Doctor of Philosophy

Association with Oral Anticoagulation and Rifampin in tuberculosis patients with non-valvular Atrial Fibrillation

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Association with Oral Anticoagulation and Rifampin in tuberculosis patients with non-valvular Atrial Fibrillation

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ABSTRACT

BACKGROUND: The use of oral anticoagulants (OAC) in patients receiving rifampin for tuberculosis (TB) treatment is often complicated by drug-drug interactions (DDI). Despite these complications, there are no studies in the literature that specifically address the issue of OAC use for non-valvular atrial fibrillation (NVAF) patients with TB. Current data mainly focuses on pharmacokinetic DDIs between OACs and rifampin in healthy volunteers or on brief case reports from clinical practice. We aimed to examine the efficacy and safety of OACs with concurrent administration of rifampin for TB treatment of NVAF patients and compare it with non-vitamin K antagonist oral anticoagulant (NOAC) use alone.

METODS: Using data from the Korean National Health Insurance Service database from January 2008 to December 2018, we included 1,468 consecutive patients taking OACs with concurrent rifampin in this study. The primary endpoint included ischemic stroke or systemic embolism and major bleeding. The patients were matched by age, sex, CHA_2DS_2-VASc score and comorbidites to NVAF patients that were administered with NOACs alone.

RESULTS: Of the 1,468 consecutive patients selected, 931 (63.4%) received warfarin and 537 (36.6%) received NOACs (52 received dabigatran, 218 received rivaroxaban, 191 received apixaban and 76 received edoxaban). In a multivariate Cox proportional hazard analysis, concurrent rifampin treatment was associated with a significantly higher risk of ischemic stroke or systemic embolism (adjusted Hazard Ratio [HR], 1.57; 95 % Confidence Interval [CI], 1.22-2.01; P <0.001) and major bleeding (adjusted HR, 1.71; 95 % CI, 1.34-2.18; P <0.001) compared with NOAC use alone. We also evaluated the efficacy and safety outcomes between NOAC and warfarin in patients taking OACs with concurrent rifampin. There was no increased risk of ischemic stroke or systemic embolism (adjusted HR, 0.90; 95% CI, 0.55-1.48; P = 0.690) and major bleeding (adjusted HR, 0.91; 95% CI, 0.57-1.45; P = 0.687) with NOAC and rifampin combination therapy.

CONCLUSION: In this real-world patient population, OACs administration with concurrent

rifampin was associated with a higher rate of ischemic stroke or systemic embolism and major bleeding compared with NOACs alone. This increased risk of adverse events suggests that OACs use should be carefully monitored in NVAF patients with concurrent administration of rifampin.

Key words: atrial fibrillation, tuberculosis, anticoagulation, rifampin, drug-drug interactions

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INTRODUCTION

Tuberculosis (TB) remains a major health problem in South Korea. In 2019, the number of new TB cases in Korea was 23,821 (46.4 per 100,000), this number was 9.9% down from the previous year. However, 47.1% of those new patients were 65 years of age or above.[1] TB infections are indolent and have a longer course of treatment when compared to other viral or bacterial infections.[2] Patients with a TB infection also have an increased risk of thromboembolic events, such as deep vein thrombosis, pulmonary thromboembolism, or ischemic stroke.[3, 4] Fixed-dose combination therapy is recommended using isoniazid and rifampin due to the presence of multi-drug resistance or human immunodeficiency virus (HIV) infective TB.[2]

Atrial fibrillation (AF) is a significant risk factor for ischemic stroke. Over the past decades, warfarin, a racemic mixture of S and R isomers which are metabolized by hepatic cytochrome P450 (CYP) system, has been recommended for primary or secondary prevention of ischemic stroke in patients with non-valvular AF (NVAF).[5-7] However, warfarin is responsible for the occurrence of food-drug and drug–drug interactions (DDIs).[8] Because warfarin has a narrow therapeutic range to achieve the ideal anticoagulation effects without excess risk of bleeding, DDIs with warfarin have frequently been reported as causes of adverse clinical outcomes.[9] Owing to this, warfarin use requires frequent dosage adjustment following an International Normalized Ratio (INR) measurements. Physician was reluctant to prescribe warfarin to elderly patients with polypharmacy.[10, 11] Non-vitamin K antagonist oral anticoagulants (NOACs) are now the preferred oral anticoagulants (OACs) for NVAF patients because they do not require frequent dosage adjustment and food restrictions to achieve target INR levels with strict laboratory monitoring.[12] However, NOACs can still cause potential DDIs that are mediated by either CYP enzyme and/or the transporter permeability glycoprotein (P-gp) system.

Rifampin is one of the first-line drugs for treating TB infection, due to its bactericidal and sterilizing capacity.[2] Therefore, the current guidelines recommend the use of the standard 6-month rifampin-containing regimen. Rifampin is a potent inducer of the hepatic CYP enzyme and the P-gp

transport systems.[13] Despites of this, there are no studies specifically addressing the issue of OAC use for NVAF patients with TB. Current data mainly focuses on pharmacokinetic DDIs between OACs and rifampin in healthy volunteer or the brief case reports in clinical practice.[14-16] We performed a population-based retrospective cohort study in South Korea to examine the efficacy and safety of OACs with concurrent administration of rifampin for treatment of TB compared with NOACs use alone in NVAF patients.

METHODS

Data Sources

This study was based on data from the nationwide administrative claims-based databases of the Korean National Health Insurance Service (NHIS). The NHIS provides a comprehensive healthcare database that include general specifications (age, gender and region), diagnosis, treatment details, procedure, medical prescription of all medical services as well as the date of procedure, surgery and hospitalization.[17] All diagnostic data are based on the International Classification of Disease, Tenth Revision (ICD-10). Using these datasets, we also obtained information on patient demographics, clinical covariates, diagnosis and procedure (inpatient and outpatient), main study drugs, and concomitant cardiovascular medication and the ICD-10 codes are listed in Supplementary Table 1. In addition, the lifestyle questionnaires (drinking, smoking, and exercise), and laboratory results were collected from the national health screening database, which are periodically provided by the NHIS to all insured subjects. The study protocol was approved by the institutional review board of the Pusan National University Yangsan Hospital (IRB No. 05-2019-072).

