ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2021) **7**, 50–58
doi:10.1093/ehjcvp/pvz072

**ORIGINAL ARTICLE**
*Atrial fibrillation*

# Non-vitamin K antagonist oral anticoagulants and warfarin in atrial fibrillation patients with concomitant peripheral artery disease

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*Received 8 July 2019; revised 13 October 2019; editorial decision 25 November 2019; accepted 26 November 2019; online publish-ahead-of-print 28 November 2019*

**Aims** To investigate the effectiveness, safety, and outcomes of lower limb events for non-vitamin K antagonist oral anticoagulants (NOACs) vs. warfarin among atrial fibrillation (AF) patients with concomitant peripheral artery disease (PAD).

**Methods and results** In this nationwide retrospective cohort study collected from Taiwan National Health Insurance Research Database, a total of 5768 and 2034 consecutive AF patients with PAD patients taking NOACs or warfarin were identified from 1 June 2012 to 31 December 2017, respectively. We used propensity score stabilized weighting to balance covariates across study groups. In the cohort, there were 89% patients were taking low-dose NOAC (dabigatran 110 mg twice daily, rivaroxaban 10–15 mg daily, apixaban 2.5 mg twice daily, or edoxaban 30 mg daily). Non-vitamin K antagonist oral anticoagulant was associated with a comparable risk of ischaemic stroke, and a lower risk of acute myocardial infarction [hazard ratio (HR): 0.61, 95% confidence interval (CI): 0.42–0.87; $P = 0.007$], lower extremity thromboembolism (HR: 0.56, 95% CI: 0.44–0.72; $P < 0.0001$), revascularization procedure (HR: 0.58, 95% CI: 0.47–0.72; $P < 0.0001$), lower limb amputation (HR: 0.32, 95% CI: 0.23–0.46; $P < 0.0001$), and all major bleeding (HR: 0.64, 95% CI: 0.50–0.80; $P = 0.0001$) than warfarin after weighting. The advantage of NOACs over warfarin persisted in high-risk subgroups including patients of ≥75 years of age, diabetes, renal impairment, or use of concomitant antiplatelet agent.

**Conclusion** This population-based study indicated that NOACs were associated with a comparable risk of ischaemic stroke, and a significantly lower risk of major adverse limb events and major bleeding than warfarin among AF patients with concomitant PAD. Therefore, thromboprophylaxis with NOACs may be considered for such patients.

**Keywords** Atrial fibrillation • Peripheral artery disease • Direct oral anticoagulant • Ischaemic stroke • Intracranial haemorrhage • Limb event • Warfarin



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# Introduction

Atrial fibrillation (AF) and peripheral arterial disease (PAD) are prevalent among the general population, and both of them are becoming global burdens of disease around the world.[1,2] Of note, both AF and PAD have similar epidemiologic patterns and risk factors and are both associated with an increased risk of cardiovascular (CV) events and mortality.[3,4] Furthermore, AF patients with the concomitant PAD had been reported to have a higher incidence of adverse events including thromboembolic events, stroke, myocardial infarction (MI), or CV death.[5,6] Current guidelines recommend the use of oral anticoagulants (OACs) rather than antiplatelet therapies (APT) for those AF patients with concomitant PAD, and a combined therapy of OAC and APT can be considered among those AF patients with concomitant PAD receiving endovascular revascularization.[7,8] Even though current guidelines recommend the use of non-vitamin K antagonist oral anticoagulants (NOACs) over warfarin, there were few studies investigating the advantage of NOACs vs. warfarin in AF patients with concomitant PAD.[7,8] Therefore, the aim of the present study was to investigate the effectiveness, safety, and the outcomes of lower limb events for NOACs vs. warfarin among AF patients with concomitant PAD in a large and national population-based database.

# Methods

## Study population

This retrospective nationwide cohort study analysed data from the Taiwan National Health Insurance Research Database (NHIRD) which had been reported to contain healthcare information of >23 million Taiwan residents with a >99% coverage rate of the entire population.[9] The NHIRD database includes registration and demographic data, drug prescriptions, interventions and examinations, outpatient clinic visits, hospitalizations, records of outpatient visits, and diagnosis of diseases. Informed consent was waived because the original identification number of each patient in the NHIRD is encrypted and de-identified to protect patient privacy by using a consistent encrypting procedure. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (104-8079B and 201801427B0).

