A case-based approach to implementing guidelines for stroke prevention in patients with atrial fibrillation: balancing the risks and benefits

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Abstract

Atrial fibrillation (AF) puts patients at risk of complications, including stroke. Warfarin therapy has been the mainstay of antithrombotic treatment for reducing the risk of stroke in AF. However, warfarin has limitations that have motivated development of several novel oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban. Clinical trials demonstrate that the NOACs offer efficacy and safety that are equivalent to, or better than, those of warfarin for reducing the risk of stroke in patients with nonvalvular AF. This review examines stroke risk reduction in patients with AF from the perspective of the clinician balancing the risks and benefits of treatment options, evaluates the most recent guidelines, and discusses 2 hypothetical patient cases to better illustrate how clinicians may apply available data in the clinical setting. We reviewed guidelines for the reduction of stroke risk in AF and data from clinical trials on the NOACs. Choosing antithrombotic treatment involves assessing the benefits of therapy versus its risks. Risk indexes, including CHADS2, CHA2DS2-VASc, and HAS-BLED can help determine how to treat patients with AF. Current guidelines suggest using these risk indexes to customize treatment to individual patients. Many current treatment guidelines also incorporate recommendations for the use of NOACs as an alternative to warfarin. As additional data emerge and guidelines are updated, these recommendations will likely evolve. In the interim, clinicians may consider published guidelines and clinical trial results on NOACs. Real-world experience will provide clinicians with additional insight into their treatment decisions.

Keywords: Risk, Benefit, Guidelines, Stroke, Atrial fibrillation

Introduction

Successful healthcare interventions improve patient outcomes and reduce costs associated with disease management. Guidelines provide a standardized, evidence-based approach to the diagnosis and treatment of disease, with a goal of optimizing health outcomes. When available, preventive measures to reduce the risk of disease complications are an important element of treatment. Atrial fibrillation (AF), which affected an estimated 5.2 million adults in the United States in 2010, is a disease state in which patients are at risk of complications, including stroke [1]. AF is a highly prevalent cardiac arrhythmia that imparts a 2- to 7-times greater risk of embolic or transient stroke [2, 3]. AF-related stroke is more severe than stroke without AF, and is associated with greater disability and subsequent medical needs [4, 5]. The high AF-related morbidity is reflected in a substantial economic burden. For 2010, the projected incremental cost of AF in the United States ranged from $6.0 billion to $26.0 billion [6].

Antithrombotic therapy can reduce the risk of stroke in patients with AF [7–11]; however, many at-risk patients are untreated or undertreated [12–15]. Antithrombotic treatment for stroke risk reduction in patients with AF has traditionally focused on anticoagulation with a vitamin K antagonist (VKA), primarily warfarin [2]. Warfarin is highly effective for reducing the risk of stroke. However, warfarin has a narrow therapeutic window and many patients have difficulty remaining within the therapeutic...
range. Under-anticoagulation may lead to stroke, whereas over-anticoagulation may result in bleeding. Warfarin can be challenging to use in the clinical setting due to dietary and drug interactions, and variability in dose response due to genetic and environmental factors [13]. Warfarin necessitates regular monitoring and dose adjustments to enable individual patients to receive safe and effective treatment [13, 16]. Many physicians overestimate bleeding risk and underestimate the benefit of stroke prevention [17]. Bleeding risk and concerns about bleeding risk, as well as other clinical features of warfarin, may lead clinicians to rule it out as a treatment option; hence, many patients remain untreated [18–20]. Until recently, aspirin was the only treatment alternative for patients unsuitable for VKA therapy. Although bleeding risk is lower and administration is simpler with aspirin, the efficacy of aspirin in stroke prevention is inferior to that of warfarin [8, 21]. Thus, the conventional treatment options of warfarin and aspirin have left a segment of the patient population untreated and/or undertreated and at increased risk of stroke [22].

The limitations of the traditional options for stroke prevention in patients with AF have motivated the development of several novel oral anticoagulants (NOACs). Recent clinical trials have found that the NOACs offer efficacy and safety equivalent to, or better than, those of warfarin for reducing the risk of stroke in patients with nonvalvular AF (NVAF) [23–26]. As more clinical experience is gained with the NOACs, changes in treatment paradigms and guidelines will undoubtedly ensue. This review examines stroke prevention in patients with AF from the perspective of the clinician trying to balance the risks and benefits of treatment options. Use of treatment guidelines and the application of findings from recent clinical trials will help facilitate high-quality and cost-effective medical care; however, effective care must be tailored to the individual patient. In addition to reviewing the most recent guidelines for stroke prevention in AF, we will discuss 2 hypothetical patient cases to better understand how clinicians may apply these measures and the available data in the clinical setting.

