Non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists in atrial fibrillation patients with previous stroke or intracranial hemorrhage: A systematic review and meta-analysis of observational studies

Zongwen Guo MD1 | Xiaoli Ding MD2 | Zi Ye MS3 | Weiling Chen MD4 | Yijian Chen MD2

1Department of Critical Care Medicine, Soochow University, Suzhou, Jiangsu Province, China
2Clinical Laboratory, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi Province, China
3Internal Medicine, Royal North Shore Hospital, St Leonards, New South Wales, Australia
4Department of Hematopathology, Gannan Medical University, Ganzhou, Jiangxi Province, China

Correspondence
Yijian Chen, MD, Clinical Laboratory, The First Affiliated Hospital of Gannan Medical University, Ganzhou, Jiangxi Province, China. Email: chenyj2005@163.com

Abstract
Several observational studies have compared the effectiveness and safety outcomes between nonvitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) in atrial fibrillation (AF) patients with a history of either stroke/transient ischemic attack (TIA) or intracranial hemorrhage. Therefore, our current meta-analysis aimed to address this issue. The Cochrane Library, PubMed, and Embase databases were systematically searched until December 2020 for all relevant observational studies. We applied a random-effects model to pool adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for this meta-analysis. A total of 10 studies were included. Among patients with a history of stroke/TIA, the use of NOACs versus VKAs was associated with decreased risks of stroke (HR, 0.82, 95% CI 0.69–0.97), systemic embolism (HR, 0.73, 95% CI 0.61–0.87), all-cause death (HR, 0.87, 95% CI 0.81–0.94), major bleeding (HR, 0.77, 95% CI 0.64–0.92) and intracranial hemorrhage (HR, 0.54, 95% CI 0.38–0.77). Among patients with a history of intracranial hemorrhage, the use of NOACs versus VKAs was associated with reduced risks of stroke (HR, 0.81, 95% CI 0.68–0.95), all-cause death (HR, 0.68, 95% CI 0.49–0.94), and intracranial hemorrhage (HR, 0.66, 95% CI 0.51–0.84). Compared with VKAs, the use of NOACs exhibited superior efficacy and safety outcomes in AF patients with previous stroke/TIA, and the use of NOACs was associated with reduced risks of stroke, all-cause death, and intracranial hemorrhage in patients with a history of intracranial hemorrhage.

KEYWORDS
anticoagulants, atrial fibrillation, intracranial hemorrhage, stroke
1 | INTRODUCTION

Oral anticoagulants (OACs) have been extensively prescribed for patients with atrial fibrillation (AF) as the first-line treatment to prevent stroke or other systemic embolisms.\(^1\)\(^2\) Vitamin K antagonists (VKAs), predominantly warfarin, were the only available class of oral anticoagulants over the past decades until 2009 when nonvitamin K antagonist oral anticoagulants (NOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban) were introduced.\(^3\) Several studies have been conducted to compare the effectiveness and safety of NOACs versus VKAs among patients with AF.

Although it has been well-demonstrated by previously published meta-analyses that NOACs have an advantageous risk–benefit profile in stroke prophylaxis, intracranial hemorrhage, and all-cause mortality in comparison with warfarin among patients with AF,\(^3\)\(^6\) the heterogeneity of the effectiveness and safety between NOACs and VKAs has not been revealed for a specific subgroup of patients, namely AF patients with a past medical history of stroke/transient ischemic attack (TIA), or intracranial hemorrhage. Given that patients in this subgroup are susceptible to recurrent cerebrovascular ischemic events\(^7\) as well as intracranial hemorrhage,\(^8\) which is the most lethal adverse effect of anticoagulants,\(^9\) it is thus of significance to scrutinize their different responses to NOAC and VKA anticoagulant therapies. In this meta-analysis of real-world studies, we address the discrepancies in effectiveness and safety outcomes between NOACs and VKAs in AF patients who have previously been diagnosed with a stroke/TIA, or intracranial hemorrhage.

2 | METHODS

Our current meta-analysis was performed based on the Cochrane handbook for systematic reviews. The results of this study were arranged based on the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses (PRISMA). Given that no patients were involved in the establishment of the research question, the outcome measures, and the design or the implementation of this meta-analysis, ethical approval was necessary. The data, methods, and materials of this study are available to others for purposes of reproducing the results or replicating procedures by contacting the corresponding author.