## Study design

The study identified a total of 186 312 patients diagnosed with AF using [*International Classification of Diseases (the ninth revision) Clinical Modification (ICD-9-CM)* codes (427.31) between 1 June 2012 and 31 December 2015 or using *ICD-10-CM codes* (I48)] between 1 January 2016 and 31 December 2017. To define the PAD study group, we used the codes for the diagnosis of PAD or PAD-related revascularization procedures which had been commonly utilized in the previous PAD cohort studies.[10–12] In order to identify records with the new diagnosis of PAD, PAD patients were required to have at least one of the following diagnosis, procedure, or medications: aortofemoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization, limb or foot amputation for arterial vascular disease, or symptomatic claudication treated with cilosatzol, which are registered using medical records, ICD-9/10-CM diagnosis codes, or ICD-9/10-CM procedure codes (Supplementary material online, *Table SI*). A total of 19 742 AF patients with concomitant PAD were identified in the present study. Among them, a total of 8307 patients taking NOAC or warfarin were identified. In order to establish a cohort of non-valvular AF taking OAC, those patients with the diagnoses indicating venous thromboembolism (pulmonary embolism or deep vein thrombosis), valvular AF (mitral stenosis or history of valvular surgery), or required joint replacement therapy within 6 months before the index date were excluded. Patients with end-stage renal disease were also excluded because NOACs are contraindicated in such patients in Taiwan. A total of 7802 patients were analysed in this study. The index date was defined as the first date of prescription for NOACs or warfarin. The follow-up period was defined as the duration from the index date until the first occurrence of any study outcome independently, or until the end date of the study period (31 December 2017), whichever came first. A flowchart of the study enrolment is summarized in *Figure 1*.

## Study outcomes

We reported several outcomes in the present study: (i) effectiveness outcomes included ischaemic stroke (IS) and acute myocardial infarction (AMI); (ii) major adverse limb events including thromboembolism of lower extremity, acute or chronic limb ischaemia requiring revascularization procedures, and lower limb amputation; and (iii) safety outcomes included intracranial haemorrhage (ICH), major gastrointestinal bleeding (GIB), other critical site bleeding, and all major bleeding events. All study outcomes should be the first discharge diagnosis to avoid misclassification. All major bleeding events were defined as the summation of hospitalized events of ICH, GIB, and other sites of critical bleeding. The diagnosis codes of NHIRD were shifted from ICD-9-CM to ICD-10-CM after 1 January 2016. The ICD-9-M and ICD-10-CM codes used to identify the study outcomes and the baseline covariates are listed in Supplementary material online, *Table SII*. Patients may have had the same outcomes more than once during the study duration, but this study only considered the same study outcome that occurred first.

## Covariates

Baseline covariates were obtained from any claim records with the diagnoses, procedures, or medication codes prior to the index date. Bleeding history was confined to events within 6 months preceding the index date. A history of any prescription medicine was confined to medications taken at least once within 3 months preceding the index date. The $CHA_2DS_2$-VASc score (congestive heart failure, hypertension, age 75 years or older for 2 points, diabetes mellitus (DM), previous stroke or transient ischaemic attack for 2 points, vascular disease, age 65–74 years, and female gender) was computed to predict the risk of ischaemic stroke/thromboembolic events in AF patients.[8] The HAS-BLED score [hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normal ratio (INR), age 65 years or older, and antiplatelet drug or alcohol use] was computed to predict the risk of bleeding in AF patients treated with OAC.[13] The definition of concomitant use of APT including aspirin, clopidogrel, ticlopidine, or ticagrelor was defined as APT duration >3 months after drug index date of NOAC or warfarin.

## Statistical analysis

We used the method of propensity score stabilized weights (PSSWs) to balance covariates across the study groups.[14] The advantage of PSSWs is to estimate the appropriate variance of main effect with the designated Type I error by preserving the sample size of the original data. We used generalized boosted model (GBM) to obtain the PSSWs among study groups. Generalized boosted model can automatically determine the best functions of covariates, including interactions or polynomial terms, to obtain the optimal balance among study groups.[14] The PSSWs obtained by GBM is less affected by large weights.[15,16] All covariates in *Table 1* except for $CHA_2DS_2$-VASc and HAS-BLED scores were included in the GBM because $CHA_2DS_2$-VASc and HAS-BLED scores were already a combination of other covariates. The balance of potential

