Oral anticoagulant use for stroke prevention in atrial fibrillation patients with difficult scenarios

Ting-Yung Chang, Jo-Nan Liao, Tze-Fan Chao *, Jennifer Jeanne Vicera, Chin-Yu Lin, Ta-Chuan Tuan, Yenn-Jiang Lin, Shih-Lin Chang, Li-Wei Lo, Yu-Feng Hu, Fa-Po Chung, Shih-Ann Chen *

Heart Rhythm Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan
Institute of Clinical Medicine, and Cardiovascular Research Institute, National Yang-Ming University, Taipei, Taiwan

Abstract

Atrial fibrillation (AF) has become the most prevalent arrhythmia and it will increase the risk of ischemic stroke, heart failure, mortality, sudden cardiac death, myocardial infarction, and dementia. Stroke prevention with oral anticoagulant is crucial for management of AF patients. Vitamin K antagonist, which inhibits the clotting factors II, VII, IX and X, has been recommended for stroke prevention for decades. Non-Vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban and edoxaban are at least as effective as warfarin in reducing ischemic stroke with a lower rate of major bleeding. With the increasing prevalence of AF, prescription of the appropriate oral anticoagulants (OACs) according to patient’s characteristics becomes a challenge. This review article aims to provide an overview of anticoagulant use in AF patients with difficult scenarios.

© 2018 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a potential for blood stasis and increased risk of thrombus formation particularly in the left atrial appendage, resulting in hospitalizations, hemodynamic abnormalities, and thromboembolic events [1]. The current prevalence of AF is about 1% in the general population, increases with age [2], and is estimated to reach 4.01% in 2050 [3]. In 2011, the lifetime risk of AF was reported to be about 1 in 7 for subjects aged ≥20 years [3]. In comparison to patients without AF, AF increases the risk of ischemic stroke (adjusted hazard ratio [aHR] = 3.34), heart failure (aHR = 3.31), mortality (aHR = 2.61), sudden cardiac death (aHR = 1.83), myocardial infarction (aHR = 1.62) and dementia (aHR = 1.56) [3]. Oral anticoagulants (OACs) reduce the risk of ischemic stroke in patients with AF who have an additional stroke risk factor. Warfarin is a vitamin K antagonist that inhibits the synthesis of clotting factors II, VII, IX and X and has been used for prevention of ischemic stroke in patients with AF [4]. However, warfarin is prone to several drug and food interactions, which needs blood testing to maintain the international normalized ratio (INR) within the therapeutic range.

Non-Vitamin K antagonist oral anticoagulants (NOACs) directly target the specific clotting factor. The factor Xa inhibitors and direct factor IIa (thrombin) inhibitors have a more predictable anticoagulant effect, that does not require regular monitoring. Four large international phase III randomized controlled trials have demonstrated that compared with warfarin, these four NOACs are non-inferior or superior for prevention of stroke and systemic embolus and reduce the risk of intracranial hemorrhage [5–9]. Current guideline [1] suggests that anticoagulation should be considered for patients with AF with a CHA2DS2-VASc score of 1 or more for men or 2 or more for women. The HAS-BLED scoring system can be used to estimate the risk of bleeding with OACs. Nevertheless, OACs should not be withheld unless the risk of bleeding is unacceptably high.

With the increasing number of AF patients, prescription of the appropriate OACs according to patient’s characteristics becomes a challenge. This review article aims to provide the evidence of warfarin and NOACs in AF patients with difficult scenarios and Tables 1 and 2 summarize those clinical studies.

2. Elderly patients

According to the ATRIA study [2], the prevalence of AF was 0.95% and it increases to 9.0% in persons aged 80 years or older from 0.1% among adults younger than 55 years. Symptomatic cerebral infarction was 2.4 times more common in older patients with paroxysmal AF than in older patients with sinus rhythm [10]. The risk of intracranial hemorrhage (ICH) in anticoagulated patients increases with advancing age [11], with mortality rates in excess of 50%, three times higher than...
that of ischemic stroke. Thus, aging is a risk factor for ischemic stroke and ICH in patients with AF and attention should be paid to balance the risks of bleeding and thrombosis.

In the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, which enrolled >7200 elderly patients (≥75 years), dabigatran 110 mg bid was associated with a similar risk in patients aged ≥75 years compared with warfarin [5]. However, a non-significant higher risk of major bleeding was observed in patients aged ≥75 years with dabigatran 150 mg bid. Both doses of dabigatran had lower rates of ICH in this trial. One real-world study that included >47,000 AF patients also demonstrated the same results [12]. In elderly patients (≥75 years), dabigatran was associated with lower rates of ICH.