**Stroke risk reduction in NVAF with NOACs**

Several NOACs are available in the United States for reducing the risk of stroke in patients with NVAF, including the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban [26–30]. A brief summary of the results of key phase 3 clinical trials comparing the NOACs with either warfarin or aspirin for reducing the risk of stroke in NVAF is provided in Table 1 [23–26, 31, 32]. These results provide support for the integration of NOACs into treatment paradigms for stroke risk reduction in AF as potential first-line options.

**Guidelines and quality measures for stroke risk reduction in AF**

Several guidelines discuss stroke risk reduction in patients with AF (Table 2), including recommendations from the American College of Cardiology (ACC), the American College of Chest Physicians (ACCP), the American Heart Association (AHA), the American Stroke Association (ASA), the Heart Rhythm Society (HRS), the European Society of Cardiology (ESC), and the American Academy of Neurology (AAN) [7–11]. In general, treatment decisions are based on an assessment of the individual patient’s stroke risk, with a concurrent assessment of bleeding risk and other patient-related factors, such as his or her ability to adhere to monitoring requirements and personal preferences [7, 10]. However, specific recommendations vary as to how to assess these risks, when to treat with antithrombotic therapy, and which treatments to use.

The CHADS2 and CHA2DS2-VASc risk indexes predict the risk of stroke in patients with AF. Both the ACC/AHA/HRS guidelines and the ESC guidelines mention the ATRIA and HEMORR3 HAGES scores for bleeding risk, but acknowledge that the HAS-BLED risk index is most predictive of bleeding events. Together, these scoring systems can be used to evaluate an approach to treatment in patients with AF. The CHADS2 score is based on patient’s history of Congestive heart failure (1 point), Hypertension (1 point), Age ≥75 years (1 point), Diabetes (1 point), and history of Stroke or transient ischemic attack (TIA, 2 points; Table 3) [33]. Scores of 0, 1, or ≥2 indicate low, moderate, or high stroke risk, respectively [8, 34]. The CHADS2 risk scoring index has been thoroughly validated [33–35]; is simple, inexpensive, and broadly applicable; and most importantly, it allows identification of patients at low risk of stroke who may not receive significant benefit from anticoagulant therapy. However, the CHADS2 risk score has limitations, primarily that patients deemed at low risk with CHADS2 still have a stroke risk of 2.2% per year, in addition, there is a lack of differentiation between stroke risk factors and risk factors that do not consistently predict stroke (i.e., congestive heart failure). As a result, some patients may be identified as moderate- rather than low-risk stroke candidates, or vice versa [33–35]. Also, in keeping the CHADS2 risk score simple, some common stroke risk factors are not included [35, 36].

The ACC/AHA/HRS and ESC advocate using the CHA2DS2–VASc score instead of the CHADS2 score to assess stroke risk. The ESC states that the CHA2DS2–VASc score more accurately identifies “truly low-risk” patients with AF who are not likely to benefit from oral anticoagulant therapy (Table 3) and, conversely, those patients who may benefit from anticoagulation because they are at risk for stroke or systemic thromboembolism [7]. The CHA2DS2–VASc score has been shown to identify some patients considered low risk by CHADS2 (score of 0) to
### Table 1: Phase 3 clinical trials of NOACs: study design and outcomes