2.1 | Search strategy

The three electronic databases (the Cochrane Library, PubMed, and Embase) were systematically searched up to December 2020 by two reviewers. We potentially included studies that evaluated the comparisons of effectiveness and safety between NOACs and VKAs in AF patients with a history of stroke and/or intracranial hemorrhage. We used the following search items including: (1) atrial fibrillation; AND (2) non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban; AND (3) vitamin K antagonists OR warfarin OR coumadin OR acenocoumarol OR phenprocoumon OR fluindione OR phenindione OR anisindione. Cross-referencing was also applied to identify potentially missed studies. The reference lists of meta-analyses and systematic reviews were reviewed and retrieved for more studies. We applied no restrictions on language in the searches.

2.2 | Study eligibility

Eligible studies were included if they met all of the following criteria: (1) observational studies focusing on nonvalvular AF patients with a history of stroke/TIA or patients with a history of intracranial hemorrhage; (2) comparisons of outcomes between NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) and VKAs (warfarin, coumadin, phenprocoumon, acenocoumarol, fluindione, phenindione, or anisindione); (3) the effectiveness outcomes included stroke, systemic embolism, and all-cause death, while the safety outcomes included major bleeding, intracranial hemorrhage, and gastrointestinal bleeding. We only included studies that reported the effect estimates: adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). If one study reported adjusted HRs in multiple models, the most adjusted model was included.

We applied the following exclusion criteria: (1) studies were duplicated publications; (2) publications had no relevant data (e.g., reviews, case reports, editorials, and comments); (3) studies focused on AF patients after interventions, such as cardioversion, ablation, or left-atrial appendage closure.

2.3 | Study selection and data collection

The retrieved pieces of literature were imported into the NoteExpress V3.0 software (Beijing Aegean Sea Music Technology Co., Ltd.; http://www.inoteexpress.com/aegean/), and we deleted duplicate records. Two reviewers independently screened the titles and abstracts of the retrieved records. Then, the full texts of the records were reviewed to identify all potentially eligible studies. Any disagreement was addressed by discussion or was resolved by an additional reviewer. For each included study, we mainly collected the following data: the first author and publication year, study design, data source, inclusion period, type of NOACs and VKAs, the reported effectiveness and safety outcomes, and the adjusted effect estimates. Two reviewers independently collected the data and compared the results to ensure coherence.