Study Population

The study population included all patients with NVAF who visited medical institution(s) at least one or more with a primary diagnosis of TB coded as A15-19 according to the ICD-10 and

received rifampin between January 1, 2008, and December 31, 2018. To begin our patient selection process, we identified a population-based cohort of consecutive patients who received OACs with a diagnosis of NVAF. We then identified a subset of these patients who received an index prescription of rifampin for TB treatment. The exclusion criteria were as follows: 1) CHA_2DS_2-VASc score < 2, 2) withdrawal of anticoagulants or ≥2 anticoagulants within 30 days after the index medication, 3) withdrawal or switching in anticoagulants during rifampin prescription, 4) patients with deep vein thrombosis, pulmonary thromboembolism or joint replacement surgery, all of which could be a potential alternative indication for OACs, and 5) patients undergoing renal replacement therapy (Figure 1).

To investigate the efficacy and safety outcomes of patients taking OACs with concurrent rifampin administration for the treatment of TB, we then identified a population-based cohort of patients with a diagnosis of NVAF who received NOAC alone. These patients were matched by age, sex, body mass index, CHA_2DS_2-VASc score, congestive heart failure, hypertension, prior history of myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, and dyslipidemia in a 1:4 ratio using risk-set matching. The date of the first administration of rifampin was defined as index date in NVAF patients who were diagnosed with TB. For patients with NVAF who received NOACs alone, the index date was defined as the date of the first prescription for any NOACs.

Clinical Variables and Outcome Assessment

Detailed information including demographics (age, sex, BMI), comorbidities (hypertension, diabetes, dyslipidemia, congestive heart failure, peripheral artery disease [PAD], chronic obstructive pulmonary disease [COPD], history of stroke/transient ischemic attack, prior myocardial infarction [MI] and chronic kidney disease [CKD]), and medication (antiplatelet agents, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins and digoxin) were collected. The CHA_2DS_2-VASc score was calculated on the basis of a point system in which 2 points are assigned for a history of stroke, or an age ≥75; and 1 point each was assigned for

an age of 65-74 years, a history of congestive heart failure, hypertension, diabetes, or vascular diseases, as well as for the female sex.

The primary efficacy outcome was a composite of ischemic stroke or systemic embolism. The primary safety outcome was major bleeding. The secondary outcomes included all-cause death, intracranial hemorrhage (ICH) or gastrointestinal (GI) bleeding. For outcome analyses, only events that occurred within 1 year after the index date were analyzed. Ischemic stroke was defined when the diagnosis of ICD-10 codes with hospitalization and concomitant imaging studies (computed tomography or magnetic resonance imaging) was identified.[17] Systemic embolism was diagnosed when it was the principal diagnosis requiring hospitalization. Major bleeding was defined as a composite outcome of ICH, GI bleeding necessitating hospitalization, or bleeding that occurred in critical sites (intraspinal, intraocular, retroperitoneal, or intramuscular with compartment syndrome).[18]

Statistical Analysis

Propensity matching scores were used to assess the efficacy and safety of the OACs in NVAF patients with concurrent administration of rifampin. Propensity scores were estimated from the logistic regression model for each patient. The covariates used for the propensity matching calculations were age, sex, BMI, CHA_2DS_2-VASc score, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, previous MI, PAD or COPD.

The comparisons between all the continuous variables are presented as the mean ± standard deviation. The descriptive variables are presented as absolute numbers and the percentage of the total patients with the available data for each group. Baseline characteristics were compared using the Student's *t* test or the Mann–Whitney *U* test for continuous variables and by the Pearson's chi-square test or Fisher's exact tests for descriptive variables. Crude incidence rates were calculated as number of each event per 100 person-years. Event-free survival curves according to groups were constructed by the Kaplan-Meier method for univariate analysis, and the differences between the groups were assessed using the log-rank test. A Cox proportional-hazard regression model that included age, sex, CHA_2DS_2-VASc score, and variables with a univariate predictive value of $P < 0.1$ between-groups comparison

was used to perform an adjusted analysis of event-free survival. The results are shown as Hazard Ratios (HRs) with the 95% Confidence Interval (CI). A value of $P<0.05$ was considered statistically significant. All statistical calculations were performed with SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Baseline Characteristics

The initial cohort included 2,465 patients with NAVF who received OACs with concurrent rifampin administration for tuberculosis therapy between January 1, 2008, and December 31, 2018. Among these patients, we identified 1,468 incident users of warfarin or NOACs who met the inclusion criteria. Of these, 931 (63.4%) received warfarin and 537 (36.6%) received NOACs (52 received dabigatran, 218 received rivaroxaban, 191 received apixaban and 76 received edoxaban).

The baseline characteristics according to treatment type are summarized in Table 1. The mean age of the matched-cohort population was 75 years, and 58% were men. The mean CHA_2DS_2-VASc score for these patients was 5.0 ± 1.5. Ischemic heart disease was present in 43.8% of patients in both groups. The rifampin group was characterized by a greater prevalence of chronic kidney disease.

