke in atrial fibrillation: the lesser the better, but this is not enough’, by A.M. Russo, https://doi.org/10.1093/eurheartj/ehab657.

Aims
The aim of this study was to evaluate the association between alcohol consumption status (and its changes) after newly diagnosed atrial fibrillation (AF) and the risk of ischaemic stroke.

Methods and results
Using the Korean nationwide claims and health examination database, we included subjects who were newly diagnosed with AF between 2010 and 2016. Patients were categorized into three groups according to the status of alcohol consumption before and after AF diagnosis: non-drinkers; abstainers from alcohol after AF diagnosis; and current drinkers. The primary outcome was incident ischaemic stroke during follow-up. Non-drinkers, abstainers, and current drinkers were compared using incidence rate differences after the inverse probability of treatment weighting (IPTW). Among a total of 97 869 newly diagnosed AF patients, 51% were non-drinkers, 13% were abstainers, and 36% were current drinkers. During 310 926 person-years of follow-up, 3120 patients were diagnosed with incident ischaemic stroke (10.0 per 1000 person-years). At 5-year follow-up, abstainers and non-drinkers were associated with a lower risk for stroke than current drinkers (incidence rate differences after IPTW, -2.03 [-3.25, -0.82] for abstainers and -2.98 [-3.81, -2.15] for non-drinkers, per 1000 person-years, respectively; and incidence rate ratios after IPTW, 0.75 [0.70, 0.81] for non-drinkers and 0.83 [0.74, 0.93] for abstainers, respectively).

Conclusion
Current alcohol consumption was associated with an increased risk of ischaemic stroke in patients with newly diagnosed AF, and alcohol abstinence after AF diagnosis could reduce the risk of ischaemic stroke. Lifestyle intervention, including attention to alcohol consumption, should be encouraged as part of a comprehensive approach to AF management to improve clinical outcomes.
Introduction

Alcohol consumption is associated with an increased risk of incident atrial fibrillation (AF).\(^1\)\(^-\)\(^3\) Not only heavy drinking but also a “low spectrum of alcohol consumption” could be a risk factor for incident AF, as reported in a recent observational study.\(^1\) Regarding the risk of AF, alcohol consumption showed a consistent linear dose–response relationship.\(^2\)\(^-\)\(^4\)

While the association and dose–response relationship between alcohol consumption and the risk of AF is well-established, the association between drinking alcohol and stroke is more controversial. In the general population, the overall association of alcohol intake with the risk of stroke was almost null, and the association with ischaemic stroke showed a marginal reduction.\(^5\) In several prior studies, the associations between alcohol consumption and cardiovascular risk, including ischaemic stroke, are varied depending on whether the study focused on an immediate effect or long-term effect or alcohol dose in the general population.\(^6\)\(^-\)\(^10\) The relationship between alcohol consumption and incident stroke in patients with AF per se remains unclear.\(^11\)

In a recent study, alcohol abstinence reduced AF recurrence in patients with paroxysmal or persistent AF.\(^12\) Alcohol abstinence in AF patients with moderate to heavy drinking showed a significant reduction in the recurrence of AF and AF burden compared to those who continue their alcohol consumption. However, this study did not report the reduction of hard clinical endpoints (e.g., stroke). Physicians also need to consider the potentially beneficial effect of low amounts of alcohol on the cardiovascular outcome (at least in the general population), but they should also consider the effect of alcohol on AF management. Considering that a greater burden of AF has associated with a higher risk of ischaemic stroke in patients with AF,\(^13\) we still need evidence of whether alcohol abstinence would reduce the risk of ischaemic stroke in patients with AF, especially from a large population-based perspective. These data would help physicians how to make recommendations on drinking alcohol to their patients with newly diagnosed AF.

Implementation of a healthy lifestyle is an important part of guideline-recommended optimal care of patients with AF.\(^14\) When a new disease is diagnosed, it can be a good opportunity to intervene with respect to the patient’s lifestyle. Although there was some evidence on the clinical impact of lifestyle modification in patients with AF, we still need more evidence-based recommendations to inform guidelines, e.g., to educate and encourage ‘alcohol abstinence’ among patients who are newly diagnosed with AF.
In this study, we aimed to evaluate the associations between alcohol consumption status (especially abstaining alcohol after newly diagnosed AF) and the risk of ischaemic stroke in a population-based nationwide observational cohort.