In a subgroup analysis of the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial [13], 6229 elderly AF patients taking warfarin or rivaroxaban were compared, and the results showed comparable efficacy and safety of rivaroxaban with warfarin in elderly patients. In a subgroup analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study, the efficacy of apixaban in reducing the incidence of ischemic stroke was evident in elderly patients. The annual rate of ischemic stroke for apixaban and warfarin in patients was 1.6%/year vs. 2.2%/year, respectively, in patients ≥75 years. Similarly, the safety of apixaban was demonstrated with a rate of major bleeding of 3.3%/year vs. 5.2%/year in patients ≥75 years compared with warfarin [8]. In the ENGAGE AF-TIMI (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction) 48 trial, 8474 elderly patients (age ≥75 years) were enrolled, and after 2.8 years of follow-up, the rates of stroke event was similar in major bleeds or ICH between warfarin and aspirin. Recently, Chao TF et al. [16] investigated the risk of ischemic stroke and ICH of OAC treatment and found that the risk of ischemic stroke was similar between AF patients aged ≥90 years treated with warfarin or NOACs, but the risk of ICH was substantially lower with warfarin, while major bleeding was significantly reduced with edoxaban [14].

Very elderly patients (age ≥90 years) are under-represented in RCTs, and even the largest prospective RCT in elderly subjects (BAFTA Infarction) 48 trial, only had modest numbers (approx. 10%) of subjects age ≥90 years) are under-represented in RCTs, and even the largest prospective RCT in elderly subjects (BAFTA Infarction) 48 trial, only had modest numbers (approx. 10%) of subjects age ≥90 years). Therefore, the effectiveness and safety of NOACs in this group are not well-established. Based on small pharmacokinetic and/or pharmacodynamic studies without clinical data, it is recommended that NOACs are considered as thromboprophylaxis for very elderly patients with NOACs and ICH.

Table 1

| Scenarios | Clinical study | OAC | HR for ischemic stroke/systemic embolism (95% CI) | HR for major bleeding (95% CI) | HR for ICH (95% CI) | Comments |
|------------|----------------|-----|-----------------------------------------------|-------------------------------|-------------------|----------|
| Elderly (≥75 year-old) | Connolly SJ, 2009 [5] | Dabigatran 150 mg | **0.67 (0.49–0.90)** | **1.18 (0.98–1.42)** | **0.42 (0.25–0.70)** | Compared with warfarin. Dabigatran 150 mg reduced ischemic stroke. Both doses reduced risk of ICH. |
| | Patel M, 2011 [7] | Dabigatran 110 mg | 0.88 (0.66–1.17) | 1.01 (0.83–1.23) | **0.37 (0.21–0.64)** | Rivaroxaban had similar safety and efficacy, compared with warfarin. |
| | | Rivaroxaban 20 mg | 0.80 (0.63–1.02) | 1.11 (0.92–1.34) | **0.80 (0.50–1.28)** | |
| | Granger CB, 2011 [8] | Apixaban | – | – | – | Apixaban had better efficacy and safety than warfarin in this subgroup. |
| | Giugliano RP, 2013 [6] | Edoxaban | 0.83 (0.66–1.04) | – | **0.83 (0.70–0.99)** | Edoxaban has better safety than warfarin. |
| Very elderly (≥90 year-old) | Chao TF, 2018 [16] | NOACs | – | – | **0.32 (0.10–0.97)** | Compared with warfarin. NOACs were associated with a lower risk of ICH. |
| CKD stage III (eGFR: 30–50 mL/min) | Connolly SJ, 2009 [5] | Dabigatran 150 mg | **0.56 (0.37–0.85)** | **1.01 (0.79–1.30)** | **0.31 (0.14–0.66)** | Compared with warfarin. Dabigatran 150 mg reduced ischemic stroke. Both doses reduced risk of ICH. |
| | Patel M, 2011 [7] | Rivaroxaban 15 mg | 0.84 (0.57–1.23) | 0.95 (0.72–1.26) | **0.81 (0.41–1.60)** | Rivaroxaban had similar safety and efficacy, compared with warfarin. |
| | Granger CB, 2011 [8] | Apixaban | 0.79 (0.55–1.14) | – | **0.50 (0.38–0.66)** | Apixaban reduces major bleeding, compared with warfarin. |
| | Giugliano RP, 2013 [6] | Edoxaban (high dose arm) | 0.93 (0.67–1.30) | – | **0.76 (0.58–0.98)** | Edoxaban has lower rate of major bleeding and ICH than warfarin. |
| CKD stage IV (eGFR: 15–30 mL/min) | FDA label | Dabigatran 75 mg | – | – | – | Based on small pharmacokinetic and/or pharmacodynamic studies without clinical data. |
| | Patel M, 2011 [7] | Rivaroxaban 15 mg | – | – | – | Limited clinical data. |
| | FDA label | Apixaban | – | – | – | Based on small pharmacokinetic and/or pharmacodynamic studies without clinical data. |
| ESRD | Sioutis KC, 2018 [31] | Apixaban | 0.88 (0.69–1.12) | – | **0.72 (0.59–0.87)** | Compared with warfarin. Apixaban was associated with lower risks of major bleeding. |
| Previous ICH | Nielsen PB, 2015 [32] | NOACs & Warfarin | – | – | – | Compared with no antithrombotic treatment, OAC reduced ischemic stroke/all-cause mortality rates (HR = 0.55). |