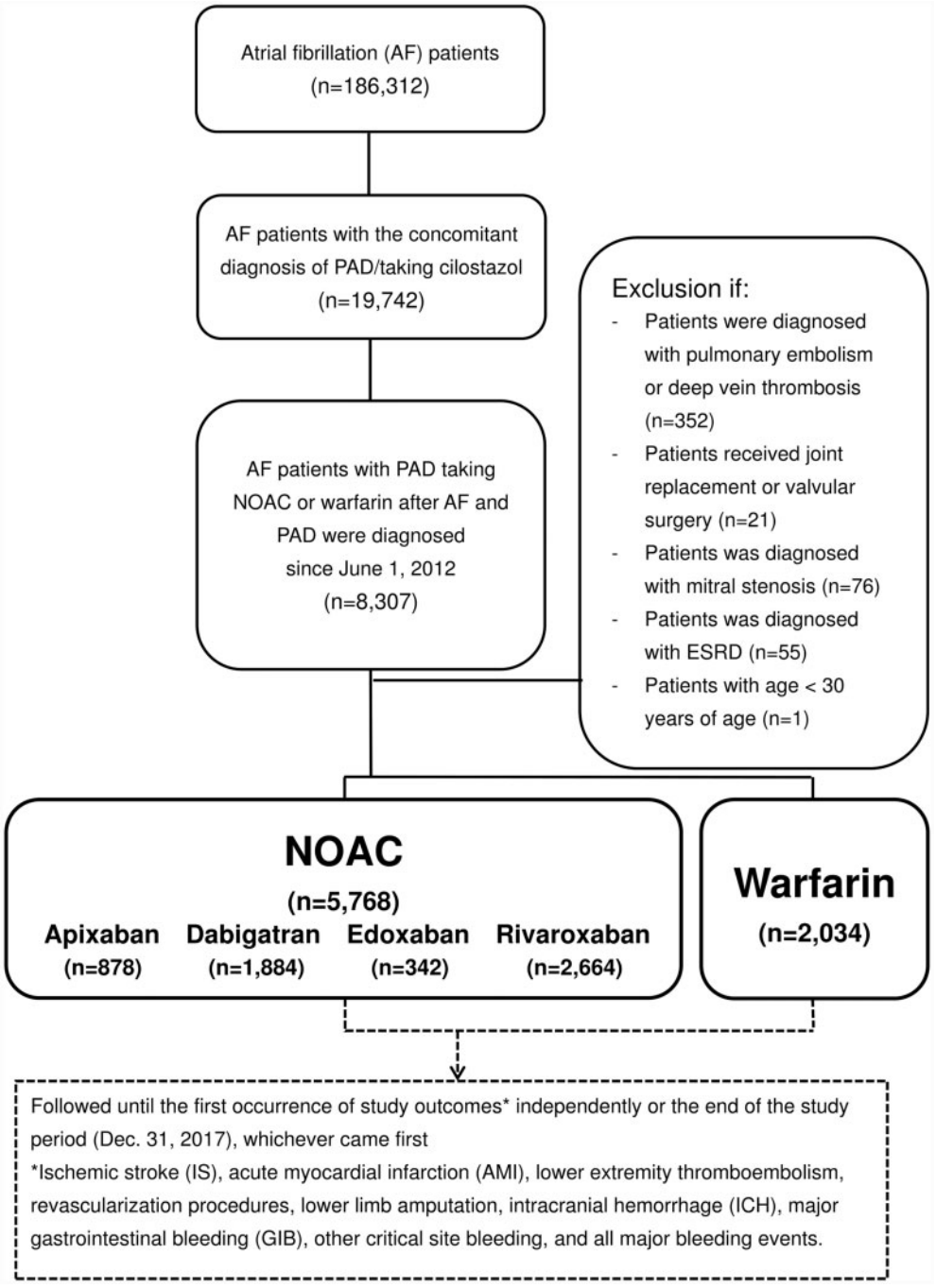


**Figure 1** Enrollment of patients with concomitant atrial fibrillation and peripheral artery disease. From 1 June 2012 to 31 December 2017, a total of 878, 1884, 342, and 2664 atrial fibrillation patients with concomitant peripheral artery disease taking apixaban, dabigatran, edoxaban, and rivaroxaban and 2034 consecutive patients taking warfarin were enrolled in the study.

confounders at baseline (index date) between each study group was assessed using the absolute standardized mean difference (ASMD) rather than statistical testing because balance is a property of the sample and not of an underlying population. The value of ASMD ≤0.1 indicated an insignificant difference in potential confounders between the two study groups.[17] The incidence rates were computed using the total number of study outcomes during the follow-up period divided by person-years at risk. The risk of study outcomes for NOACs vs. warfarin (reference) was obtained using survival analysis (Kaplan–Meier method and log-rank test for univariate analysis and Cox proportional hazards model for multivariate analysis). Subgroup analysis was made to determine whether the NOAC group continued to have a lower risk of study outcomes when compared with the warfarin group in specific subgroup. Of note, the PSSWs were re-estimated for each subgroup analysis so that the NOAC

**Table 1 Baseline characteristics of atrial fibrillation patients with concomitant peripheral artery disease taking non-vitamin K antagonist oral anticoagulants before and after propensity score stabilized weighting**