Clinical Outcomes in NVAF patients in Relation to Interaction of Rifampin and OACs

The mean follow-up period was 8.3 months in patients with NVAF who received OACs with concurrent rifampin and 8.5 months in the patients receiving NOAC alone. The crude incidence rates per 100 person-years related to the primary and secondary outcomes are summarized in Table 2. The patients receiving OACs with concurrent rifampin had a higher crude incidence rate of ischemic stroke or systemic embolism (8.72 versus 5.25 per 100 person-years, $P<0.001$) and major bleeding (10.09 versus 4.82 per 100 person-years, $P<0.001$) compared with those receiving NOAC alone

(Figure 2). Survival analysis by Kaplan-Meier method revealed that event-free survival rate for all-cause death, ICH, and GI bleeding were significantly higher in patients with concurrent rifampin treatment than those with NOAC alone (Figure 3). In the multivariate Cox proportional hazard analysis, concurrent rifampin treatment was associated with a significantly higher risk of ischemic stroke or systemic embolism (adjusted HR, 1.57; 95 % CI, 1.22-2.01; P <0.001) and major bleeding (adjusted HR, 1.71; 95 % CI, 1.34-2.18; P <0.001) compared with NOAC alone. Thus, the OACs administration with concurrent rifampin was associated with a higher risk of ICH (adjusted HR, 2.18; 95% CI, 1.08-4.38; P = 0.030) but no difference in GI bleeding risk (adjusted HR, 1.36; 95% CI, 0.99-1.85; P = 0.054).

The crude incidence rates of all-cause death were 63.6 per 100 person-years and 26.2 per 100 person-years for concurrent rifampin and NOAC alone group, respectively. Patients receiving OACs with concurrent rifampin had a higher risk of all-cause death (adjusted HR, 2.12; 95% CI, 1.92-2.34; P <0.001).

Comparison between the warfarin and NOACs group with concurrent rifampin.

We also evaluated efficacy and safety outcomes among patients taking OACs with concurrent rifampin. Patients receiving warfarin with concurrent rifampin were more likely to have comorbidities including diabetes, prior stroke, PAD, prior MI, and chronic kidney disease (Table 3). The CHA_2DS_2-VASc score was similar between the two groups (4.98 ± 1.47 for NOAC group versus 4.94 ± 1.59 for warfarin group, P =0.618). Detailed data for crude incidence rates and HRs according to combination therapy are summarized in Table 4. No significant difference was found between NOAC and warfarin group, although unadjusted and adjusted HRs for ischemic stroke or systemic embolism, major bleeding, all-cause death, ICH, and GI bleeding were below one (Figure 4).

DISCUSSION

In our nationwide population-based study, we examined the efficacy and safety of OACs in NVAF patients receiving rifampin for TB treatment compared to a matched cohort of NVAF patients receiving NOACs for stroke prevention. The study yielded three major findings: 1) our study showed that NVAF patients receiving OACs administration with concurrent rifampin were more likely to develop the risk of ischemic stroke or systemic embolism and major bleeding compared with those receiving NOACs alone. 2) Furthermore, concurrent rifampin administration had a significantly increased risk of all-cause mortality and ICH compared with patients who did not receive rifampin. 3) NOAC use was associated with a significantly higher risk of ischemic stroke or systemic embolism compared with warfarin in NVAF patients with concurrent rifampin administration for treatment of TB, although this combination therapy is not currently recommended in the guidelines.

To the best of our knowledge, our study is the first to evaluate the clinically relevant efficacy and safety of OACs in NVAF patients with concurrent rifampin administration for treatment of TB. Previous studies have mainly reported pharmacokinetic drug interactions between rifampin and warfarin.[8, 15, 19] In patients receiving warfarin for stroke prevention, rifampin has been reported to increase warfarin metabolism and necessitate a sequential increase in warfarin dosage to achieve a therapeutic INR value. Additionally, CYP enzyme or P-gp transport system induction has been documented to be maintained in approximately 2 weeks after rifampin administration was discontinued.[20] Krajewski et al.[21] reported that DDIs remained after rifampin discontinuation and the gradual reduction of warfarin dosage were required to reach the initial regimen over three to four months. Therefore, more careful titration of the warfarin dosage was needed when rifampin administration was initiated for treatment of TB. Subsequently, the warfarin dosage was gradually reduced over the next 2 months following the withdrawal of rifampin.

NOACs are now recommended as the preferred alternative to warfarin for reducing the risk of stroke associated with NVAF.[12] The therapeutic advantages of NOACs include a more rapid and predictable anticoagulant response, limited need for routine laboratory monitoring, and fewer drug-

food and DDIs. However, NOACs also have potential DDIs.[22, 23] Based on the pharmacokinetic data resulting from NOACs treatment with concurrent rifampin administration in healthy volunteers, strong inducers of P-gp and/or CYP3A4, such as rifampin, significantly reduce NOAC concentrations. Therefore, concurrent administration should be avoided or used with great caution and careful monitoring.[24] Following administration of rifampin, dabigatran exposure over 7- day period resulted in a 67% reduction in the dabigatran area under the plasma concentration-time curve from zero to infinity. In pharmacokinetic analysis of factor Xa inhibitors, co-administration of rifampin decreases apixaban exposure by up to 54%, rivaroxaban by up to 50%, and edoxaban by up to 35%.[22, 24] While the anticoagulant effect of NOAC depends on drug exposure, the relationship between plasma concentration and clinical outcomes is more complex. Interestingly, higher NOAC concentrations are associated with a greater risk for major bleeding, but not the risk reduction in ischemic stroke.[24-26] Recently, Chang et al.[27] found the clinical risk of bleeding when NOACs were combined with concurrent medications such as amiodarone, fluconazole, rifampin, and phenytoin. The concurrent rifampin administration with NOACs had a significant increase in major bleeding. However, those investigators found contradictory results that concomitant administration of dronedarone, a strong CYP3A4 and P-gp inhibitor, did not increase the risk of bleeding.

Our results also have the conflicting result that concurrent administration of OACs and rifampin is associated with a significantly increased risk of ischemic stroke or systemic embolism and major bleeding events compared with NOAC use alone.