2.4 | Quality assessment

For the observational studies, two reviewers independently evaluated the methodological quality using the Newcastle-Ottawa Scale (NOS) tool. This tool involved three blocks: the selection of cohorts, the comparability of cohorts, and outcome evaluation. A study can be
| Included studies         | Data source                          | Study period                     | Age (y)               | Females (%) | HAS-BLED (mean) | CHADS2-VASc (mean) | AF population | Number of participants | NOACs   | VKAs      | Outcomes of interest | Follow-up (years) | Quality assessment |
|--------------------------|--------------------------------------|----------------------------------|-----------------------|-------------|----------------|-------------------|---------------|------------------------|---------|-----------|----------------------|------------------|-------------------|
| Yang L-2020              | Medicare Part D                      | January 2013–December 2014      | 76.42 ± 8.66          | 56.10       | 3.64 ± 0.94    | 4.54 ± 1.76       | Stroke/TIA    | 4927                   | DA; RIV; API   | Warfarin  | IS, SE, GIB           | 0.66             | 7 points          |
| Seiffge DJ-2019          | European and Japanese prospective, observational cohorts | NA                               | 77.33 ± 9.65          | 48.00       | 3.00 ± 1.48    | 5.00 ± 1.48       | IS            | 4912                   | NOACs   | Phenprocoumon, warfarin | At least 0.25   | 9 points          |
| Xian Y-2019              | Patient-Centered Research into Outcomes Stroke Patients Prefer and Effectiveness Research study; Get with The Guidelines-Stroke program | October 2011–December 2014      | 80.00 ± 8.91          | 56.30       | NA             | 4.00 ± 1.48       | IS            | 11 662                  | NOACs   | Warfarin  | Death, IS, SE, ICH, GIB | 3.12             | 8 points          |
| Larsen TB-2014           | Danish national prescription registry | August 2011–May 2013 (DA); August 2009–May 2013 (warfarin) | 76.77 ± 9.26          | 47.47       | 2.93 ± 0.94    | 4.73 ± 1.33       | Stroke/TIA    | 6141                   | DA      | Warfarin  | IS, TIA, IS/TIA        | 1.04             | 8 points          |
| Komen JJ-2019            | Stockholm Healthcare Database        | September 2011–June 2018         | 73.61 ± 10.96         | 44.30       | NA             | 3.29 ± 1.92       | IS; ICH       | 4967                   | NOACs   | Warfarin  | Death               | 2.00             | 7 points          |
| Park J-2019              | National Health Insurance Service of Korea | January 2010–April 2018           | 75.20 ± 9.10          | 49.00       | 420 ± 1.10     | 5.90 ± 1.40       | Stroke        | 61 568                  | DA; RIV; API; EDO | Warfarin  | Stroke, MB, death     | 0.70             | 8 points          |
| Coleman CI-2017          | US Truven MarketScan data           | January 2012–June 2015           | 72.72 ± 13.03         | 53.07       | 394 ± 0.82     | 5.00 ± 1.48       | Stroke/TIA    | 9684                   | DA; RIV; API   | Warfarin  | IS, ICH, MB            | 0.55             | 7 points          |
| Nielsen PB-2019          | Danish nationwide databases         | January 2003–April 2017          | 77.4 ± 9.0            | 42.80       | NA             | 4.30 ± 1.60       | ICH           | 622                    | NOACs   | Warfarin  | IS, ICH              | 3.00             | 8 points          |
| Tsai C-2020              | Taiwan National Health Insurance Research Database | January 2012–December 2016      | 76.3 ± 10.2           | 45.5        | 431 ± 1.15     | 5.43 ± 1.81       | ICH           | 4540                   | NOACs   | Warfarin  | IS, ICH, MB, death    | 5.00             | 8 points          |
| Lee S-2020               | Korean Health Insurance Review and Assessment database | January 2010–April 2018          | 73.7 ± 9.6            | 44.2        | 440 ± 1.20     | 4.00 ± 1.50       | ICH           | 5712                   | NOACs   | Warfarin  | IS, ICH              | 9.27             | 8 points          |

Note: Hypertension, age ≥ 75 years, diabetes mellitus, prior stroke/transient ischemic attack (2 points); CHADS2-VASc, congestive heart failure/left ventricular ejection fraction ≤40%, hypertension, age ≥ 75 years (2 points), diabetes mellitus, prior stroke/transient ischemic attack/thromboembolism (2 points), vascular disease, age 65–74 years, female sex.

Abbreviations: API, apixaban; CHADS2, congestive heart failure; DA, dabigatran; EDO, edoxaban; GIB, gastrointestinal bleeding; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, Drugs/alcohol concomitantly; ICH, intracranial hemorrhage; IS, ischemic stroke; NA, not available; NOACs, non-Vitamin K antagonist oral anticoagulants; RIV, rivaroxaban; SE, systemic embolism; TIA, transient ischaemic attack; VKAs, vitamin K antagonists.
awarded a maximum of one point for each numbered item within the selection and outcome categories. A maximum of two points can be given for comparability. A study with an NOS score of <6 was defined as low quality.10,11 Disputable issues were resolved by consensus, or discrepancies were resolved by an additional reviewer.

2.5 | Statistical analysis

The statistical analyses were performed using Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark). We used heterogeneity analysis to quantify the degree of heterogeneity of $I^2$ calculations. $I^2 > 50\%$ of the value indicated substantial heterogeneity. The natural logarithms of HRs and standard errors of the included studies were calculated.12 Considering the possible heterogeneity existing in the eligible studies, we applied a random-effects model with an inverse variance method for this meta-analysis. To verify the robustness of the results, sensitivity analyses were performed by excluding the studies one by one or using a fixed-effects model. Subgroup analyses could not be performed due to the limited data. According to the Cochrane handbook, the funnel plot should generally not be considered when the included studies were less than 10. The comparisons were considered two-sided, and $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Included study features

The flow diagram of the literature search is shown in Supplemental Figure 1. A total of 4685 studies were identified during the electronic search, and we deleted 1624 duplicate publications among the the Cochrane Library, PubMed, and Embase. A total of 3006 studies were
excluded based on title and abstract screenings. Then, 55 studies were screened based on the full texts. Finally, a total of 10 observational studies were potentially included in this meta-analysis.13-22 Six13-16,18,19 and three studies20-22 focused on AF patients with a history of stroke/TIA, and a history of intracranial hemorrhage, respectively, and one study assessed these two populations.17 The baseline characteristics of the included studies are shown in Table 1 and Supplemental Tables 1-2. Regarding the quality assessment, the 10 observational studies exhibited acceptable quality.