| | Before PSSW | | | After PSSW | | |
|---|---|---|---|---|---|---|
| | NOACs ($n$ = 5768) | Warfarin ($n$ = 2034) | ASMD | NOACs ($n$ = 5768) | Warfarin ($n$ = 2034) | ASMD |
| Age (years) | | | | | | |
| Mean | 78 ± 9.3 | 75.1 ± 11.3 | 0.2712 | 77.4 ± 9.7 | 77.3 ± 9.9 | 0.0100 |
| <65 | 525 (9.1%) | 418 (20.55%) | 0.3343 | 664.63 (11.68%) | 235.78 (12.09%) | 0.0174 |
| 65–74 | 1421 (24.64%) | 493 (24.24%) | | 1388.97 (24.41%) | 464.28 (23.8%) | |
| 75–84 | 2450 (42.48%) | 712 (35%) | | 2321.31 (40.8%) | 799.87 (41.01%) | |
| >85 | 1372 (23.79%) | 411 (20.21%) | | 1314.64 (23.11%) | 450.47 (23.1%) | |
| Male | 3069 (53.21%) | 1032 (50.74%) | 0.0494 | 3002.42 (52.77%) | 1030.75 (52.85%) | 0.0016 |
| $CHA_2DS_2$-VASc | 4.47 ± 1.63 | 4.35 ± 1.81 | 0.0644 | 4.43 ± 1.65 | 4.41 ± 1.67 | 0.0112 |
| HAS-BLED | 3.46 ± 1 | 3.53 ± 1.08 | 0.0626 | 3.48 ± 1 | 3.46 ± 1.02 | 0.0168 |
| Hypertension | 5259 (91.18%) | 1856 (91.25%) | 0.0026 | 5186.45 (91.16%) | 1790.13 (91.78%) | 0.0227 |
| Diabetes mellitus | 2966 (51.42%) | 1124 (55.26%) | 0.077 | 2974.1 (52.27%) | 1010.49 (51.81%) | 0.0094 |
| Dyslipidaemia | 3574 (61.96%) | 1134 (55.75%) | 0.1264 | 3445.41 (60.56%) | 1169.79 (59.98%) | 0.0120 |
| Chronic live disease | 969 (16.8%) | 353 (17.35%) | 0.0148 | 966.81 (16.99%) | 321.33 (16.48%) | 0.0141 |
| Chronic kidney disease | 2063 (35.77%) | 1163 (57.18%) | 0.4395 | 2323.05 (40.83%) | 813.09 (41.69%) | 0.0177 |
| Gout | 1653 (28.66%) | 599 (29.45%) | 0.0174 | 1656.64 (29.12%) | 562.95 (28.86%) | 0.0057 |
| Congestive heart failure | 795 (13.78%) | 355 (17.45%) | 0.1012 | 834.46 (14.67%) | 290.22 (14.88%) | 0.0061 |
| Ischaemic heart disease | 947 (16.42%) | 432 (21.24%) | 0.1235 | 984.1 (17.3%) | 328.97 (16.87%) | 0.0116 |
| Stroke/TIA | 1305 (22.62%) | 360 (17.7%) | 0.123 | 1216.45 (21.38%) | 404.81 (20.76%) | 0.0155 |
| Malignancy | 416 (7.21%) | 114 (5.6%) | 0.0657 | 386.12 (6.79%) | 133.18 (6.83%) | 0.0017 |
| PCI | 577 (10%) | 276 (13.57%) | 0.1107 | 606.99 (10.67%) | 201.73 (10.34%) | 0.0108 |
| CABG | 52 (0.9%) | 66 (3.24%) | 0.1650 | 71.35 (1.25%) | 27.83 (1.43%) | 0.0152 |
| History of bleeding | 120 (2.08%) | 73 (3.59%) | 0.0910 | 134.96 (2.37%) | 45.39 (2.33%) | 0.0030 |
| Use of NSAIDs | 1467 (25.43%) | 542 (26.65%) | 0.0277 | 1463.26 (25.72%) | 501.64 (25.72%) | 0.0000 |
| Use of PPI | 790 (13.7%) | 420 (20.65%) | 0.1851 | 865.65 (15.21%) | 295.84 (15.17%) | 0.0013 |
| Use of $H_2$ blocker | 1991 (34.52%) | 793 (38.99%) | 0.0928 | 2015 (35.42%) | 688.37 (35.29%) | 0.0026 |
| Use of ACEI/ARB | 890 (15.43%) | 474 (23.3%) | 0.2002 | 985.36 (17.32%) | 345.59 (17.72%) | 0.0107 |
| Use of beta-blocker | 3184 (55.2%) | 1197 (58.85%) | 0.0737 | 3193.76 (56.13%) | 1094.89 (56.14%) | 0.0001 |
| Use of verapamil/diltiazem | 1375 (23.84%) | 553 (27.19%) | 0.0769 | 1386.75 (24.37%) | 478.89 (24.55%) | 0.0042 |
| Use of statin | 630 (10.92%) | 334 (16.42%) | 0.1605 | 679.83 (11.95%) | 240.83 (12.35%) | 0.0124 |

ASMD ≤0.1 indicates an insignificant difference in potential confounders.
ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor antagonists; ASMD, absolute standardized mean difference; CABG, coronary artery bypass graft; $CHA_2DS_2$-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischaemic attack, vascular disease, age 65–74 years, female; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use. Labile INR could not be determined from claims and was excluded from our scoring; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, non-steroid anti-inflammatory drugs; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; TIA, transient ischaemic attack.

and warfarin subgroup maintained a balance of varied covariates across groups. Statistical significance was defined as a $P$-value <0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

# Results

## Main analysis of non-vitamin K antagonist oral anticoagulant vs. warfarin

Among the 19 742 AF patients with concomitant PAD, we identified a total of 5768 and 2034 patients taking NOACs and warfarin, respectively (*Figure 1*). The baseline characteristics of AF patients with concomitant PAD treated with or without any OAC were summarized in Supplementary material online, *Table SIII*. Those AF patients treated with OAC had a higher $CHA_2DS_2$-VASc and HAS-BLED score, a lower prevalence of chronic kidney disease (CKD), a higher prevalence of congestive heart failure and stroke/transient ischaemic attack than those without taking OAC. We then compared the baseline characteristics among those AF patients treated with NOACs vs. warfarin. After PSSW, both study groups were well-balanced in all characteristics (all ASMD <0.1) (*Table 1*).