There are several possible explanations for these conflicting results. First, the propensity score method was used to reduce the effects of confounding factors. However, the chance of TB infection is high in medically fragile patients with alcohol abuse, medical treatments such as corticosteroids or organ transplants, and lower body weight.[28] The EINSTEIN investigators performed a subgroup analysis of the risk of major bleeding in fragile patients, and they found that fragile patients have a higher risk of major bleeding compared with nonfragile patients.[29] Additionally, for fragile patients, there was significantly less major bleeding in the rivaroxaban group than the warfarin group (1.1% vs. 3.6%; HR, 0.27; 95% CI, 0.07–0.96). In our study, rifampin group was associated

with a higher increased risk of all-cause death compared with NOAC alone (HR, 2.12; 95% CI, 1.92-2.34; P <0.001). We acknowledged that rifampin was prescribed in more fragile patients, which might lead to probable conflicting results.

Second, our study population included a higher proportion of patients who received warfarin (63.4%). This combination of warfarin and rifampin is consistent with the current guidelines.[12] Several case reports have shown difficulty achieving a therapeutic INR level when warfarin was co-administrated with rifampin as potent CYP inducer.[14, 21] Labile INR control was associated with bleeding risk.[30] As with warfarin, NOAC had a favorable risk-benefit with significant reductions in ischemic stroke and intracranial hemorrhage, but increased gastrointestinal bleeding.[31] Also, consistent with the results of previous studies our findings suggest that the incidence rate of major bleeding including ICH in the NOAC with concurrent rifampin is relatively lower (0.80 per 100 person-years) compared with warfarin with concurrent rifampin (1.43 per 100 person-years).

Third, all the NOACs were dependent on some degree to renal function for elimination, so a decrease in renal function led to an increase in NOAC exposure.[26, 32] The mean age of our population was 75 years older and the incidence of chronic kidney disease is relatively greater in patients receiving OACs with concurrent rifampin. It has not yet been validated for the influence of renal impairment in elderly patients who take the combination therapy with rifampin and OACs.

Finally, our study population consisted of an unexpectedly high percentage of patients receiving OAC plus anti-platelet agent combination therapy, which increases the occurrence of major bleeding and ischemic stroke.

Limitations

Our study had several limitations. First, our results are based on the Korea NHIS claims database, which generate data for reimbursement, rather than for research. Therefore, there are some unmeasurable confounding factors including physician's decisions and detailed laboratory findings. Second, the current guidelines recommend the use of the standard 6-month rifampin-containing regimen. However, the mean time for rifampin withdrawal in this study was 108.4 days (median 63

days). In addition, the causes of rifampin withdrawal in the studies were lacking. Third, NOAC use is not generally recommended in combination with rifampin that are potent inducer of both CYP3A4 and P-gp system. Specific dosing algorithms for the different NOACs might be evaluated in large Phase III clinical trials. So, detailed NOAC dosage information was not analyzed in our study. Fourth, TB is a common opportunistic infection in HIV or acquired immunodeficiency syndrome (AIDS) patients with a weakened immune system. A mere 2 cases of the HIV infection or AIDS are included in our study. It is lack of evidence to make these therapeutic decisions in HIV infection or AIDS patients.

CONCLUSION

In our population-based study, we evaluated the efficacy and safety of OACs with concurrent rifampin administration in NVAF patients with TB. We found that rifampin administration was associated with a significantly increased risk of stroke or systemic embolism and major bleeding in patients treated concurrently with OACs compared with NOAC alone. Furthermore, there was no statically significant difference in the occurrence of ischemic stroke or systemic embolism and major bleeding between NOAC and warfarin with concurrent rifampin administration for treatment of TB. These results provide no support that OACs and rifampin combination therapy have a higher risk of adverse effects in NVAF patients with TB. In clinical practice, OACs use should be carefully monitored in NVAF patients with concurrent administration of rifampin. Further randomized comparisons are needed to investigate the efficacy and safety of NOACs and warfarin with concurrent rifampin administration in NVAF patients.

Table 1. Baseline characteristics between OACs group with concurrent rifampin and NOAC alone group

	With Rifampin (n = 1468)	Without Rifampin (n = 5870)	P value
Age, years	74.8 ± 10.4	75.4 ± 9.9	0.038
Male gender –n (%)	863 (58.8)	3450 (58.8)	0.992
Body Mass Index (kg/m^2)	22.9 ± 3.4	24.3 ± 3.6	0.010
CHA_2DS_2-VASc score	4.95 ± 1.55	5.03 ± 9.9	0.038
Comorbidities –n (%)			
Congestive heart failure	1053 (71.7)	4262 (72.6)	0.523
Hypertension	1348 (91.8)	5536 (94.3)	0.001
Diabetes mellitus	1049 (71.5)	4259 (72.6)	0.419
Ischemic heart disease	643 (43.8)	2569 (43.8)	0.980
Previous MI	184 (12.5)	726 (12.4)	0.898
Peripheral artery disease	223 (15.2)	825 (14.1)	0.284
prior stroke/TIA/SSE	723 (49.3)	2914 (49.6)	0.881
COPD	806 (54.9)	3329 (56.7)	0.223
Chronic kidney disease	576 (39.2)	1433 (24.4)	< 0.001
Dyslipidemia	1152 (78.5)	4697 (80.0)	0.189
Concurrent Medication			
Aspirin	886 (60.4)	3649 (63.2)	0.213
$P2Y_{12}$ inhibitor	479 (32.6)	2352 (40.1)	< 0.001
Beta-blocker	988 (67.3)	3833 (65.3)	0.157
Calcium-channel blocker	1,046 (71.3)	4043 (68.9)	0.083
ACE inhibitor or ARB	1,002 (68.3)	3791 (64.6)	0.009
Statin	719 (49.0)	3506 (59.7)	< 0.001
Digoxin	652 (44.4)	1643 (28.0)	< 0.001
Oral Anticoagulants			< 0.001
Warfarin	931 (63.4)	0 (0.0)	
Dabigatran	52 (3.5)	754 (12.8)	
Rivaroxaban	218 (14.9)	2220 (37.8)	
Apixaban	191 (13.0)	1867 (31.8)	
Edoxaban	76 (5.2)	1029 (17.5)	

Data are presented as mean ± standard deviation, or number (percentage).