3.2 | NOACs versus VKAs in patients with previous stroke/TIA

Seven included studies reported AF patients with a history of stroke/TIA.13-19 Regarding effectiveness outcomes, compared with VKA use, the use of NOACs was associated with decreased risks of major bleeding (HR, 0.77, 95% CI 0.64-0.92; p = .004; I² = 16%) and intracranial hemorrhage (HR, 0.54, 95% CI 0.38-0.77; p = .0006; I² = 21%). There was no significant difference in the rate of gastrointestinal bleeding (HR, 1.13, 95% CI 0.95-1.35; p = .17; I² = 40%) (Figure 2).

3.3 | NOACs versus VKAs in patients with previous intracranial hemorrhage

A total of four studies evaluated the comparisons of effectiveness and safety between NOACs and VKAs in AF patients with a history of intracranial hemorrhage.17,20-22 As shown in Figure 3, compared with VKA use, the use of NOACs was associated with reduced risks of stroke (HR, 0.81, 95% CI 0.68-0.95; p = .009; I² = 0%), all-cause death (HR, 0.68, 95% CI 0.49-0.94; p = .02; I² = 89%), and intracranial hemorrhage (HR, 0.66, 95% CI 0.51-0.84; p = .0008; I² = 14%). Only 1 study by Tsai et al reported the outcome of major bleeding between NOACs and VKAs (HR, 0.65, 95% CI 0.53-0.67), whereas none of the included studies focused on the outcomes of systemic embolism and gastrointestinal bleeding. The results of this
3.4 | Sensitivity analysis

After we excluded one study at a time, the corresponding results of this meta-analysis were stable. In addition, the corresponding results did not change substantially when we reperformed the analyses by using a fixed-effects model.

4 | DISCUSSION

To compare the effectiveness and safety outcomes between NOACs and VKAs, our meta-analysis pooled the data from seven\textsuperscript{13-19} and four\textsuperscript{17,20-22} observational studies for AF patients with stroke/TIA and intracranial hemorrhage, respectively. For patients with histories of stroke/TIA, NOACs illustrated superior effectiveness and safety outcomes compared with VKAs, with statistically significant reductions in stroke or systemic embolic events, all-cause mortality, major bleeding, and intracranial hemorrhage. Moreover, NOACs showed lower risks of stroke, all-cause mortality, and intracranial hemorrhage than VKAs for patients with previous intracranial hemorrhage. In general, NOACs were associated with a favorable effectiveness profile for stroke and all-cause mortality and superior safety outcomes of intracranial hemorrhage compared with VKAs for AF patients with a history of stroke/TIA or intracranial hemorrhage.

The superior effectiveness and safety outcomes of NOACs in stroke and intracranial hemorrhage shown in our results are consistent with similar RCTs and observational studies for AF patients with prior stroke/TIA or intracranial hemorrhage.\textsuperscript{11} Previous studies have elaborated that this superiority is predominantly attributed to significant prevention against hemorrhagic stroke. Given that hemorrhagic stroke is included in both stroke and intracranial hemorrhage, NOACs consequently reduce their risk profiles by halving the risk of hemorrhagic stroke.\textsuperscript{3} As the most lethal complication of anticoagulant treatment, intracranial hemorrhage is a well-recognized factor in risk–benefit assessment for ischaemic stroke prophylaxis among patients with AF.\textsuperscript{8,23} Anticoagulant treatment accounts for one in six hospital admissions for intracranial hemorrhage, resulting in up to 40% 30-day mortality.\textsuperscript{9,20,24} Our study revealed a significantly lower incidence of intracranial hemorrhage in patients on NOACs compared with patients on VKAs for both stroke/TIA and intracranial hemorrhage subgroups. This finding is consistent with evidence from RCTs for patients with AF.\textsuperscript{3} However, several observational studies illustrated that compared with VKAs, NOACs had lower or similar rates of intracranial hemorrhage in AF patients with a history of stroke/TIA or intracranial hemorrhage.
intracranial hemorrhage, suggesting that NOACs are at least non-
inferior to VKAs regarding the outcome of intracranial hemorrhage.
Due to the limited number of included studies, further investigation
is necessary to reveal the discrepancies in intracranial hemorrhage risk
profiles between AF patients with and without prior stroke/TIA or
intracranial hemorrhage.