**Methods**

We used data from the Korean National Health Insurance Service (NHIS) and the National Health Screening databases for our analysis. The Korean NHIS is a mandatory health insurance coverage provided by the government for the entire Korean population (~50 million people). The Korean NHIS database includes demographic information as well as information related to the medical records and expenses of enrollees, such as diagnoses, examinations, prescriptions, and procedures. Diagnoses were coded using the International Classification of Diseases, Tenth Revision, Clinical Modification codes. We also used data from the National Health Screening database linked with the Korean NHIS database. All enrollees of the Korean NHIS aged 40 years or older are recommended to undergo a biennial health screening. The health examination includes anthropometric measurement, assessment of blood pressure, laboratory investigations, as well as a self-reported questionnaire on health behaviours such as smoking, alcohol consumption, and physical activity. The present study complied with the Declaration of Helsinki. This study was exempted from review by the institutional review board of Seoul National University Hospital (E-2007-071-1141).

**Study design and study population**

The study design and flowchart of population enrolment are presented in Figures 1 and 2, respectively. We included subjects who were newly diagnosed with AF between 1 January 2010 and 31 December 2016 (n = 5,231,741). Patients diagnosed with valvular AF and those younger than 20 years of age were excluded. Patients who underwent health examinations within 2 years before and after the diagnosis of AF were included. Patients with missing values in the health examination data were excluded. To enhance accuracy in the diagnosis of stroke as a primary outcome, we excluded patients with a prior history of stroke before the second health examination (index date). Detailed definitions of the diagnoses, namely, AF, valvular AF, and prior stroke, are presented in Supplementary material online, Table S1.

Alcohol consumption status was evaluated using a self-reported questionnaire at the first and second health examinations. Subjects were categorized into three groups based on the status of alcohol consumption before and after the diagnosis of AF: (i) non-drinkers; (ii) abstainers from alcohol after the diagnosis of AF; and (iii) current drinkers, including sustained (persistent) drinkers and new drinkers after the diagnosis of AF (Figure 1). Data on the frequency of alcohol intake per week (0–7) and amount of alcohol intake per session (0 to <32 g, 32 to <56 g, 56 to...

![Figure 1](https://example.com/fig1.png)  
**Figure 1** Study design. AF, atrial fibrillation.

![Figure 2](https://example.com/fig2.png)  
**Figure 2** Flowchart of enrolment of the study population. AF, atrial fibrillation.
ever came first (stroke, death, or end of the study period (31 December 2017), which-
lowed up starting from the index date until the occurrence of ischaemic
formed within two years after AF diagnosis (%). The potential effect modification by sex, age (<65 years, 65–74 years, and
>75 years), underlying stroke risk of patients assessed by the CHA2DS2-
VASc score (<3 and ≥3), and baseline smoking status (never smoker, ex-
smoker, and current smoker) were evaluated by subgroup analyses and interaction tests. To account for the possible influence of the accumula-
tive alcohol intake, we stratified each group based on alcohol intake per
week at the first health examination. In addition, to account for the im-
 pact of current alcohol consumption and the risk of ischaemic stroke, we
categorized each group based on the frequency of drinking per week, al-
cohol amount per session, and the total amount of alcohol intake per
week at the second health examination. Subgroup analyses performed
using multivariable Cox proportional hazard regression models and P
for interaction <0.1 was considered significant interaction.

Sensitivity analyses
First, to provide complementary analyses, we performed a multivariable-
adjusted Cox proportional hazards model analysis. The multivariable
model was adjusted for the same variables that included PS calculation.
Before creating a final adjusted model, models that were adjusted sequen-
tially based on a priori considerations for baseline covariates were also
evaluated (models 1–5, Supplementary material online, Methods). HRs
are presented with non-drinkers as the reference group and also presented
with current drinkers as the reference group to more intuitively present
the relative risk (RR) of each group compared to current drinkers.