| Trial name | Trial design | No. of patients | Outcomes (annual rate vs. comparator, %/y) |
|------------|--------------|----------------|------------------------------------------|
|            |              |                | Stroke/Systemic embolism | All-cause mortality | Major bleeding | Intracranial hemorrhage |
| RE-LY[^a^] (dabigatran) [23, 31] | PROBE design[^b^] | N = 18113 | Dabigatran 150 mg: RR 0.66 (95 % CI 0.53, 0.82; p < 0.001 for superiority) | Major bleeding: Dabigatran 150 mg: RR 0.88 (95 % CI 0.77, 1.00; p = 0.051) | Dabigatran 150 mg: RR 0.40 (95 % CI 0.27, 0.60; p < 0.001) |
|           |              | n = 6076 | Dabigatran 110 mg: RR 0.91 (95 % CI 0.74, 1.11; p < 0.001 for noninferiority) | Dabigatran 110 mg: RR 0.91 (95 % CI 0.80, 1.03; p = 0.13) | Dabigatran 110 mg: RR 0.31 (95 % CI 0.20, 0.47; p < 0.001) |
|           |              | Warfarin (adjusted dose, target INR 2.0–3.0): n = 6022 | HR 0.79 (95 % CI 0.66, 0.95; p = 0.001 for noninferiority) | HR 0.89 (95 % CI 0.80, 0.998; p = 0.047) | HR 0.42 (95 % CI 0.30, 0.58; p < 0.001) |
| ROCKET-AF (rivaroxaban) [25] | Randomized, double-blind, double-dummy, noninferiority trial | N = 14264 | Rivaroxaban 20 mg/d: HR 0.85 (95 % CI 0.70, 1.02; p = 0.07) | Major and CRNM bleeding: HR 1.03 (95 % CI 0.96, 1.11; p = 0.44) | HR 0.67 (95 % CI 0.47, 0.93; p = 0.02) |
|           |              | n = 7131 | Warfarin (adjusted dose, target INR 2.0–3.0): n = 7133 | HR 0.88 (95 % CI 0.75, 1.03; p < 0.001 for noninferiority; p = 0.12 for superiority)^[^f^] | Major bleeding: HR 1.04 (95 % CI 0.90, 1.20; p = 0.58) |
| ENGAGE AF-TIMI 48 (edoxaban) [26] | Randomized, double-blind, double-dummy, noninferiority trial | N = 21105 | Edoxaban 60 mg: HR 0.79 (95.7 % CI 0.63, 0.99; p < 0.001 for noninferiority; p = 0.08 for superiority)^[^f^] | Major bleeding: Edoxaban 60 mg: HR 0.89 (95 % CI 0.71, 0.91; p < 0.001) | Edoxaban 60 mg: HR 0.47 (95 % CI 0.34, 0.63; p < 0.001) |
|           |              | n = 7035 | Edoxaban 30 mg: HR 1.07 (95 % CI 0.87, 1.31; p = 0.005 for noninferiority; p = 0.10 for superiority)^[^f^] | Edoxaban 30 mg: HR 0.87 (95 % CI 0.79, 0.96; p = 0.006) | Edoxaban 30 mg: HR 0.30 (95 % CI 0.21, 0.43; p < 0.001) |
|           |              | Warfarin (adjusted dose, target INR 2.0–3.0): n = 7036 | HR 0.79 (95 % CI 0.66, 0.95; p = 0.001 for noninferiority) | HR 0.89 (95 % CI 0.80, 0.998; p = 0.047) | HR 0.42 (95 % CI 0.30, 0.58; p < 0.001) |
| ARISTOTLE (apixaban) [24] | Randomized, double-blind, double-dummy, noninferiority trial | N = 18201 | Apixaban 5 mg bid: n = 9120 | HR 0.79 (95 % CI 0.66, 0.95; p = 0.001 for noninferiority; p = 0.01 for superiority) | Major bleeding: HR 0.69 (95 % CI 0.60, 0.80; p < 0.001) |
|           |              | Apixaban 5 mg bid: n = 9120 | HR 0.79 (95 % CI 0.66, 0.95; p = 0.001 for noninferiority; p = 0.01 for superiority) | HR 0.89 (95 % CI 0.80, 0.998; p = 0.047) | HR 0.42 (95 % CI 0.30, 0.58; p < 0.001) |
| AVERROES (apixaban) [32] | Randomized, double-blind, double-dummy, superiority trial[^g^] | N = 5599 | Apixaban 5 mg bid: n = 2808 | HR 0.45 (95 % CI 0.32, 0.62; p < 0.001) | HR 0.79 (95 % CI 0.62, 1.02; p = 0.07) | HR 0.85 (95 % CI 0.38, 1.90; p = 0.69) |

[^a^]: NOACs were compared with warfarin in the RE-LY, ROCKET-AF, ENGAGE AF-TIMI 48 and ARISTOTLE trials and with aspirin in the AVERROES trial.
[^b^]: p values are for superiority.
[^c^]: Values for RE-LY are given as RR.
[^d^]: PROBE design.
[^e^]: ITT population.
[^f^]: Modified ITT (mITT) population.
[^g^]: This study was terminated early due to treatment benefit in favor of apixaban.