Abbreviations: OAC, oral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and sex (female); MI, myocardial infarction; TIA, transient ischemic accident; SSE, systemic embolism; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker

Table 2. Unadjusted and Adjusted HR of prespecified endpoints for Patients who taking oral anticoagulants with concurrent rifampin versus NOAC alone

Outcome	No. of event (IR per 100 person-years)		Unadjusted		Adjusted	
	With Rifampin (N = 1468)	Without Rifampin (N = 5680)	HR (95% CI)	P value	HR (95% CI)	P value
Ischemic stroke or SE	85 (8.72)	255 (5.25)	1.55 (1.21-1.98)	< 0.001	1.57 (1.22-2.01)	< 0.001
Major bleeding	98 (10.09)	235 (4.82)	1.96 (1.55-2.49)	< 0.001	1.71 (1.34-2.18)	< 0.001
All cause death	643 (63.60)	1306 (26.20)	2.30 (2.09-2.53)	< 0.0001	2.12 (1.92-2.34)	< 0.001
ICH	12 (1.19)	24 (0.48)	2.32 (1.16-4.63)	0.018	2.18 (1.08-4.38)	0.030
GI bleeding	54 (5.50)	169 (3.46)	1.42 (1.04-1.93)	0.025	1.36 (0.99-1.85)	0.054

Abbreviation: NOAC, non-vitamin K antagonist oral anticoagulant; SE, systemic embolism; ICH, intracranial hemorrhage; GI, gastrointestinal; IR, incidence rate; HR, hazard ratio; CI, confidence interval

Table 3. Baseline characteristics between NOAC and warfarin with concurrent rifampin

	NOAC (n = 537)	Warfarin (n = 931)	P value
Age, years	77.6 ± 8.8	73.1 ± 10.8	<0.001
Male gender –n (%)	304 (56.6)	559 (60.0)	0.198
Body Mass Index (kg/m^2)	23.1 ± 3.4	22.8 ± 3.3	0.618
CHA_2DS_2-VASc score	4.98±1.47	4.94±1.59	0.652
Comorbidities –n (%)			
Congestive heart failure	405 (75.4)	648 (69.6)	0.020
Hypertension	448 (90.9)	860 (92.4)	<0.001
Diabetes mellitus	348 (64.8)	701 (75.3)	<0.001
Ischemic heart disease	240 (44.7)	403 (43.3)	0.601
Previous MI	55 (10.2)	129 (13.9)	0.053
Peripheral artery disease	66 (12.3)	157 (16.9)	0.023
prior stroke/TIA/SSE	212 (39.5)	511 (54.9)	<0.001
COPD	282 (52.51)	524 (56.28)	0.179
Chronic kidney disease	160 (29.8)	416 (44.7)	<0.001
Dyslipidemia	442 (82.3)	710 (76.3)	0.007
Concurrent Medication			
Aspirin	295 (54.9)	519 (55.7)	0.805
$P2Y_{12}$ inhibitor	180 (33.5)	299 (32.1)	0.621
Beta-blocker	360 (67.0)	628 (67.5)	0.916
Calcium-channel blocker	393 (73.2)	653 (70.1)	0.231
ACE inhibitor or ARB	347 (64.6)	655 (70.4)	0.027
Statin	294 (54.7)	425 (45.6)	0.001
Digoxin	201 (37.4)	451 (48.4)	<0.001
Oral Anticoagulants			<0.001
Warfarin	0 (0.0)	931 (100.0)	
Dabigatran	52 (9.7)	0 (0.0)	
Rivaroxaban	218 (40.6)	0 (0.0)	
Apixaban	191 (35.5)	0 (0.0)	
Edoxaban	76 (14.2)	0 (0.0)	

Data are presented as mean ± standard deviation, or number (percentage). Abbreviations as in Table 1.

Table 4. Unadjusted and Adjusted HR of prespecified endpoints for Patients who taking NOAC and warfarin administration with concurrent rifampin

Outcomes	No. of event (IR per 100 person-years)		Unadjusted		Adjusted	
	NOAC (N = 537)	Warfarin (N = 931)	HR (95% CI)	P value	HR (95% CI)	P value
Ischemic stroke or systemic embolism	25 (6.84)	60 (9.85)	0.71 (0.44-1.12)	0.142	0.90 (0.55-1.48)	0.690
Major bleeding	28 (7.68)	70 (11.54)	0.67 (0.44-1.05)	0.078	0.91 (0.57-1.45)	0.687
All cause death	221 (58.54)	422 (66.53)	0.89 (0.76-1.05)	0.157	0.87 (0.73-1.03)	0.112
ICH	3 (0.80)	9 (1.43)	0.57 (0.16-2.11)	0.401	0.69 (0.18-2.70)	0.594
GI bleeding	16 (4.34)	38 (6.20)	0.72 (0.40-1.29)	0.264	0.85 (0.46-1.58)	0.612

Abbreviations as in Table 2.