Second, focusing on the beneficial effect of alcohol abstinence after AF
diagnosis, PS matching (PSM) analysis was performed between the ab-
stainer group and current drinker group. The propensity for being in each
group was calculated using a logistic regression model with baseline covari-
ates included in the final multivariable Cox analysis. Patients were
matched in a one-to-one manner between the two groups using the
greedy, nearest-neighbor method without replacement with a caliper of
0.01 of the PS. The balance of baseline characteristics between two
groups was evaluated using the ASD. An ASD of ≤0.1 (10%) indicates that
study groups were well balanced. After PSM between the two
groups, the cumulative incidence curve of PS matched cohort was pre-
sented with IR, IRD with 95% CI, and IRR with 95% CI.

Third, we performed a competing risk analysis considering death as a
competing risk using the Fine and Gray proportional hazards model for
the redistribution of a competing risk.

Subgroup analyses
The potential effect modification by sex, age (<65 years, 65–74 years, and
>75 years), underlying stroke risk of patients assessed by the CHA2DS2-
VASc score (<3 and ≥3), and baseline smoking status (never smoker, ex-
smoker, and current smoker) were evaluated by subgroup analyses and interaction tests. To account for the possible influence of the accumula-
tive alcohol intake, we stratified each group based on alcohol intake per
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cohol amount per session, and the total amount of alcohol intake per
week at the second health examination. Subgroup analyses performed
using multivariable Cox proportional hazard regression methods and P
for interaction <0.1 was considered significant interaction.

Results
A total of 97 869 patients newly diagnosed with AF (mean age
61.3 ± 12.3 years, 62.4% men, mean CHA2DS2-VASc score 2.3 ± 1.5)
were included. The mean time interval between the first health
examination and diagnosis of AF, between diagnosis of AF and
the second health examination and between the first and second
health examinations was 1.1 ± 0.5, 0.9 ± 0.5 and 2.0 ± 0.5 years,
respectively.

Among the total study population, 51% (n = 49 781) were non-
drinkers, 13% (n = 12 789) were abstainers after AF diagnosis, and
36% (n = 35 299) were current drinkers. The baseline charac-
teristics of the study population are shown in Table 1 and
Supplementary material online, Table S2. Current drinkers were
younger and more likely to be men than abstainers and non-drinkers.
Current drinkers had the lowest mean CHA2DS2-VASc score among
the three groups, with a lower prevalence of most comorbidities.
The prevalence of heart failure, peripheral artery disease, chronic
obstructive pulmonary disease, chronic kidney disease, and cancer was higher in non-drinkers and abstainers than current drinkers. The maximum ASD of these comorbidities before IPTW was ≥0.1 (Table 1). In association with a relatively low CHA2DS2-VASc score, current drinkers demonstrated a lower prevalence of OAC use than non-drinkers and abstainers. Current drinkers included a larger proportion of current smokers and a lower proportion of subjects in the low-income category compared to non-drinkers and abstainers. Furthermore, current drinkers included a larger proportion of subjects who performed regular exercise than the other groups. Among current drinkers, 58.8% were mild drinkers, 23.5% were moderate drinkers, and 17.8% were heavy drinkers at the second health examination.

### Alcohol status and ischaemic stroke

During 310 926 person-years of follow-up, 3120 patients were diagnosed with incident ischaemic stroke (10.0 per 1000 person-years). After IPTW, the baseline characteristics of the three groups were...
well-balanced (Table 1). Weighted cumulative incidence curves are presented in Figure 3. At 5 years, the weighted IR of stroke was lower in non-drinkers and abstainers than in current drinkers (IRDs, -2.98 [-3.81, -2.15] for non-drinkers vs. current drinkers and -2.03 [-3.25 to -0.82] for abstainers vs. current drinkers). Consistent with the results of the main analysis, IRRs at 5 years after IPTW suggested that abstainers and non-drinkers were associated with a lower risk for stroke than current drinkers (IRRs, 0.75 [0.70, 0.81] for non-drinkers vs. current drinkers, and 0.83 [0.74, 0.93] for abstainers vs. current drinkers). The results of weighted Cox proportional hazards regression models with IPTW were also consistent with the main results.