CKD = chronic kidney disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = Hazard ratio; ICH = intracranial hemorrhage; NCB = net clinical benefit; NOAC = Non-Vitamin K antagonist oral anticoagulants; OAC = oral anticoagulants; PCI = percutaneous coronary intervention; RR = relative risk. Bold and italic values indicate statistically significant difference between two groups.
Table 2
Evidence from clinical studies for efficacy and safety of OACs in difficult scenarios of patients with atrial fibrillation, part II.

| Scenarios               | Study                                      | OAC                        | HR for ischemic stroke/systemic embolism (95% CI) | HR for major bleeding (95% CI) | HR for ICH (95% CI) | Comments                                                                 |
|-------------------------|--------------------------------------------|----------------------------|--------------------------------------------------|--------------------------------|---------------------|--------------------------------------------------------------------------|
| VHD                     | Ezekowitz MD, 2016 [35]                    | Dabigatran 150 mg          | 0.59 (0.37–0.93)                                 | 0.82 (0.64–1.06)               | 0.36 (0.17–0.77)    | Dabigatran 150 mg reduced ischemic stroke and ICH, compared with warfarin. |
|                         |                                            | Dabigatran 110 mg          | 0.97 (0.65–1.45)                                 | 0.73 (0.56–0.95)               | 0.29 (0.13–0.68)    | Dabigatran 110 mg has similar rates of ischemic stroke and reduced major bleeding and ICH, compared with warfarin. |
|                         | Avezum A. 2015 [36]                       | Apixaban                   | 0.7 (0.51–0.97)                                  | 0.79 (0.61–1.04)               | 0.28 (0.14–0.57)    | Apixaban reduces ischemic stroke and ICH, compared with warfarin.       |
|                         | De Caterina, 2017 [38]                    | Edoxaban (High dose arm)   | 0.71 (0.43–1.18)                                 | 0.74 (0.53–1.02)               | 0.39 (0.15–0.98)    | Both doses of edoxaban have similar rate of ischemic stroke and lower rate of ICH. Low dose edoxaban has lower major bleeding, compared with warfarin. |
|                         |                                            | Edoxaban (Low dose arm)    | 1.11 (0.71–1.73)                                 | 0.41 (0.28–0.60)               | 0.29 (0.11–0.79)    |                                                                           |
|                         | Breithardt G [37]                         | Rivaroxaban                | 0.83 (0.55–1.27)                                 | 1.56 (1.14–2.14)               | 1.27 (0.58–2.79)    | Rivaroxaban has similar efficacy and ICH rate, but increases major bleeding, compared with warfarin. |
|                         | Renda G, 2017 [39]                        | NOACs (higher-dose)        | RR = 0.7 (0.58–0.86)                             | RR = 0.93 (0.68–1.27)          | RR = 0.47 (0.24 to 0.93) | NOACs reduce stroke and ICH compared with warfarin. Apixaban, dabigatran, and edoxaban reduce bleeding. Major bleeding is increased in VHD patients treated with rivaroxaban. |
|                         | Pan KL, 2017 [40]                         | NOACs (higher-dose)        | 0.70 (0.60–0.82)                                 | 0.93 (0.67–1.28)               | 0.47 (0.24–0.92)    |                                                                           |
| Bioprosthetic heart valve | Pokorney SD, 2015 [43]                    | Apixaban                   | –                                                 | –                              | –                   | No difference in risk of stroke and major bleeding between the apixaban and warfarin group. |
|                         | Carnicelli AP, 2017 [44]                  | Edoxaban (high dose arm)   | 0.37 (0.1–1.42)                                  | 0.5 (0.15–1.67)                | –                   | Higher-dose edoxaban has similar rates of stroke and major bleeding compared with warfarin. Lower-dose edoxaban has similar rates of stroke but lower rates of major bleeding. |
|                         |                                            | Edoxaban (low-dose arm)    | 0.53 (0.16–1.78)                                 | 0.12 (0.01–0.95)               | –                   |                                                                           |
| Concomitant PCI          | Dewilde WJ, 2013 [46]                     | warfarin plus clopidogrel  | In comparison to triple therapy (warfarin plus aspirin and P2Y12 inhibitor), HR = 0.60 (0.38–0.94) for secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularization, and stent thrombosis) |                                                                           |                                                                           | Warfarin use was associated with a lower risk of ischemic stroke and positive NCB compared with non-treatment. |
|                         | Cannon CP, 2017 [47]                      | Dabigatran 150 mg plus P2Y12 inhibitor | In comparison to triple therapy (warfarin plus aspirin and P2Y12 inhibitor), HR = 0.36 (0.26–0.50) for any bleeding |                                                                           |                                                                           |                                                                           |
|                         |                                            | Dabigatran 110 mg plus P2Y12 inhibitor | Dual-Therapy Group (110 mg), HR = 0.52 (0.42–0.63); Dual-Therapy Group (150 mg), HR = 0.72 (0.58–0.88) for major or clinically relevant non-major bleeding events. |                                                                           |                                                                           |                                                                           |
|                         | Gibson CM, 2016 [48]                      | Rivaroxaban 15 mg plus P2Y12 inhibitor | Dual-Therapy Groups (Combined), HR = 1.04 (0.84 to 1.29) for risk of thromboembolic events. |                                                                           |                                                                           |                                                                           |
|                         |                                            | Rivaroxaban 2.5 mg plus aspirin and P2Y12 inhibitor | Low dose Rivaroxaban Group, HR = 0.59 (0.47–0.76); very low dose Rivaroxaban Group, HR = 0.63 (0.50–0.80) for clinically significant bleeding. |                                                                           |                                                                           |                                                                           |
| Cirrhosis               | Kuo L, 2017 [49]                         | Warfarin                   | 0.76 (0.58–0.99)                                 | –                              | 1.27 (0.82–1.95)    |                                                                           |