The reintroduction of OACs for ischemic event prophylaxis in
patients with AF sustaining intracranial hemorrhage should balance
the recurrent bleeding risk if the risk of stroke is left untreated.31
There was a universal exclusion of patients with a previous intracra-
nial hemorrhage for all four landmark NOAC trials.32-35 Therefore,
the present study included all available observational studies comparing
the effectiveness or safety between NOACs and VKAs for this under-
represented AF patients sustaining intracranial hemorrhage. To the
best of our knowledge, this was the first meta-analysis emphasizing
real-world data that were lacking in RCTs and providing complemen-
tary information to the existing evidence regarding anticoagulation
treatment for stroke prophylaxis.

In addition to the associations of NOACs being associated with
lower incidences of stroke and intracranial hemorrhage, the all-cause
mortality correlated with NOAC use was significantly reduced com-
pared with that correlated with VKA use. Nevertheless, reductions in
all-cause mortality were not indicated in most Phase 3 NOAC
trials,32,33,35 except for apixaban34 and low-dose edoxaban.35 Our
meta-analysis provides more robust estimates to detect differences in
secondary outcomes and subgroups.

4.1 | Limitations

Some limitations have been identified in our study. First, our statisti-
cal analysis was performed without individual participant data for all
the included observational studies. Although each study’s methodo-
logical quality was evaluated by using the NOS tool, we pooled the
data from these studies, of which the quality and robustness were
unavoidably variable and inconsistent. Second, the severity, imaging,
and functional disabilities of prior stroke/TIA or intracranial hemor-
rhage were not addressed and adjusted, which might have con-
ounded the study outcomes. Third, the protocol of the systematic
review and meta-analysis was not registered in the PROSPERO data-
bases. Fourth, although the adjusted data from the included studies
were used in our pooled analysis, the residual confounders still
existed due to the nature of the observations studies. Fourth, the
time in the therapeutic range of warfarin users was not considered
in our pooled analysis due to the limited data. As such, we should
interpret the results of this meta-analysis cautiously, and our find-
ings might not be completely generalizable to all the patients in real-
world settings. Finally, only one study by Tsai et al. reported the out-
come of major bleeding between NOACs and VKAs, whereas none
of the included studies focused on the outcomes of systemic embo-
lism and gastrointestinal bleeding. Further studies should examine
these outcomes between NOACs and VKAs in AF patients with a
history of intracranial hemorrhage.

5 | CONCLUSION

Compared with VKAs, the use of NOACs exhibited superior efficacy
and safety outcomes in AF patients with a history of stroke/TIA, and
the use of NOACs was associated with reduced risks of stroke, all-
cause death, and intracranial hemorrhage in patients with a history of
intracranial hemorrhage.

CONFLICT OF INTEREST

All authors declare that they have no potential conflicts of
interest that might be relevant to the contents of this review.

AUTHOR CONTRIBUTIONS

Data curation: Zongwen Guo, Xiaoli Ding. Formal analysis: Zongwen
Guo, Xiaoli Ding. Investigation: Zongwen Guo, Weiling Chen. Method-
ology: Zongwen Guo, Xiaoli Ding. Software: Zi Ye. Supervision: Yijian
Chen. Validation: Zongwen Guo. Writing—original draft: Zongwen Guo,
Xiaoli Ding, Zi Ye. Writing—review and editing: Yijian Chen.

DATA AVAILABILITY STATEMENT

Availability of data and materials have been described in the manu-
script. They are freely available to any scientist who wishes to use
them without breaching participant confidentiality.