### Sensitivity analyses

In a multivariable-adjusted Cox proportional hazards model analysis, results were consistent with the main analysis (Figure 4A). Results of a final fully adjusted model were consistently observed in all adjusted models (Supplementary material online, Figure S1).

After PSM, the baseline characteristics of abstainers and current drinkers were well-balanced (Supplementary material online, Table S3). Cumulative incidence curves of the PS-matched cohort are presented in Figure 3. At 5 years, the IR of stroke was lower in abstainers than in current drinkers (IRD, -1.90 [-3.39, -0.41]). IRR estimated after PSM suggested that abstainers were associated with a lower risk for stroke compared to current drinkers (IRR, 0.85 [0.74, 0.97]), consistent with the main results.

The crude event numbers and IRs of all-cause death and cardiovascular and non-cardiovascular death were different among the three groups (Supplementary material online, Table S4). The results were also consistent when adjusting for the competing risks of death (Supplementary material online, Table S5).

### Subgroup analyses

In each subgroup stratified, according to sex, age, CHA2DS2-VASc score, and smoking status, the overall results were consistent with...
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The main results. Furthermore, there were no significant interactions with respect to ischaemic stroke between different groups categorized by alcohol status and all subgroups (Supplementary material online, Figure S2).

Alcohol consumption amount at the first health examination
To account for the influence of previous cumulative alcohol intake, abstainers and current drinkers were stratified according to the amount of alcohol consumed per week as described in the Methods section (mild [0 to <105 g], moderate [105 to <210 g], and heavy [≥210 g]). Event numbers and crude IRs are presented in Supplementary material online, Table S6. As shown in Supplementary material online, Figure S3, abstainers who consumed mild or moderate amounts of alcohol per week and stopped drinking after the diagnosis of AF had a similar risk of ischaemic stroke as non-drinkers. Ex-heavy drinkers showed a significantly higher risk of ischaemic stroke than non-drinkers, despite the cessation of drinking after the diagnosis of AF (adjusted HR 1.433, 95% CI 1.122–1.831). All current drinkers showed a higher risk of ischaemic stroke compared to non-drinkers, regardless of the amount of alcohol consumed previously.

Alcohol consumption amount at the second health examination
Current drinkers were stratified according to the frequency of drinking per week, the amount of alcohol consumed per session, and the total amount of alcohol intake per week at the second health examination. Event numbers and crude IRs are presented in Supplementary material online, Table S7. Among current drinkers, a greater amount of alcohol consumption per week was associated with a higher risk of ischaemic stroke (Figure 4B). Both frequent drinking and binge drinking per each drinking session were significant risk factors for incident ischaemic stroke (Figure 4C and D).

Discussion
In this study on a large nationwide cohort of patients with incident AF, our principal findings were as follows: (i) a substantial proportion (36%) of subjects with newly diagnosed AF remained current drinkers, and 13% stopped drinking after the diagnosis; (ii) current drinkers with any amount of alcohol intake (even mild-to-moderate intake) had a significantly higher risk of ischaemic stroke compared to non-drinkers; and (iii) abstinence from alcohol after the diagnosis of AF was associated with a lower risk of ischaemic stroke compared to...
current drinkers (Graphical abstract). These observations have implications for promoting lifestyle modifications as part of the holistic and integrated approach in the care of patients with AF.\(^{14,23}\)

The strengths of the present study lie in the inclusion of a large number of patients who were available for serial health examination before and after the diagnosis of AF. Based on the availability of the serial self-reported questionnaires before and after the diagnosis of AF, we identified non-drinkers, abstainers, and current drinkers and demonstrated the association between each alcohol intake status and the risk of ischaemic stroke in the patients after the diagnosis of AF.