CKD = chronic kidney disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = Hazard ratio; ICH = intracranial hemorrhage; NCB = net clinical benefit; NOAC = Non-Vitamin K antagonist oral anticoagulants; OAC = oral anticoagulants; PCI = percutaneous coronary intervention; RR = relative risk. Bold and italic values indicate statistically significant difference between two groups.
The prevalence of AF among individuals with chronic kidney disease (CKD) is much higher than in the general population and increases with age and advancing CKD [17]. In a multiethnic cohort of non-CKD patients with eGFR of 30 to 49 mL/min (including those on dialysis), the prevalence of AF was nearly 12% [19]. In general, the presence of CKD is also associated with increased hemorrhagic events, including intracerebral hemorrhage [20] and gastrointestinal bleeding [21].

As the risk of bleeding increases with the severity of CKD, patients with severe CKD were excluded from randomized phase III trials of OACs for stroke prevention in AF. The use of OACs in these patients is challenging because limited trial data are available to suggest optimal treatment strategies. All NOACs depend on renal clearance to varying degree (dabigatran 80%, rivaroxaban 66%, apixaban 27%, edoxaban 50%), so accumulation in patients with impaired renal function will increase the risk of bleeding.

Warfarin has been shown to reduce ischemic stroke in populations with mild to moderate CKD. Recent observational data from Danish registries [22] concluded that prescription of warfarin in non-dialysis-dependent CKD patients with CHA2DS2-VASc scores >2 was associated with a lower composite risk for fatal stroke and fatal bleeding.

In the RE-LY trial, dabigatran 150 mg bid was demonstrated to decrease the hazard of ischemic stroke among participants with estimated glomerular filtration rate (eGFR) of 30 to 49 mL/min in comparison to warfarin treatment, with similar risk for major bleeding between dabigatran and warfarin. However, dabigatran 110 mg bid versus warfarin had similar hazards of both ischemic stroke and bleeding [23]. In the ROCKET AF trial [7], patients with eGFR of 30 to 49 mL/min were prescribed 15 mg rivaroxaban daily and the results showed equivalent rates of the primary efficacy endpoint of ischemic stroke and the safety endpoint of major bleeding between rivaroxaban and warfarin.

In the ARISTOTLE trial, among patients with eGFR of 25 to 50 mL/min, apixaban was related to significantly lower risk for major bleeding with equivalent risk for ischemic stroke [24]. In the ENGAGE AF-TIMI 48 trial [14], among patients in high-dose edoxaban group, 19.5% had an eGFR of 30 to 50 mL/min and received half-dose edoxaban (30 mg daily). In this CKD subgroup, no difference was noted between edoxaban versus warfarin in terms of the efficacy endpoints, but risk for major bleeding and ICH were significantly lower with edoxaban compared to warfarin. In summary, among patients with moderate CKD, all 4 NOACs are generally non-inferior to warfarin in the reduction of ischemic stroke in non-valvular AF, except for dabigatran 150 mg bid, which demonstrated superiority endpoints.