Supplementary Table 1. Definitions of comorbidities and clinical outcomes according to ICD-10 codes

Disease	ICD-10 codes	Additional definition
Atrial fibrillation	I48	
Mitral stenosis *	I05.0 I05.2	Or claim code for open commissurotomy or percutaneous valvuloplasty
Mechanical valve*	Z95.2–Z95.4	Or claim code for surgical valve replacement
Received joint replacement*	N0711, N0714, N0715, N0717, N0719, N2070–9, N2710–9	Received joint replacement Claim code for surgical joint replacement
End-stage renal disease*	O7020, O9991, O7061, O7062, O7071, O7072, O7073, O7074, V001, V003, V005	Claim code for hemodialysis or peritoneal dialysis
Deep vein thrombosis *	I80.2	
Pulmonary embolism *	I26	
Congestive heart failure	I11.0, I13.0, I13.2, I42, I50	
Hypertension	I10–I13, I15 and minimum 1 prescription of anti-hypertensive drug	Admission ≥ 1 or outpatient department ≥ 2
Diabetes	E10–E14, and minimum 1 prescription of anti-diabetic drugs	Admission ≥ 1 or outpatient department ≥ 2
Dyslipidemia	E78	Admission ≥ 1 or outpatient department ≥ 1
COPD	J41-44	Admission ≥ 1 or outpatient department ≥ 1
Myocardial infarction	I21–I23	
Ischemic heart disease	I20-I25	
Aortic plaque	I70.0	
Peripheral artery disease	I70.1–I70.9	
Abnormal kidney function	I12, I13, N00-05, N07, N11, N14, N17-19, Q61	
Transient ischemic attack	G45	Admission ≥ 1 or outpatient department ≥ 1

Ischemic stroke†	I63, I64	With Hospitalization and brain imaging (CT or MRI)
Systemic embolism†	I74	With Hospitalization
Extracranial or unclassified major bleeding†	D62, H05.2, H35.6, H43.1, J94.2, M25.0, R04.2	
Gastrointestinal bleeding†	I85.0, K22.1, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.8, K55.2, K57.0, K57.1, K57.2, K57.3, K57.4, K57.5, K57.8, K57.9, K62.5, K66.1 K92.0, K92.1, K92.2	Hospitalization and RBC ≥1 pack
Intracranial hemorrhage†	I60–I62	With hospitalization and brain imaging (CT or MRI)

Abbreviation: COPD, chronic obstructive pulmonary disease; RBC, red blood cell
* Used in exclusion criteria
† Used for outcome measurement

Figure 1. Flowchart of the study population, OACs indicates oral anticoagulants; NVAF, non-valvular atrial fibrillation; TB, tuberculosis; NOAC, non-vitamin K antagonist oral anticoagulant.

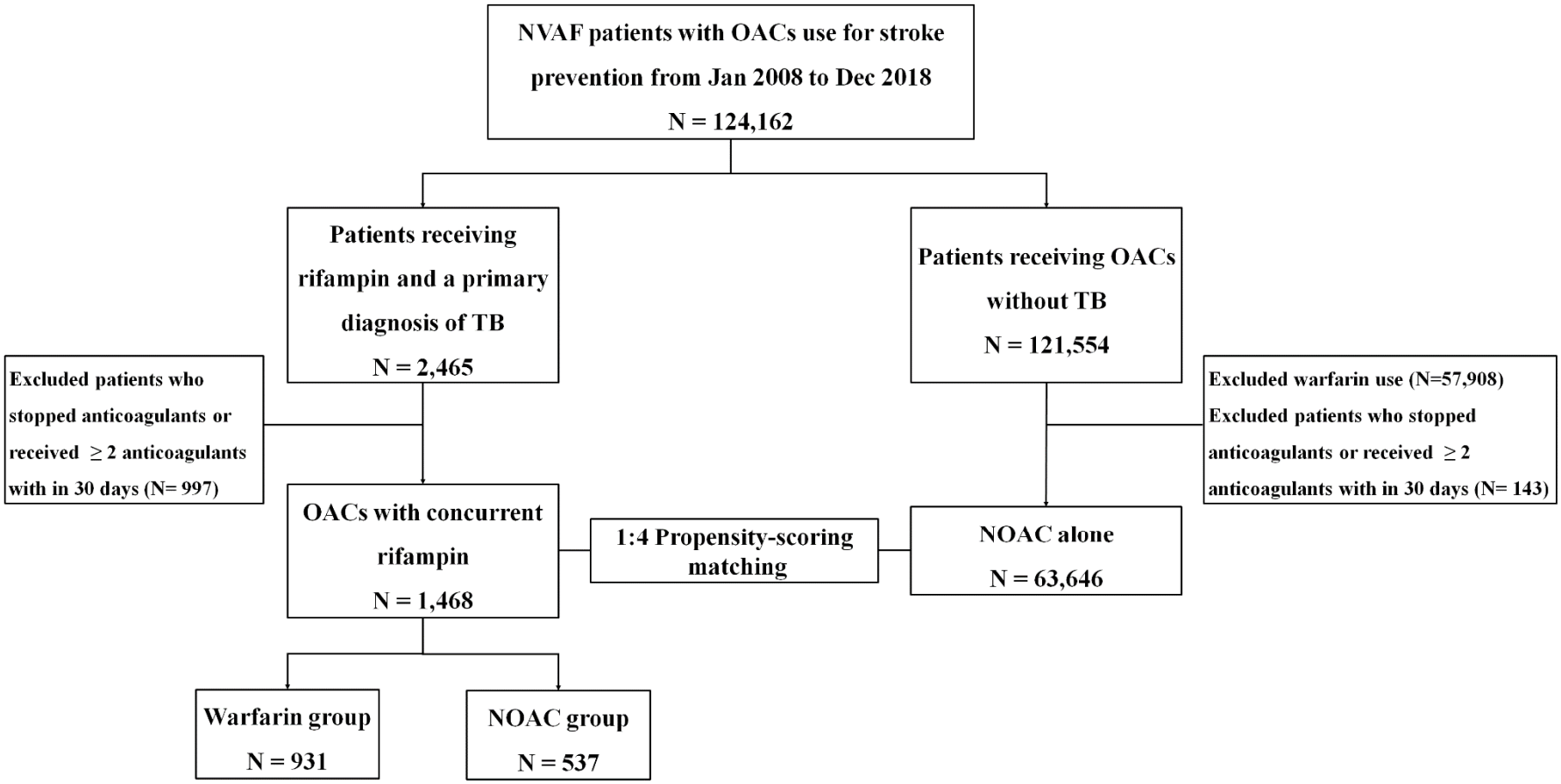


Figure 2. Event-free survival of the efficacy (A) and safety outcomes (B) in patients with OACs with concurrent rifampin and NOAC alone.