Alcohol consumption has been reported to be associated with an increased risk of incident AF, and a linear dose–response relationship is well established between the two parameters.\(^{1–4}\) Binge drinking, as well as habitual alcohol consumption, has been implicated in the increased risk of developing AF.\(^{3}\) Excessive alcohol consumption causes acute electrophysiological effects, including decreased atrial effective refractory period and slow intra-atrial conduction.\(^{24}\) Binge drinking also increases the susceptibility to atrial arrhythmias by mishandling of calcium in the sarcoplasmic reticulum.\(^{25}\)

Alcohol exposure may lead to atrial electrical and structural remodelling. The atrial tissue has been reported to be more susceptible to toxicity even at lower doses of alcohol than doses associated with alcohol-induced cardiomyopathy in the ventricles.\(^{26}\) Thus, regular mild-to-moderate consumption of alcohol has been associated with lower atrial voltages or the presence of low-voltage zones, conduction slowing, and enlargement of the left atrium.\(^{27–29}\) In a recent randomized clinical trial that included regular drinkers with AF, abstainers showed significantly lower recurrence and burden of AF compared to sustained drinkers.\(^{12}\) Proactive abstinence from alcohol intake is therefore recommended in patients with AF to control AF itself. Moreover, the reduction of recurrence and burden of AF might lower AF-related complications.\(^{13}\)

Although the amount of alcohol intake shows a linear relationship with incident AF, and alcohol abstinence is an important modifiable factor for effective rhythm control in patients with AF, there has been limited evidence on recommendations regarding optimal care of such patients, especially in relation to stroke prevention. In the general population, the association between alcohol intake and the risk of stroke showed a U-shaped relationship, wherein light to moderate alcohol consumption was associated with a reduced risk of stroke compared to abstinence.\(^{5,7,10,30}\) However, there has been no definitive answer to the question of whether a U-shaped relationship exists between alcohol intake and the risk of stroke in the population with AF.

A previous study reported that heavy drinking was associated with an increased risk of the composite of thromboembolism and death in
the population with AF. However, this result was mainly driven by death, and the numbers were insufficient to address the beneficial effect of abstinence from alcohol and establish a dose–response relationship for the risk of stroke. Al-Khalili et al. reported that prior alcohol-related hospitalization was associated with a two-fold increased risk of ischaemic stroke in young patients with AF (18–64 years, median 55 years) at low risk for ischaemic stroke stratified by CHA2DS2-VASc score (0 in men and 1 in women). However, a direct relationship between alcohol intake and ischaemic stroke was not demonstrated in this prior study.

The present study showed that any current alcohol intake in patients with AF was associated with a higher risk of ischaemic stroke compared to non-drinkers. Moreover, there was a linear dose–response relationship between the amount of current alcohol intake and the risk of ischaemic stroke. Furthermore, abstinence from alcohol might reduce the risk of ischaemic stroke in patients with newly diagnosed AF.

The differences in the population with AF compared to the general population could be explained by several mechanisms. In previous studies, light to moderate regular alcohol intake was also reported to cause electrical and structural atrial remodelling, which eventually led to atrial myopathy. The latter refers to atrial fibrotic remodelling with electrical and autonomic remodelling, associated with an increased risk of stroke. In patients with AF, the presence of any AF events lasting over 6 min was found to be associated with an increased risk of stroke, which was even greater in cases with the AF burden lasting over 24 h. Thus, reduction in the recurrence and the burden of arrhythmia by alcohol abstinence might be beneficial in preventing stroke in patients with AF. Although the cumulative incidence between abstainer and current drinker groups was not significantly different in the early period (<1 year), the absolute difference of IR and IRR after 2-year follow-up remained consistent. We assumed that the beneficial effect of alcohol abstinence, such as reduction of AF burden and atrial reverse remodelling, might need time to present as a risk reduction of hard endpoint (e.g. stroke).