ORCID

Zi Ye https://orcid.org/0000-0002-4554-7451
Yijian Chen https://orcid.org/0000-0002-5757-684X

REFERENCES

1. Lip GYH, Freedman B, De Caterina R, Potpara TS. Stroke prevention
in atrial fibrillation: past, present and future. Thromb Haemost. 2017;
117(07):1230-1239. https://doi.org/10.1160/TH16-11-0876.
2. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the
management of atrial fibrillation developed in collaboration with
EACTS. Eur Heart J. 2016;37(38):2893-2962. https://doi.org/10.
1093/eurheartj/ehw210.
3. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the effi-
cacy and safety of new oral anticoagulants with warfarin in patients
with atrial fibrillation: a meta-analysis of randomised trials. Lancet.
2014;383(9921):955-962. https://doi.org/10.1016/S0140-6736
(13)62343-0.
4. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-
analysis of efficacy and safety of new oral anticoagulants (dabigatran,
riloxaban, Apixaban) versus warfarin in patients with atrial fibrilla-
tion. Am J Cardiol. 2012;110(3):453-460. https://doi.org/10.1016/j.
amcard.2012.03.049.
5. Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, Agno G. Effi-
cacy and safety of the novel oral anticoagulants in atrial fibrillation.
Circulation. 2012;126(20):2381-2391. https://doi.org/10.1161/
CIRCULATIONAHA.112.115410.
6. Lip GYH, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons
of new oral anticoagulant drugs for efficacy and safety when used for
stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60(8):
738-746. https://doi.org/10.1016/j.jacc.2012.03.019.
7. Hankey GJ. Secondary stroke prevention. Lancet Neurol. 2014;13(2):
178-194. https://doi.org/10.1016/S1474-4422(13)70255-2.
8. Brønnum Nielsen P, Larsen TB, Gorst-Rasmussen A, Skjøth F,
Rasmussen LH, Lip GYH. Intracranial hemorrhage and subsequent
ischemic stroke in patients with atrial fibrillation. Chest. 2015;147(6):1651-1658. https://doi.org/10.1378/chest.14-2099.

Van Asch CJ, Luitse MJ, Rinkel GJ, Van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167-176. https://doi.org/10.1016/S1474-4422(09)70340-0.

Liao X-Z, Fu Y-H, Ma J-Y, Zhu W-G, Yuan P. Non-vitamin K antagonist Oral anticoagulants versus warfarin in patients with atrial fibrillation and peripheral artery disease: a systematic review and meta-analysis. Cardiovasc Drugs Ther. 2020;34(3):391-399. https://doi.org/10.1007/s10557-020-06962-6.

Liu X, Xu ZX, Yu P, Yuan P, Zhu WG. Non-vitamin K antagonist Oral anticoagulants in secondary stroke prevention in atrial fibrillation patients: an updated analysis by adding observational studies. Cardiovax Drugs Ther. 2020;34(4):569-578. https://doi.org/10.1007/s10557-020-06961-7.

Zhou Y, Ma J, Zhu W. Efficacy and safety of direct Oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis. Am J Cardiovasc Drugs. 2020;20(1):51-60. https://doi.org/10.1007/s40256-019-00362-4.

Yang L, Brooks MM, Glynn NW, Zhang Y, Saba S, Hernandez I. Real-world direct comparison of the effectiveness and safety of Apixaban, dabigatran, rivaroxaban, and warfarin in Medicare beneficiaries with atrial fibrillation. Am J Cardiol. 2020;126:29-36. https://doi.org/10.1016/j.jamcard.2020.03.034.

Seifghe DJ, Paciaroni M, Wilson D, et al. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. Ann Neurol. 2019;85(6):823-834. https://doi.org/10.1002/ana.25489.

Xian Y, Xu H, O’Brien EC, et al. Clinical effectiveness of direct Oral anticoagulants vs warfarin in older patients with atrial fibrillation and ischemic stroke: findings from the patient-centered research into outcomes stroke patients prefer and effectiveness research (PROSPER) study. JAMA Neurol. 2019;76(10):1192-1202. https://doi.org/10.1001/jama-neurol.2019.2099.

Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjæth F, Lane DA, Lip GYH. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. Am J Med. 2014;127(12):1172-1178.e5. https://doi.org/10.1016/j.amjmed.2014.07.023.

Komen JJ, Forslund T, Mantel-Teeuwisse AK, Klungel OH, Von Euler M, Braunischweig F, Wallén H, Hjmdahl P. Association of Preceding Antithrombotic Therapy in atrial fibrillation patients with ischemic stroke, intracranial hemorrhage, or gastrointestinal bleed and mortality. Eur Heart J Cardiovasc Pharmacother. 2019. doi: https://doi.org/10.1016/j.ehjcpv.2019.03.001.