For the effectiveness outcome, the NOAC group had a comparable cumulative risk of IS and a lower cumulative risk of AMI when compared with the warfarin group after PSSW (*Figure 2*). For the major adverse limb events, NOAC was associated with a lower cumulative risk of lower extremity embolism, revascularization procedures, and lower limb amputation than warfarin (*Figure 3*). For the

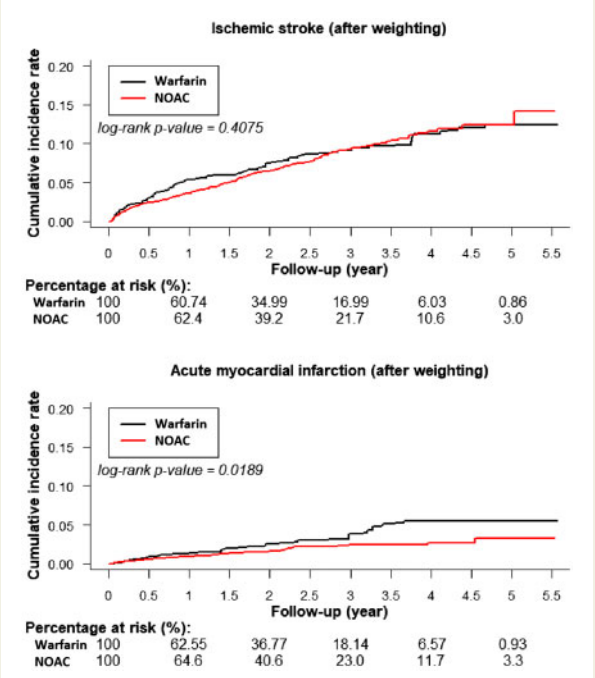


**Figure 2** Cumulative incidence rates of effectiveness outcomes for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting. Cumulative incidence curves of effectiveness outcomes including ischaemic stroke and acute myocardial infarction for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting are presented. Non-vitamin K antagonist oral anticoagulant was associated with a comparable risk of ischaemic stroke and was associated with a significantly lower risk of acute myocardial infarction than warfarin among atrial fibrillation patients with concomitant peripheral artery disease. AF, atrial fibrillation; AMI, acute myocardial infarction; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; PSSW, propensity score stabilized weighting.

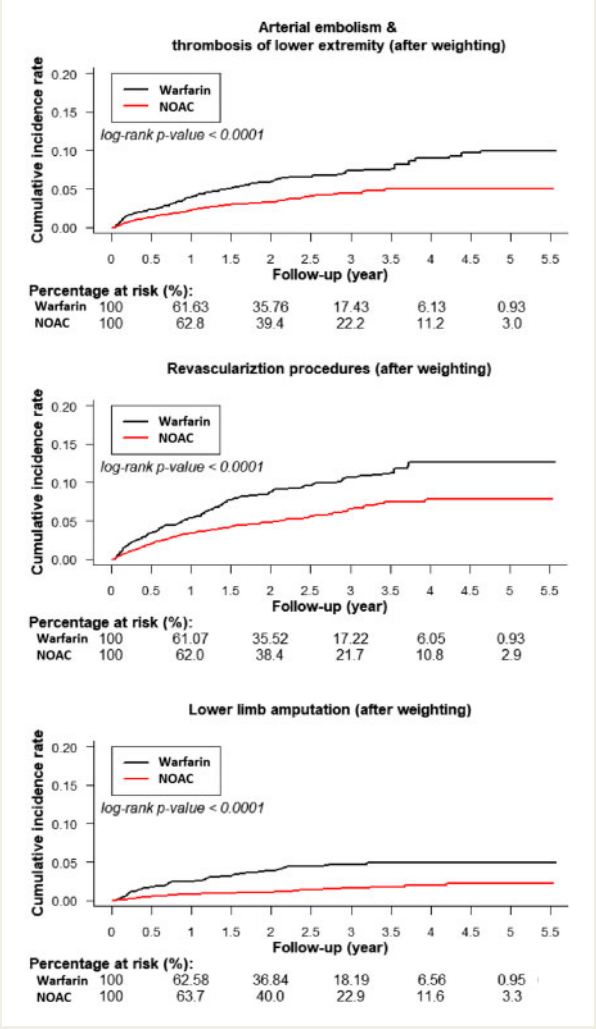


**Figure 3** Cumulative incidence rates of major limb outcomes for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting. Cumulative incidence curves of major limb outcomes including lower extremity thromboembolism, revascularization procedure, and lower limb amputation for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting are presented. Non-vitamin K antagonist oral anticoagulant was associated with a lower risk of all major adverse limb events than warfarin among atrial fibrillation patients with concomitant peripheral artery disease. AF, atrial fibrillation; AMI, acute myocardial infarction; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; PSSW, propensity score stabilized weighting.

safety outcomes, NOAC was associated with a lower cumulative risk of major GIB, other critical site bleeding, and all major bleeding than warfarin (*Figure 4*).