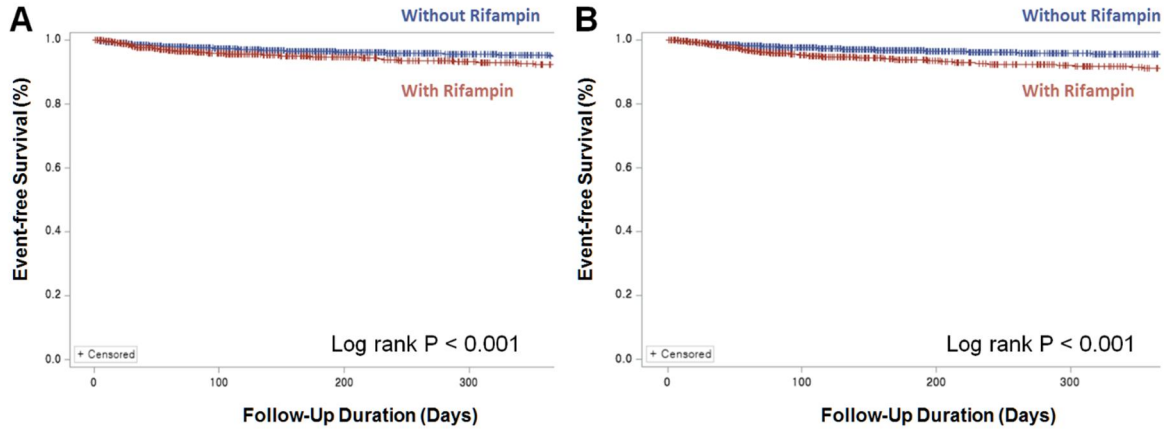


Figure 3. Kaplan-Meier survival curve for all-cause death (A), intracranial hemorrhage (B) and gastrointestinal bleeding (C) in patients with OACs with concurrent rifampin and NOAC alone.

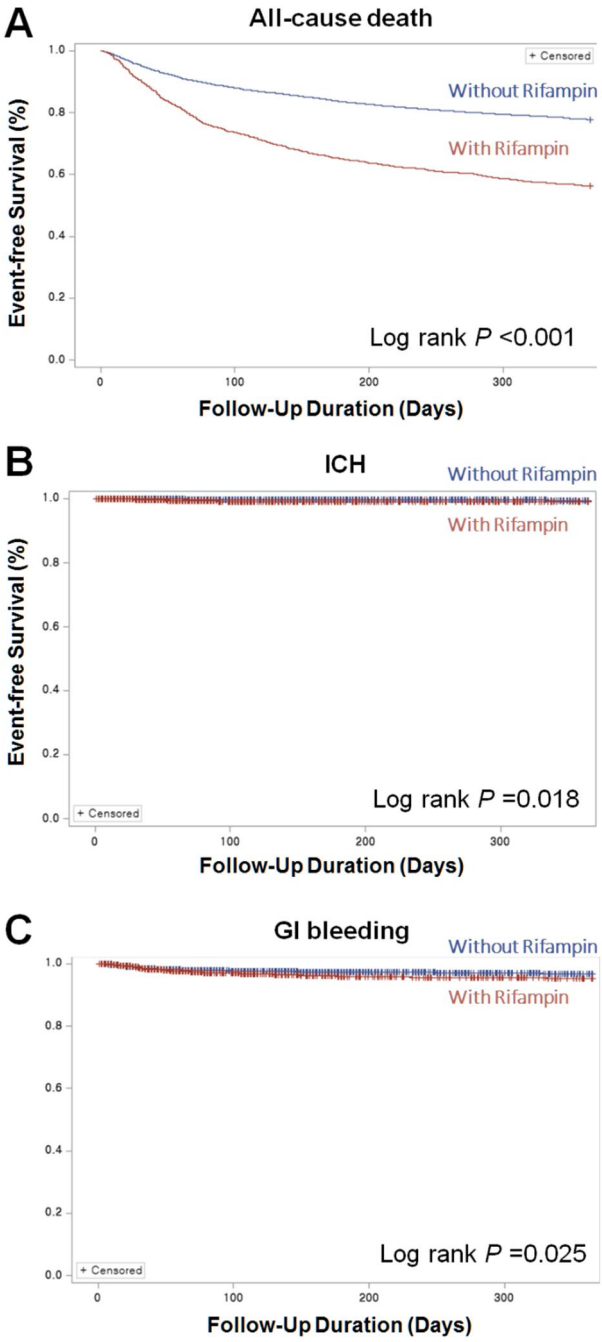
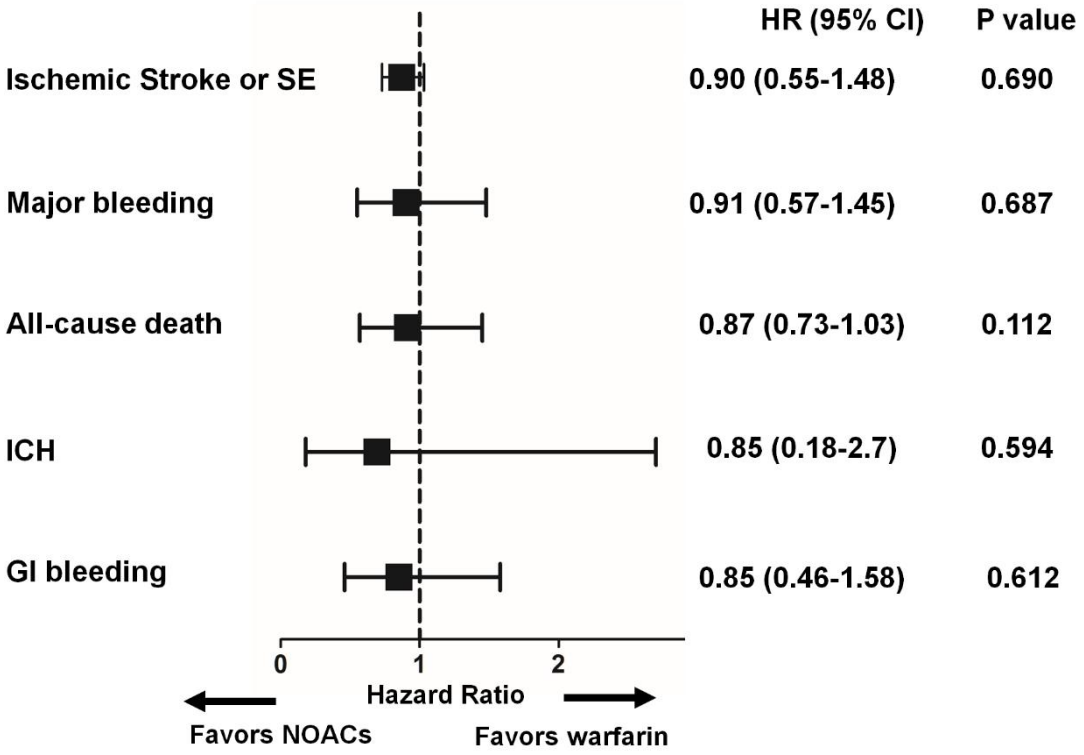