To evaluate the risk of stroke in patients with AF, the impact of age is crucial. Before IPTW, current drinkers were younger than abstainers and non-drinkers, and the crude IRs of ischaemic stroke were higher in non-drinkers and abstainers than current drinkers (10.7, 9.7, and 9.3 per 1000 person-years, respectively, in Figure 4A). After IPTW, age differences were well-balanced, and weighted IRs of ischaemic stroke were highest in current drinkers (11.7 per 1000 person-years) than in abstainers and non-drinkers (10.1 per 1000 person-years and 8.8 per 1000 person-years, respectively). Hence, although age is a strong factor associated with the risk of stroke, non-drinkers and abstainers showed significantly lower risks of stroke than current drinkers after balancing the baseline characteristics. In the subgroup analysis by age, the P-for-interaction was not significant; however, the beneficial effect of abstinence from alcohol was attenuated in patients aged 75 years or older. This finding could be explained by the strong association between age and the risk of stroke. Age is the strongest risk factor for AF-related stroke and is also associated with irreversible remodelling of a substrate in the left atrium.

Given the increased focus on integrated care of patients with AF, lifestyle changes are part of the ‘C’ criterion of the ABC pathway, focusing on the management of comorbidities. The results of the present study provide support for lifestyle changes in the management of patients with AF, wherein proactive reduction and abstinence from alcohol consumption were associated with better outcomes.

### Study limitations

This study had several limitations. First, alcohol intake could affect comorbidities, such as hypertension and obesity, and these conditions could also modify risk factors associated with stroke. To minimize this, we adjusted for the comorbidities evaluated at the second examination; however, a possibility of residual confounding persists. Second, alcohol status was evaluated using a self-reported questionnaire, which could be associated with recall bias. Nonetheless, many published retrospective and prospective observational studies, or even randomized controlled trials, have collected information about alcohol intake using similar self-reported questionnaires.

Third, the beneficial effect of alcohol abstinence and the dose–response relationship between the amount of alcohol intake and the risk of stroke might be mediated by atrial electrical/structural remodelling and the burden of arrhythmia. However, this aspect could not be evaluated, considering the inherent limitation of the database. Lastly, the impact of heavy drinking in the general population on the risk of stroke differs according to the subtype of stroke (ischaemic vs. haemorrhagic). For example, the RR of haemorrhagic stroke was higher (RR, 2.18) than that of ischaemic stroke (RR 1.69) due to heavy drinking (>60 g/day). Furthermore, the association between alcohol consumption and the RR of stroke was J-shaped for ischaemic and linear-shaped for haemorrhagic stroke. In the present study, we focused on ischaemic stroke, especially since data on haemorrhagic stroke could not be differentiated from claims databases of intracranial haemorrhage due to other causes.

### Conclusion

Current alcohol consumption was associated with an increased risk of ischaemic stroke in patients with newly diagnosed AF. Compared to non-drinkers, current drinkers with mild amount of alcohol consumption still showed a significantly higher risk of ischaemic stroke and a linear dose–response relationship between the amount of current alcohol intake and the risk of ischaemic stroke. Furthermore, alcohol abstinence after the diagnosis of AF could reduce the risk of ischaemic stroke. Lifestyle interventions, including attention to alcohol consumption, should be encouraged as part of a comprehensive approach in the management of patients with a new diagnosis of AF to improve clinical outcomes.

### Supplementary material

Supplementary material is available at European Heart Journal online.

### Declaration of Helsinki

The present study complied with the Declaration of Helsinki. This study was exempted from review by the institutional review board of Seoul National University Hospital (E-2007-071-1141).
Funding
This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, Republic of Korea, the Ministry of Food and Drug Safety) (Project Number: 202013B14) and by the Korea National Research Foundation funded by the Ministry of Education, Science and Technology (grant 2020R1F1A106740).

Conflict of interest: S.-R.L., J.-H.K., K.-D.H., and S.O. report no conflict of interest. E.-K.C. reports research grant from Bayer, BMS/Pfizer, Biosense Webster, Chong Kun Dang, Daichi-Sankyo, Dreamtech Co., Ltd., Medtronic, Sanonipharm, Sanofi-Aventis, Seers Technology, Skylabs, and Yuhan. G.Y.H.L. reports consultant for BMS/Pfizer, Boehringer Ingelheim and Daichi-Sankyo; but no fees are received personally; no other relationships or activities that could appear to have influenced the submitted work.

Data availability
All data generated and analyzed during the current study are available at the National Health Insurance Data Sharing Service (accessed at https://nhiss.nhis.or.kr/brd/ab/bdabata000eng.do).

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