Park J, Lee S-R, Choi E-K, et al. Effectiveness and safety of direct Oral anticoagulant for secondary prevention in Asians with atrial fibrillation. J Clin Med. 2019;8(12):2228. https://doi.org/10.3390/jcm8122228.

Coleman CI, Peacock WF, Bunz TJ, Alberts MJ. Effectiveness and safety of Apixaban, dabigatran, and rivaroxaban versus warfarin in patients with Nonvalvular atrial fibrillation and previous stroke or transient ischemic attack. Stroke. 2017;48(8):2142-2149. https://doi.org/10.1161/STROKEAHA.117.017474.

Nielsen PB, Skjæth F, Segård M, Kjeldgaard JN, Lip GYH, Larsen TB. Non-vitamin K antagonist Oral anticoagulants versus warfarin in atrial fibrillation patients with intracerebral hemorrhage. Stroke. 2019;50(4):939-946. https://doi.org/10.1161/STROKEAHA.118.023797.

Tsai CT, Liao JN, Chiang CE, et al. Association of Ischemic Stroke, major bleeding, and other adverse events with warfarin use vs non-vitamin K antagonist Oral anticoagulant use in patients with atrial fibrillation with a history of intracerebral hemorrhage. JAMA Neurol. 2020;76(6):206424. https://doi.org/10.1001/jamaneurolopen.2020.6424.

Lee SR, Choi EK, Kwon S, et al. Oral anticoagulation in Asian patients with atrial fibrillation and a history of intracranial hemorrhage. Stroke. 2020;51:416-423. https://doi.org/10.1161/STROKEAHA.119.028030.

Lopes RD, Guimarães PO, Kolls BJ, et al. Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy. Blood. 2017;129(22):2980-2987. https://doi.org/10.1182/blood-2016-08-731638.

Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med. 2007;120(8):700-705. https://doi.org/10.1016/j.amjmed.2006.07.034.

Chen S-J, Yeh S-J, Tang S-C, Lin S-Y, Tsai L-K, Jeng J-S. Similar outcomes between vitamin K and non-vitamin K antagonist oral anticoagulants associated intracerebral hemorrhage. J Formos Med Assoc. 2020;119(1):106-112. https://doi.org/10.1016/j.jfma.2019.02.008.

Hagi J, Tomita H, Metoki N, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment. Stroke. 2014;45(9):2805-2807. https://doi.org/10.1161/STROKEAHA.114.006661.

Inohara T, Xian Y, Liang L, et al. Association of intracerebral hemorrhage among patients taking non-vitamin K antagonist vs vitamin K antagonist oral anticoagulants with in-hospital mortality. JAMA. 2018;319(9):463-473. https://doi.org/10.1001/jama.2017.21917.

Kurogi R, Nishimura K, Nakai M, et al. Comparing intracerebral hemorrhages associated with direct oral anticoagulants or warfarin. Neurology. 2018;90(13):e1143-e1149. https://doi.org/10.1212/WNL.0000000000005207.

Wilson D, Charidimou A, Shakeshaft C, et al. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. Neurology. 2016;86(4):360-366. https://doi.org/10.1212/WNL.000000000002310.

Tsivgoulis G, Katsanos AH, Seifghe DJ, et al. Fatal intracranial haemorrhage occurring after oral anticoagulant treatment initiation for secondary stroke prevention in patients with atrial fibrillation. Eur J Neurol. 2020;27(8):1612-1617. https://doi.org/10.1111/ene.14280.

Nielsen PB, Larsen TB, Skjæth F, Gorst-Rasmussen A, Rasmussen LH, Lip GYH. Restarting anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding. Circulation. 2015;132(6):517-525. https://doi.org/10.1161/CIRCULATIONAHA.115.015735.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-1151. https://doi.org/10.1056/NEJMoa090561.

Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in Nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891. https://doi.org/10.1056/NEJMoa1009638.

Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation receiving anticoagulation therapy. N Engl J Med. 2011;365(11):981-992. https://doi.org/10.1056/NEJMoa1107039.

Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-2104. https://doi.org/10.1056/NEJMoa1310907.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.