After PSSWs, the annual incidence of IS [3.39%/y vs. 3.61%/y, hazard ratio (HR): 0.91, 95% confidential interval (CI): 0.74–1.12; $P = 0.3639$] and ICH (0.98%/y vs. 1.29%/y, HR: 0.74, 95% CI: 0.52–1.04; $P = 0.0838$) were comparable between the NOAC and warfarin group. The NOAC group had a significantly lower annual incidence of AMI (0.80%/y vs. 1.28%/y, HR: 0.61, 95% CI: 0.42–0.87; $P = 0.007$), lower extremity thromboembolism (1.67%/y vs. 2.81%/y, HR: 0.56, 95% CI: 0.44–0.72; $P < 0.0001$), revascularization procedure (2.48%/y vs. 4.06%/y, HR: 0.58, 95% CI: 0.47–0.72; $P < 0.0001$), lower limb amputation (0.58%/y vs. 1.71%/y, HR: 0.32, 95% CI: 0.23–0.46; $P < 0.0001$), and all major bleeding (2.13%/y vs. 3.21%/y, HR: 0.64, 95% CI: 0.50–0.80; $P = 0.0001$) than warfarin (Supplementary material online, *Table SIV* and *Figure 5*). Falsification was also conducted by examining whether NOAC was associated with adverse events irrelevant to the thromboembolism and major bleeding (e.g. bone fractures or cancer) when compared with warfarin. The falsification analysis indicated that NOAC was not associated with a decreased or increased risk of cancer or bone fracture than warfarin after PSSW (*Figure 5*).

## Subgroup analysis of high-risk patents

In total, 90%, 96%, 74%, and 71% patients were taking low-dose dabigatran (110 mg twice daily), rivaroxaban (10/15 mg once daily),

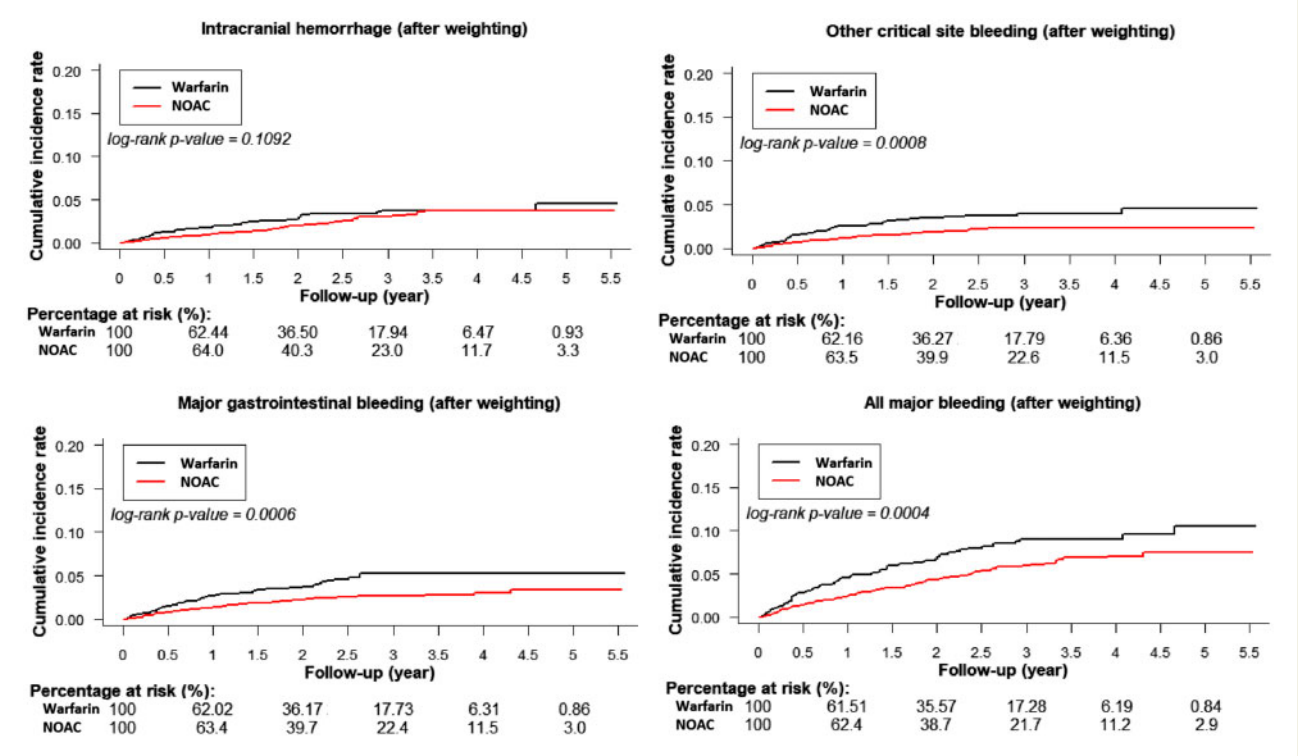


**Figure 4** Cumulative incidence rates of safety outcomes for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting. Cumulative incidence curves of safety outcomes including intracranial haemorrhage, major gastrointestinal bleeding, other critical site bleeding, and all major bleeding for atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting are presented. Non-vitamin K antagonist oral anticoagulant was associated with a lower risk of gastrointestinal bleeding, other critical site bleeding, and all major bleeding than warfarin among atrial fibrillation patients with concomitant peripheral artery disease. AF, atrial fibrillation; AMI, acute myocardial infarction; GIB, gastrointestinal bleeding; ICH, intracranial haemorrhage; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; PSSW, propensity score stabilized weighting.