Figure 4. Adjusted Hazard Ratios of primary and secondary outcomes in NOAC versus warfarin with concurrent rifampin



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국문요약

배경: 항응고제를 복용하는 비판막성 심방세동 환자에서 결핵 치료를 위한 리팜핀을 추가하는 경우 약물상호작용(drug−drug interaction)에 의한 부작용이 발생할 수 있으므로 신중한 주의가 필요하다. 하지만, 항응고제와 리팜핀 병용시 경구 항응고제의 치료의 효과와 안정성에 대한 연구가 부족하다. 주로 건강한 피험자를 대상으로 두 약물간의 약동학적 상호작용에 대한 연구 또는 병용시 발생하는 부작용에 대한 증례들이 보고되고 있다. 본 연구에서는 결핵 치료를 위해 리팜핀을 투여받는 비판막성 심방세동 환자에서 항응고 치료의 효과와 안정성을 살펴보고자 한다.

방법 : 본 연구는 항응고제를 복용하는 비판막성 심방세동 환자에서 결핵 치료를 위한 리팜핀을 추가하는 경우 뇌졸중과 출혈 위험을 평가하기 위하여 2008년부터 2018년까지 11년 동안 건강보험 청구자료를 이용하여 분석하였다. 비판막성 심방세동으로 진단받고 결핵 치료를 위해 리팜핀을 복용하는 환자를 연구 대상자로 분류하고 리팜핀 복용 후 일년 까지 항응고제 치료의 효과와 안정성에 대해 분석하였다. 결핵 치료를 위해 리팜핀과 항응고제를 복용하는 군과 결핵 기왕력이 없이 항응고제 단독으로 처방받는 환자군을 1:4 성향점수매칭을 진행하였다. 성향점수의 산출에는 나이, 성별, CHA_2DS_2−VASc 점수, 그리고 동반질환를 포함하였다. 본 연구의 primary efficacy outcome은 뇌졸중 또는 전신 색전증 그리고, primary safety outcome은 주요 출혈(major bleeding)으로 정의하였다.

결과: 비판막성 심방세동 환자 중 결핵 치료를 위해 리팜핀과 경구 항응고제를 병용하는 1,468명의 환자 중에서 931명 (63.4 %)이 와파린을 537명(36.6 %)이 비−비타민 K 경구용 항응고제 (Non−Vitamin K Oral Anticoagulants, NOAC)를 투여 받았다(다비가트란 52 명, 리바록사반 218 명, 아픽사반 191 명은, 에독사반 76 명). 리팜핀과 항응고제 병용 치료는 NOAC 단독 사용하는 심방세동 환자와 비교하면 뇌졸중 또는 전신 색전증(위험비, 1.57; 95 % 신뢰 구간, 1.22−2.01; P <0.001) 및 주요 출혈(위험비, 1.71; 95 % 신뢰 구간, 1.34−2.18; P <0.001)의 발생률이 통계적으로 유의하게 높았다. 그리고, 리팜핀을 복용하는 환자에서 NOAC과 와파린의 효과와 안정성에 대해 추가적으로 분석하였다. 리팜핀과 NOAC의 병용 치료는 와파린 병용 치료에 비교하여 뇌졸중 또는 전신 색전증(위험비, 0.90; 95 % 신뢰 구간, 0.55−1.48; P

= 0.690) 및 주요 출혈(위험비, 0.91; 95 % 신뢰 구간, 0.57−1.45; P = 0.687)의 발생률이 감소하는 경향을 보이나 통계적인 유의성은 없었다.

결론: 비판막성 심방세동 환자에서 경구 항응고제와 결핵 치료를 위한 리팜핀 병용 투여는 결핵의 기왕력이 없이 항응고제 치료만을 받는 환자와 비교할 때 뇌졸중 또는 전신색전증 및 주요 출혈의 발생률이 높았다. 그러므로. 리핌핀과 경구 항응고제를 병용 치료하는 동안 환자를 주의깊게 평가하고 모니터링하면서 투여하여야 하겠다.

중심단어: 심방세동, 결핵, 항응고제, 리팜핀, 약물상호작용