On the basis of pharmacological modelling, rivaroxaban, apixaban and edoxaban (but not dabigatran) have been approved in Europe for thromboprophylaxis in patients with severe CKD (eGFR 15–29 mL/min) not on dialysis, using reduced-dose regimens [25]. Based on pharmacokinetic studies, the US Food and Drug Administration (FDA) also approved the use of reduced-dose dabigatran (75 mg bid) in patients with AF with an eGFR of 15–29 mL/min as well as the use of apixaban (5 mg bid) in patients with AF and end-stage renal disease (ESRD) on dialysis [26,27]. Among patients with ESRD with non-valvular AF, the benefit of anticoagulation therapy is controversial due to conflicting evidence demonstrated in observational studies. Data from Danish registries showed a benefit in association of warfarin in reducing ischemic stroke without significant increase in risk for bleeding, accompanied by reduction of all-cause mortality [22]. However, data from a US dialysis registry showed opposite results, warfarin therapy was associated with higher risk for new stroke [28]. In a large meta-analysis that enrolled 56,146 patients with ESRD with non-valvular AF, the benefit of anticoagulation therapy was associated with significantly lower all-cause mortality [22]. The absence of efficacy and the increased bleeding risk gives rise to the question of the role of warfarin for non-valvular AF in patients with ESRD.

Although the 4 NOAC trials excluded patients with ESRD, one observational study concluded that bleeding events were similar between apixaban and warfarin in patients with eGFR <25 mL/min (including those on dialysis) [30]. One recent retrospective cohort study of 25,523 patients with ESRD on dialysis and AF demonstrated that in the matched cohorts, apixaban was associated with a significantly lower risk of major bleeding compared to warfarin [31]. Further clinical studies are needed before routine use of NOACs can be recommended in patients with eGFR <30 mL/min.

### 4. Patients with previous intracranial hemorrhage

Although NOACs have a more favorable safety profile than warfarin, the annual risk of ICH among NOAC-treated patients is 0.5% [5–8]. The acute development of ICH confers a poor prognosis with a high rate of mortality and disability, whether or not a NOAC is used. Patients with AF who survive an ICH are at an increased risk of subsequent ischemic stroke [32], hence, restarting OAC after ICH should be considered in patients with stable condition. However, patients with prevalent ICH were excluded from randomized clinical trials of OAC for stroke prevention.

In one study of Danish nationwide registries cohort [33], the authors enrolled patients with incident ICH and stratified those patients according to treatment regimens (no treatment, OACs with warfarin or NOACs,
and antiplatelet therapy) after the intracranial hemorrhage. After 1 year of follow-up, the rate of ischemic stroke and all-cause mortality (per 100 person-years) for patients treated with OACs was 13.6, in comparison with 27.3 for nontreated patients and 25.7 for patients receiving antiplatelet therapy. The adjusted hazard ratio of ischemic stroke and all-cause mortality was 0.55 in patients on OACs in comparison with no treatment. Thus, OACs were associated with a significant reduction in ischemic stroke and all-cause mortality rates, supporting OACs with warfarin or NOACs reintroduction after ICH as feasible.

5. Patients with valvular heart disease

Current guidelines suggest NOACs for patients with non-valvular AF and warfarin for “valvular” AF. There is no clear consensus about the term “valvular” AF, however. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society AF guidelines define “valvular” AF related to rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair. The 2016 ESC guidelines avoided the term ‘valvular AF’ and referred simply to ‘AF related to hemodynamically significant mitral stenosis or prosthetic mechanical heart valves’ [34].

Current approval of apixaban, dabigatran, edoxaban, and rivaroxaban by European Medicines Agency (EMA) and US FDA only includes the indication of patients with non-valvular AF. Nevertheless, these 4 anticoagulants have data in patients with certain types of valvular AF. The RE-LY trial [5] excluded patients with significant mitral stenosis, prosthetic heart valves, and valvular heart disease (VHD) needing an intervention. A subgroup analysis of the RE-LY trial found that 3950 (21.8%) participants had VHD, and the most common type was mitral regurgitation [35]. Patients with VHD who received dabigatran 150 mg bid had a significantly lower risk of ischemic stroke compared with those who received warfarin, and patients with VHD who received dabigatran 110 mg bid had similar rates of ischemic stroke compared with those who received warfarin, regardless of the treatment assignment.

The ARISTOTLE trial [8] excluded patients with moderate to severe mitral stenosis and mechanical heart valves, but enrolled patients with other types of VHD. Among the participants, 4808 (26.4%) patients had a history of moderate or severe VHD or previous heart valve surgery. The majority of VHD had mitral or tricuspid regurgitation. A subgroup analysis of VHD patients in the ARISTOTLE trial [36] found that patients with VHD treated with apixaban had less bleeding than those with VHD treated with warfarin.