[^CI]: confidence interval, CRNM: clinically relevant nonmajor, HR: hazard ratio, INR: international normalized ratio, ITT: intention-to-treat, NOAC: novel oral anticoagulant, PROBE: prospective, randomized, open, blinded end-point, RR: relative risk.
| Stroke risk | Guideline recommendations by stroke risk | 2012 AHA/ASA: Scientific Advisory [8] | 2012 ACCP [11] | 2012 ESC [7] | 2014 AAN [9] * | 2014 ACC/AHA/HRS [10] |
|----------------|--------------------------------------|----------------------------------------|----------------|----------------|----------------|----------------------------|
| Low CHADS\(_2\) = 0 | Aspirin, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring | CHADS\(_2\) = 0 | CHADS\(_2\) = 0 | CHA\(_2\)DS\(_2\)-VASc = 0 | Clinicians might not offer anticoagulation to patients with NVAF who lack additional risk factors | CHA\(_2\)DS\(_2\)-VASc = 0 |
| | No therapy suggested rather than antithrombotic therapy | | | No antithrombotic therapy recommended | Clinicians might offer antithrombotic therapy with aspirin or no therapy at all | Reasonable to omit antithrombotic therapy |
| | If antithrombotic therapy chosen, aspirin (75–325 mg/d) suggested rather than OAC or aspirin plus clopidogrel \(b\) | | | | | |
| Moderate CHADS\(_2\) = 1 | Aspirin, based on patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring or adjusted-dose warfarin in appropriate patients | CHADS\(_2\) = 1 | CHADS\(_2\) = 1 | CHA\(_2\)DS\(_2\)-VASc = 1 | | CHA\(_2\)DS\(_2\)-VASc = 1 |
| | OAC suggested rather than no therapy. OAC suggested rather than aspirin alone or aspirin plus clopidogrel \(b\). If OAC unsuitable or not desired, aspirin plus clopidogrel \(b\) suggested rather than aspirin alone | | | OAC therapy with adjusted-dose VKA (INR 2.0–3.0); a direct thrombin inhibitor (dabigatran); an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) should be considered, based upon an assessment of the risk of bleeding complications and patient preferences. For female patients aged 65 years with lone AF (CHA\(_2\)DS\(_2\)-VASc = 1 due to sex), no antithrombotic therapy should be considered | Not discussed | No therapy or OAC or aspirin may be considered |
| | | | | | | |
| High CHADS\(_2\) ≥ 2 | Adjusted-dose warfarin in appropriate patients (in patients unsuitable for warfarin, aspirin plus clopidogrel \(b\) offers more protection against stroke than aspirin but with an increased risk of major bleeding) | CHADS\(_2\) ≥ 2 | CHADS\(_2\) ≥ 2 | CHA\(_2\)DS\(_2\)-VASc ≥ 2 | Clinicians should routinely offer anticoagulation to patients with NVAF and a history of TIA or stroke | CHA\(_2\)DS\(_2\)-VASc ≥ 2 |
| | | | | OAC therapy with adjusted-dose VKA (INR 2.0–3.0); a direct thrombin inhibitor (dabigatran); an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) recommended, unless contraindicated | Clinicians should routinely offer anticoagulation to patients with NVAF and a history of TIA or stroke | OAC recommended (warfarin, dabigatran, rivaroxaban, or apixaban) |