apixaban (2.5 mg twice daily), and edoxaban (30 mg once daily), respectively ($P < 0.001$). In addition, the NOAC group had a lower prescribing rate of concomitant APT than warfarin group (25% vs. 42%; $P < 0.001$) The subgroup analysis showed consistent results for effectiveness, major adverse limb evens, and safety for NOACs vs. warfarin among those patients with/without DM as well as the main analysis (Supplementary material online, *Figure SI*). It is noted that NOAC was associated with a lower risk of AMI than warfarin among patients with DM (HR: 0.40, 95% CI: 0.26–0.62; $P < 0.0001$). For the CKD subgroup analysis, NOAC was associated with a lower risk of lower limb amputation, major GIB, other critical site bleeding, and all major bleeding than warfarin among those patients with or without CKD. Of note, the advantage of a lower risk of AMI, lower extremity thromboembolism, and revascularization for NOAC vs. warfarin was majorly contributed from the CKD subgroup (Supplementary material online, *Figure SII*). For the age subgroup analysis, it is noted that NOAC was associated with a lower risk of AMI, all major averse limb events, and all safety outcomes including ICH than warfarin among those patients of ≥75 years of age (Supplementary material online, *Figure SIII*). For the subgroup analysis of patients taking concomitant APT, the advantage of a lower risk of major bleeding for NOAC vs. warfarin was majorly from the APT (-) subgroup (Supplementary material online, *Figure SIV*).

## Discussion

To our knowledge, this is the largest population-based study to investigate the effectiveness, safety, and major limb outcomes for NOACs vs. warfarin in AF patients with concomitant PAD. Our results indicated that NOACs were associated with a comparable risk of IS, and were associated with a lower risk of AMI, major adverse limb events, and all major bleeding when compared with warfarin among AF patients with concomitant PAD. The advantage of NOACs over warfarin persisted in several high-risk subgroups including those patients of ≥75 years of age, the presence of underlying DM, CKD, or concomitant use of APT.

Although NOACs had been recommended over than warfarin for the AF population with concomitant PAD according to the guidelines, current evidences were still very limited.[7,8] There were only two studies investigating the use of NOACs in AF patients with concomitant PAD from *post hoc* subgroup analysis of the NOAC

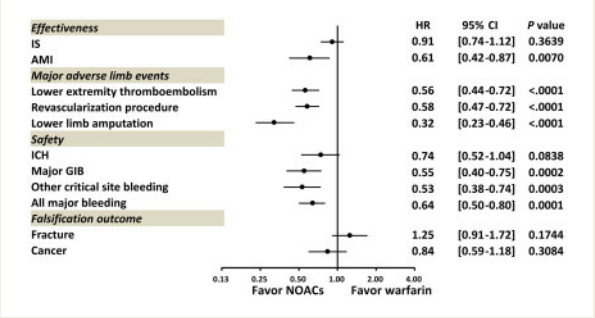


**Figure 5** Forest plot of hazard ratio of outcomes for non-vitamin K antagonist oral anticoagulant vs. warfarin among atrial fibrillation patients with concomitant peripheral artery disease taking oral anticoagulants after propensity score stabilized weighting. Non-vitamin K antagonist oral anticoagulant was associated with a comparable risk of ischaemic stroke and was associated with a significantly lower risk of acute myocardial infarction, major adverse limb events, and major bleeding events than warfarin among atrial fibrillation patients with concomitant peripheral artery disease. The falsification analysis indicated that non-vitamin K antagonist oral anticoagulant was not associated with an increased or decreased risk of bone fracture or cancer than warfarin after propensity score stabilized weighting. AF, atrial fibrillation; AMI, acute myocardial infarction; CI, confidential interval; HR, hazard ratio; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; PSSW, propensity score stabilized weighting.

trials.[18,19] The subgroup analysis of the ROCKET AF trial indicated that rivaroxaban had a similar risk of thromboembolism but a higher risk of major bleeding than warfarin among 839 AF patients with concomitant PAD.[18] The subgroup analysis of ARISTOTLE trial showed a comparable risk of thromboembolism and bleeding events between apixaban and warfarin in 884 AF patients with concomitant PAD.[19] Of note, those results are both derived from *post hoc* subgroup analysis of the pivotal NOAC studies, and should be interpreted carefully as hypothesis-generating rather than definitive.

Our present study showed a compatible result indicating that NOAC was associated with a comparable risk of ischaemic stroke to warfarin among those AF patients with concomitant PAD. In contrast to previous two studies, our result indicated that NOAC was associated with a lower risk of major bleeding than warfarin among the AF population with concomitant PAD. The benefit may be explained by the results from the *post hoc* analyses of four pivotal studies of NOACs, showing that NOACs exhibit a more reduction of major bleeding over warfarin for Asians vs. non-Asians.[20] Our analysis is also compatible with a recent study showing that NOACs may be associated with a lower risk of AMI than warfarin in a large real-life cohort setting.[21] Warfarin inhibits the carboxylation Matrix Gla protein, an inhibitor of calcification, which may worsen vascular calcification and atherosclerosis.[21–23] Furthermore, patients with PAD have a higher risk of bleeding events compared to those without PAD, and the bleeding events may further increase the risk of ischaemic events in PAD patients (e.g. discontinue OAC or APT due to bleeding may cause consequent ischaemic event like AMI).[24] Nevertheless, the present study uses a real-world, observational, and non-randomized cohort, which may be prone to be confounding by indication even after statistical adjustment [e.g. a perceived risk may result in conscious avoidance in use of specific NOAC (e.g. dabigatran) in specific patient populations (e.g. patients with a high risk of AMI)]. Whether NOACs associated with a lower risk of AMI than warfarin in an AF population with concomitant PAD requires further elucidation.