The ROCKET AF trial excluded patients with mitral stenosis or artificial heart valves, but a subgroup analysis in 2003 (14%) patients with significant valve disease, defined as aortic stenosis, aortic regurgitation or mitral regurgitation [37], found that though risk of ischemic stroke in patients treated with rivaroxaban compared with warfarin were consistent among patients with VHD and without VHD, Rivaroxaban was related to an increased risk of major bleeding compared with warfarin in patients with mitral or aortic regurgitation.

The ENGAGE AF-TIMI 48 trial excluded patients with moderate to severe mitral stenosis or a mechanical heart valve. Among the enrolled patients, 2824 (13%) patients had a history of moderate or severe VHD, and the most common type was mitral regurgitation. The subgroup study [38] reported that in the VHD group, patients treated with both doses of edoxaban had similar rate of ischemic stroke and lower rate of ICH. The low dose arm had lower rate of major bleeding.

About 13% to 26% of patients in the 4 landmark trials had VHD and in the subgroup analysis of these trials, the presence of VHD did not affect the efficacy or safety of NOACs, except for Rivaroxaban, which was related to an increased risk of major bleeding compared with warfarin in patients with mitral or aortic regurgitation. Data from 2 meta-analyses pooling the results from the sub-analyses of the 4 major trials demonstrated that NOACs can reduce the risk of ischemic stroke in patients with AF and VHD compared with those with AF without VHD [39,40]. Based on these results, patients with AF and specific types of VHD are suitable for anticoagulation with NOACs.

6. Patients with prosthetic valve

According to 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease [41], after the sixth postoperative month, patients with mitral or aortic valve biological replacement in sinus rhythm can be treated without warfarin therapy, in the absence of other thrombogenic condition.

The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Exetilate in Patients After Heart Valve Replacement (RE-ALIGN) study enrolled and randomized 252 patients with a mechanical bileaflet mitral or aortic valve to receive dabigatran or warfarin [42]. The study was stopped early due to an interim safety analysis that determined that there was excess risk and absence of benefit for the patients in the dabigatran group. Nine (5%) patients in the dabigatran group had stroke while no patient in the warfarin group did. Bleeding occurred in 45 (27%) dabigatran-treated patients in comparison to 10 (12%) patients in the warfarin group. The RE-ALIGN study suggested that dabigatran at the doses studied was less effective than warfarin for stroke prevention in patients with mechanical heart valves and was associated with an increased risk of bleeding. Therefore, dabigatran should not be considered in patients with mechanical heart valves.

A subgroup analysis of patients with bioprosthetic valves enrolled in the ARISTOTLE trial [43] showed that there was no difference in the risk of stroke and major bleeding between the apixaban group and the warfarin group. Another subgroup analysis of patients enrolled in the ENGAGE AF-TIMI 48 trial who underwent a bioprosthetic heart valve replacement ~30 days prior to study randomization demonstrated that this subgroup had similar rates of ischemic stroke whether they received edoxaban (30 mg or 60 mg) or warfarin [44]. Patients with bioprosthesis valves treated with edoxaban 60 mg had similar risk of major bleeding as those treated with warfarin, and those who received edoxaban 30 mg had lower risk of bleeding compared with those who received warfarin.

For now, based on the RE-ALIGN study, patients with mechanical valves should receive warfarin treatment. However, the subgroup analysis of the ARISTOTLE and ENGAGE AF-TIMI 48 trials suggested that apixaban and edoxaban were reasonable alternatives to warfarin in patients with AF and remote bioprosthesis valve replacement. These studies paved the way for future studies of routine NOACs use in patients with prosthetic heart valve.

7. Patients receiving percutaneous coronary intervention

The 2018 Joint European consensus suggested that triple therapy in the form of OAC, aspirin and clopidogrel should be considered for 1—6 months after an acute coronary syndrome (ACS) [45]. The optimal duration of such triple therapy depends on the patient’s ischemic and bleeding risks. A NOAC is generally safer than warfarin, with respect to bleeding risk and is the preferred option in the absence of contraindications to these drugs.

The WOEST trial randomized 573 patients who were treated with long-term OACs undergoing percutaneous coronary intervention (PCI) to clopidogrel alone or clopidogrel plus aspirin [46]. Among the enrolled patients, 25% had an ACS. After a median follow-up of 358 days, the combined secondary endpoint of death (myocardial infarction, stroke, target-vessel revascularization, and stent thrombosis) was lower with clopidogrel and OAC (dual therapy), as was the secondary endpoint of all-cause death. The primary endpoint of bleeding was significantly lower with dual therapy compared with triple therapy.

The RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous
Coronary Intervention] trial enrolled ~2700 patients with AF undergoing PCI. Among these patients, dabigatran (110 mg or 150 mg bid) plus a P2Y12 inhibitor was compared to triple therapy (warfarin plus aspirin and P2Y12 inhibitor) [47]. The results demonstrated that both doses of dabigatran reduced the risk of major bleeding, while the risk of stroke was equivalent between dabigatran plus a P2Y12 group and triple therapy group. The risks of MI and stent thrombosis were similar between the dual and triple therapy, suggesting a role for dabigatran plus single antiplatelet therapy (SAPT) in patients with AF undergoing PCI.

The role of rivaroxaban in patients with AF receiving PCI was investigated in the PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial [48]. Around 2000 Patients were randomized into three groups: rivaroxaban 15 mg once daily plus SAPT for 12 months, rivaroxaban 2.5 mg twice daily plus dual antiplatelet therapy (DAPT) for a duration of 1, 6 or 12 months or triple therapy with warfarin plus DAPT for a duration of 1, 6 or 12 months. The results demonstrated that both doses of rivaroxaban had lower risk of the composite safety endpoint of clinically relevant bleeding in comparison to triple therapy. In terms of efficacy outcomes, both rivaroxaban-based groups were associated with similar risks of ischemic stroke in comparison to triple therapy.

In patients with a low risk of bleeding, triple therapy may be extended to 3–6 months depending on the clinical scenario. After this period of triple therapy, OAC plus aspirin or clopidogrel should be considered for up to 12 months after PCI. After 1 year it is reasonable to maintain OAC alone. In cases of high bleeding risk, dual therapy (OAC plus aspirin or clopidogrel) may be considered from the time of discharge and continued for 1 year, followed thereafter by OAC alone. When NOACs are used, in general, dose reduction below the approved doses for stroke prevention is not recommended.

8. Patients with cirrhosis

Liver cirrhosis is a late stage of liver fibrosis frequently characterized by thrombocytopenia and coagulopathy which is prone to bleeding events. Nevertheless, the co-existence of AF in patients with liver cirrhosis not only increases the risk of ICH but also increases the risk of ischemic stroke [49]. Therefore the use of OAC in patients with AF and liver cirrhosis remains challenging and judicious decisions are warranted. Randomized clinical trials of NOACs for stroke prevention in atrial fibrillation particularly excluded patients with liver cirrhosis because of a certain degree of liver metabolism present in all NOACs. In one nationwide study using the National Health Insurance Research Database in Taiwan [49], patients with AF, liver cirrhosis and a CHA2DS2-VASc score ≥2 were divided into 3 groups: no treatment, antiplatelet therapy and warfarin groups. The analysis showed that warfarin use was associated with a lower risk of ischemic stroke and positive net clinical benefit compared with the no treatment group. Therefore, warfarin can be a potential choice of anticoagulant for these patients. However, the recommended cut-off value of INR remains unknown. Table 3 provides an abbreviations/terminology section.

9. Conclusion

As AF becomes the most prevalent arrhythmia that is associated with an increased risk of ischemic stroke, stroke prevention is crucial for management of AF patients. The NOACs, such as dabigatran, rivaroxaban, apixaban and edoxaban, are at least as effective as warfarin in reducing ischemic stroke with a lower rate of major bleeding. This review article provides the evidence on the performance of NOACs in AF patients with different clinical conditions. Despite the evidence from recent trials, further research is necessary for patients undergoing PCI, bioprosthetic valve replacement, transcatheter aortic valve intervention, Mitraclip and for those requiring long-term antiplatelet therapy over anticoagulation.

Disclosure

This work was supported in part by grants from the Ministry of Science and Technology (MOST 107-2314-B-075-022-MY3) and Taipei Veterans General Hospital (V107C-200, V107B-001, V107B-022), Taipei, Taiwan.

Conflict of interests

None.

References

[1] C.T. January, L.S. Wann, J.S. Alpert, H. Calkins, J.E. Cigarroa, J.C. Cleveland Jr, J.R. Conti, P.T. Ellinor, M.D. Ezekowitz, M.E. Field, K.T. Murray, R.L. Sacco, W.G. Stevenson, P.J. Tchou, CM. Tracy. CW. Yancy, American College of Cardiology/American Heart Association Task Force on Practice Guidelines, 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, J. Am. Coll. Cardiol. 64 (2014) e1–e76.

[2] A.S. Co, E.M. Hylek, K.A. Phillips, Y. Chang, L.E. Hesault, J.V. Selby, D.E. Singer, Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, JAMA 285 (2001) 2370–2375.