**Table 2** Guidelines for the management of stroke in NVAF

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**Treatment options**

| Adjusted-dose VKA | Guideline recommendations by agent |
|------------------|----------------------------------|
| See recommendations by CHADS\(_2\) score | Patients with AF and mitral stenosis |
| | INR of 2.0–3.0 likely reduces frequency and severity of ischemic stroke vs lower INR levels |
| | Patients with mechanical heart valve (target INR 2.0–3.0 or 2.5–3.5 based on type and location of prosthesis) |
| | Patients with NVAF and CHA\(_2\)DS\(_2\)-VASc ≥ 2 with end-stage CKD (CrCl <15 mL/min) or on hemodialysis |
| Adjusted-dose VKA | Patients with AF and stable CAD |
| Drug          | Dosing and Recommendations                                                                                                                                                                                                 |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dabigatran   | 150 mg bid is an efficacious alternative to warfarin in patients with NVAF who have ≥1 additional risk factor for stroke and CrCl >30 mL/min. Reduce dosage to 75 mg bid in patients with moderate renal impairment (CrCl 15–30 mL/min). |
|              | Recommended over adjusted-dose VKA in cases where OAC recommended. Dabigatran 150 mg bid recommended for most patients. Elderly patients (aged ≥80 y), concomitant use of interacting drugs, HAS-BLED ≥3, moderate renal impairment (CrCl 30–49 mL/min). |
|              | Hemorrhage risk was similar overall between dabigatran 150 mg and warfarin; ICH was less frequent with dabigatran 150 mg than warfarin; GI bleeding more frequent with dabigatran 150 mg than with warfarin. |
|              | Recommended for patients unable to maintain a therapeutic INR level with warfarin. May be considered in patients with renal impairment: 150 mg bid in patients with mild renal impairment (CrCl >30 mL/min); 150 mg or 75 mg bid in patients with moderate renal impairment (CrCl >30 mL/min); 75 mg bid in patients with severe renal impairment (CrCl 15–30 mL/min). |
| Rivaroxaban   | 20 mg/d is a reasonable alternative to warfarin in patients with NVAF at moderate to high risk of stroke (prior history of TIA, stroke, or SE, or ≥2 additional risk factors). 15 mg/d may be considered in patients with renal impairment (CrCl 15–50 mL/min). |
|              | Recommended over adjusted-dose VKA in cases where OAC recommended. Rivaroxaban 20 mg/d recommended for most patients. Rivaroxaban 15 mg/d recommended for: HAS-BLED ≥3, moderate renal impairment (CrCl 30–49 mL/min). |
|              | In patients with NVAF at high risk of cerebral or systemic embolism, probably as effective as warfarin for prevention of cerebral and systemic embolism, with no difference in risk of major bleeding episodes except GI bleeding. |
|              | Recommended for patients unable to maintain a therapeutic INR level with warfarin. May be considered in patients with renal impairment: 20 mg/d for patients with mild renal impairment (CrCl >50 mL/min); 15 mg/d for patients with moderate or severe renal impairment (CrCl 15–50 mL/min). |
| Apixaban      | As an alternative to warfarin or aspirin, 5 mg bid is relatively safe and efficacious in patients with NVAF who have ≥1 additional risk factor and ≤1 of the following additional criteria: |
|              | Not approved at time of guideline preparation. Recommended over adjusted-dose VKA in cases where OAC recommended apixaban 5 mg bid. Associated with lesser frequency of ICH and fatal bleeding compared with warfarin. |
|              | In patients with NVAF at moderate risk of embolism, 5 mg bid is likely more effective than warfarin. Recommended for patients unable to maintain a therapeutic INR level with warfarin. |

* NVAF: Non-valvular atrial fibrillation  
* OAC: Oral anticoagulation  
* VKA: Vitamin K antagonist  
* INR: International normalized ratio  
* CAD: Coronary artery disease  
* TIA: Transient ischemic attack  
* SE: Stroke equivalent  
* CrCl: Creatinine clearance  
* ICH: Intracerebral hemorrhage  
* GI: Gastrointestinal  
* HAS-BLED: Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concommitance
Table 2 Guidelines for the management of stroke in NVAF (Continued)

| Age ≥80 y, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL | Apixaban 2.5 mg bid recommended for patients with renal impairment | Superiority is related to decreased risk of bleeding and reduced mortality, while its effect on reduction in risk of cerebral and systemic embolism is not superior to warfarin | 5.0 mg bid in patients with mild or moderate renal impairment or 2.5 mg bid in patients who meet dose reduction criteria (CrCl ≥1.5 mg/dL, 280 years of age, body weight ≤60 kg) |
| Should not be used in patients with severe renal impairment (CrCl <25 mL/min) | Not approved at time of guideline preparation | Not recommended in patients with severe renal impairment (CrCl <30 mL/min) | Likely more effective than aspirin for decreasing risk of stroke or SE in patients with NVAF who have moderate risk of embolism and are not candidates for warfarin |
| Edoxaban | Not approved at time of guideline preparation | Not approved at time of guideline preparation | Not approved at time of guideline preparation |
| Other agents | Not approved at time of guideline preparation | Not approved at time of guideline preparation | Not approved at time of guideline preparation |

*Superiority is related to decreased risk of bleeding and reduced mortality, while its effect on reduction in risk of cerebral and systemic embolism is not superior to warfarin.*

*Apixaban 2.5 mg bid may be considered in patients with ≥2 of the additional criteria described above.*

*None of the available anticoagulant regimens have been extensively evaluated in the setting of renal impairment. AAN recommends that clinicians use risk stratification tools to help determine stroke risk in patients with NVAF, but cautions physicians not to rigidly interpret anticoagulation thresholds suggested by these tools and does not stratify recommendations using a scoring system.*