PAD patients have been emphasized on taking APT to reduce the risk of adverse CV events, but there were limited studies to investigate OAC or APT regimens for the outcomes of adverse limb events in PAD patients.[7] Although the subgroup analyses from PEGASUS-TIMI 54 trial showed that ticagrelor significantly reduced the risk of major adverse limb events comparing with aspirin among patients with prior MI and concomitant PAD, the EUCLID trial showed no significant difference of limb outcomes between ticagrelor and clopidogrel group among a population of pure PAD.[25,26] Recently, the COMPASS trial showed a strategy of combined therapy with aspirin and rivaroxaban (2.5 mg twice per day) or rivaroxaban alone (5 mg twice per day) had a significant reduction in major adverse limb events than aspirin alone in a stable PAD population, which indicated a potential benefit of OAC in improving the limb outcome in such patient population.[27] Of note, our data indicated that NOAC was superior to warfarin regarding the outcomes of adverse limb events among AF patients with concomitant PAD. Nevertheless, further randomized and prospective studies are necessary to evaluate the limb outcomes among AF population with concomitant PAD treated with NOACs vs. warfarin.

## Limitations

First, our study is a retrospective cohort study. Although inverse propensity score weighting with several variables allowed the balance of comorbidities among the study groups, residual confounding by unmeasured variables and selective prescribing behaviour could not be excluded in the present study. Second, the NHIRD does not contain serum creatinine. The coding of CKD depends on the physician's choice, the results of CKD population may have been biased. The renal function may interfere with the decision regarding the choices for OACs or the use of dosage for each patient. Third, as with many similar registries globally (whether from USA, Europe, Asia, Australia, etc.), we are unable to obtain INR values for patients treated with warfarin from NHIRD database. It had been reported that the time in therapeutic range (TTR; INR in target of 2.0–3.0) in Asians was substantially lower than patients in other regions of the world.[28] Therefore, the superiority of NOACs over warfarin may be partly due to low TTR for those patients taking warfarin.[20] In addition, a high prevalence of low-dose NOAC prescription was noted in the present study group; therefore, whether the advantage of a lower bleeding risk of NOACs over warfarin persisted in patients taking standard-dose NOACs remains unclear. Fourth, although we utilized several criteria for selecting clinical evidence of PAD, our PAD study patients may be only a part of the whole PAD population. Clinically, PAD patients are hard to be completely screened out, possibly due to a high prevalence of under-diagnosis or under-treatment in PAD population; therefore, the incidence of asymptomatic PAD may be higher than symptomatic PAD.[29,30] Fifth, miscoding and misclassification of the underlying comorbidities and outcomes registered by each physician is another limitation. Nevertheless, we only

considered primary discharge diagnoses to improve the outcome accuracy. Sixth, the diagnosis codes of NHIRD were shifted from ICD-9-CM to ICD-10-CM after 1 January 2016. In the present study, we adopted the ICD-9-CM coding indicating each patient's comorbidities and outcomes according to previous studies investigating the effectiveness and safety of NOAC vs. warfarin in AF patients.[31–33] On the other hand, we adopted the ICD-10-CM coding indicating the same comorbidities and outcomes according to other two studies.[34,35] The potential bias due to the transition of different coding systems cannot be ruled out in the present study. Finally, a previous study showed that NOACs may be more effective and safer in Asians than in non-Asians.[20] Thus, whether our results can be extrapolated to the non-Asian population remained unclear.

# Conclusions

Non-vitamin K antagonist oral anticoagulant was associated with a comparable risk of ischaemic stroke and was associated with a significantly lower risk of major adverse limb events and major bleeding events than warfarin among those AF patients with concomitant PAD. Thromboprophylaxis with NOACs may be considered for such patient population, and further prospective study is necessary to evaluate the effectiveness, safety, and limb outcomes for NOACs vs. warfarin with/without concomitant APT among the patient population in the future.

# Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

## Acknowledgments

This study is based in part on data from the National Health Insurance. Research Database provided by the National Health Insurance Administration, Ministry of Health and Welfare, Taiwan. The interpretation and conclusions contained herein do not represent those of the National Health Insurance Administration, Ministry of Health and Welfare, or National Health Research Institutes.

## Funding

This study was supported by grants 108-2314-B-182-053-MY2, 105-2628-B-182A-003-MY3, and 105-2628-B-182-014-MY3 from the Ministry of Science and Technology and grants CMRPG3J0841, CMRPG3J1371, and CMRPG3K0021 from Chang Gung Memorial Hospital, Linkou, Taiwan.

**Conflict of interest:** G.Y.H.L.: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. The remaining authors have no conflict of interest to declare.

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