[3] T.F. Chao, C.J. Liu, T.C. Tuan, T.J. Chen, M.H. Hoieh, G.Y.H. Lip, S.A. Chen, Lifet ime risks, projected numbers, and adverse outcomes in Asian patients with atrial fibrillation: a report from the Taiwan Nationwide AF cohort study, Chest 153 (2) (2018 Feb) 453–466.

[4] P. Petersen, C. Boyesen, J. Godtfredsen, E.D. Andersen, B. Andersen, Placebo-con trolled, randomised trial of warfarin and aspirin for prevention of thromboemolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study, Lancet 1 (8631) (1989 Jan 28) 175–179.

[5] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, J. Pogue, P.A. Reynolds, E. Thelemes, J. Varrone, S. Wang, M. Alings, D. Xavier, J. Zhu, R. Diaz, B.S. Lewis, H. Darius, H.C. Diener, C.D. Joyner, L. Wallentin, RE-LY Steering Committee and Investigators, Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (12) (2009 Sep 17) 1193–1205.

[6] R.P. Giugliano, C.T. Ruff, E. Braunwald, S.A. Murphy, S.D. Wiviott, J.L. Halperin, A.L. Waldo, M.D. Ezekowitz, J.L. Weitz, J. Spinar, W. Ruzyllo, M. Ruda, Y. Koetseune, J. Betcher, M. Shi, L.T. Grip, S.P. Patel, I. Patel, J.J. Hanyok, M. Mercuri, E.M. Antman, ENGAGE AF-TIMI 48 Investigators, Edoxaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 360 (22) (2013 Nov 28) 2093–2104.

[7] M.R. Patel, K.W. Mahaffey, J. Garg, P. Gan, D.E. Singer, W. Hacke, G. Breithardt, J.L. Halperin, G.J. Hankey, J.P. Riccini, R.C. Becker, C.C. Nessel, J.P. Failli, S.D. Berkowitz, K.A. Fox, R.M. Califf, ROCKET AF Investigators, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N. Engl. J. Med. 365 (10) (2011 Sep 8) 883–891.

[8] C.B. Granger, J.H. Alexander, J.J. Truwer, E.P. Eom, S.D. Lash, J. Harn, H.R. Al-Khalidi, J. Ansell, D. Atar, A. Avezum, M.C. Bahit, R. Diaz, J.D. Easton, J.A. Eikelboom, G. Flaker, D. Garcia, M. Geraldes, B.J. Gersh, S. Golitsyn, S. Goto, A.G. Hermosillo, S.H. Hohnloser, J. Horwitz, P. Mohan, P. Jansky, B.S. Lewis, J.L. Lopez-Sendon, P. Pias, A. Parkhomenko, F.W. Verheugt, J. Zhu, L. Wallentin, ARISTOTLE Committees and Investigators, Apixaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 365 (11) (2011 Sep 15) 981–992.

[9] C.T. Ruff, R.P. Giugliano, E. Braunwald, B.E. Hoffman, N. Deedwania, M.D. Ezekowitz, A.J. Camm, J.L. Weitz, B.S. Lewis, A. Parkhomenko, Y. Yamashita, E.M. Antman, Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials, Lancet 383 (9921) (2014 Mar 15) 955–962.

[10] H. Yamanouchi, T. Mizutani, S. Matsushita, Y. Esaki, Paroxysmal atrial fibrillation: high frequency of embolic brain infarction in elderly autopsy patients, Neurology 49 (6) (1997 Dec) 1601–1604.

[11] M.C. Fang, Y. Chang, E.M. Hylek, J. Rosand, S.M. Greenberg, A.S. Go, D.E. Singer, Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation, Ann. Intern. Med. 141 (1) (2004 Nov 16) 745–752.

[12] M. Avgil-Tsadok, C.A. Jackevicius, V. Essebag, M.J. Eisenberg, R.M. Califf, ROCKET AF Investigators, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation: a phase 3 trial, Circulation 130 (2) (2014 Jul 8) 138–146.
S.H. Hohnloser, Z. Hijazi, L. Thomas, J.H. Alexander, J. Amerena, M. Hanna, M. Keltai, B.E. Stanton, N.S. Barasch, K.B. Tellor, Comparison of the safety and effectiveness of D. Zimmerman, M.M. Sood, C. Rigatto, R.M. Holden, S. Hiremath, C.M. Clase, System-when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial, Eur. Heart J. 33 (22) (2012 Nov) when compared with warfarin in relation to renal function in patients with atrial fibrillation: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 64 (23) (2014 Dec 21) 2571–2589. K. Jensvold, N.L. Robinson, D.L. Dries, L. Bazzano, E.R. Mohler, J.T. Wright, H.J. Balkrishnan, X. Yao, P.A. Noseworthy, N.D. Shah, R. Saran, B.K. Nallamothu, Out-