*Recommendations made; however, safety and efficacy have not been established.*

*In the United States, clopidogrel and the more recently developed antiplatelet agents, prasugrel and ticagrelor, are used in patients with ACS, but none are indicated for stroke prevention in AF.*

*AAN recommends that clinicians use risk stratification tools to help determine stroke risk in patients with NVAF, but cautions physicians not to rigidly interpret anticoagulation thresholds suggested by these tools and does not stratify recommendations using a scoring system.*

*Rivaroxaban should be administered once daily with the evening meal.*

*2.5 mg bid if any 2 patient characteristics present: CrCl ≥1.5 mg/dL, ≥80 years of age, body weight ≤60 kg.*
Table 3: Stroke risk scoring systems: CHADS<sub>2</sub> and CHA<sub>2</sub>D<sub>2</sub>-VASc

| Risk factor | CHADS<sub>2</sub> score | Stroke rates associated with CHADS<sub>2</sub> score | Calculated stroke rate (%/y) <sup>a</sup> <sup>b</sup> (95% CI) | Risk of stroke |
|-------------|------------------------|-----------------------------------------------------|----------------------------------------------------------|----------------|
| C CHF       | 1                      | 1.9 (1.2, 3.0)                                       | Low                                                      |
| H Hypertension | 1                  | 2.8 (2.0, 3.8)                                       | Moderate                                                 |
| A Age ≥75 y | 1                      | 4.0 (3.1, 5.1)                                       | High                                                    |
| D Diabetes  | 1                      | 5.9 (4.6, 7.3)                                       |                                                        |
| S<sub>p</sub> Prior stroke/TIA | 2     | 8.5 (6.3, 11.1)                                     | High                                                    |
| VV Cerebral vascular disease (prior MI, PAD, or aortic plaque) | 1 5 | 3.2 (0.7, 9.0)                                      |                                                        |
| Age 65–74 y | 1                      | 3.6 (0.4, 12.3)                                      |                                                        |
| S<sub>c</sub> Sex category (female sex) | 1 7 | 8.0 (1.0, 26.0)                                     |                                                        |

CHADS<sub>2</sub> score

| Risk factor | CHA<sub>2</sub>D<sub>2</sub>-VASc score | Stroke rates associated with CHA<sub>2</sub>D<sub>2</sub>-VASc score | TE rate during 1 year (95% CI) <sup>c</sup> | Risk of stroke |
|-------------|----------------------------------------|---------------------------------------------------------------|------------------------------------------|----------------|
| C CHF/LV dysfunction | 1 0 | 0.6 (0.0, 3.4)                                      | Moderate                                  |
| H Hypertension | 1 2 | 1.6 (0.3, 4.7)                                      | High                                     |
| A Age ≥75 y | 1 3 | 3.9 (1.7, 7.6)                                      | High                                     |
| D Diabetes  | 1 4 | 1.9 (0.5, 4.9)                                      | High                                     |
| S<sub>v</sub> Vascular disease (prior MI, PAD, or aortic plaque) | 1 5 | 3.2 (0.7, 9.0)                                      |                                                        |
| Age 65–74 y | 1 6 | 3.6 (0.4, 12.3)                                      |                                                        |
| S<sub>c</sub> Sex category (female sex) | 1 7 | 8.0 (1.0, 26.0)                                     |                                                        |

CHF: congestive heart failure, CI: confidence interval, LV: left ventricular, MI: myocardial infarction, PAD: peripheral artery disease, TE: thromboembolism, TIA: transient ischemic attack

a Adapted from Gage BF et al. JAMA. 2001;285:2864-70 [33]
b Adjusted stroke is expected stroke rate per 100 person-years from exponential survival model, assuming no aspirin was taken
c Adjusted p value for trend = 0.003

d Significant

e Adapted from Lip GYH et al. Chest. 2010;137:263-72 [34]

Table 4: Bleeding risk scoring system: HAS-BLED. Adapted from Pisters R et al. Chest. 2010;138;1093–100 [42]

| Risk factor | Points |
|-------------|--------|
| H Hypertension | 1      |
| A Abnormal renal and liver function (1 point each) | 1 or 2 |
| S Stroke | 1      |
| B Bleeding | 1      |
| L Labile INRs | 1      |
| E Elderly (age >65 y) | 1      |
| D Drugs or alcohol (1 point each) | 1 or 2 |

Risk score: Bleeds per 100 patient-years

| Risk score | Risk of bleeding |
|-----------|------------------|
| 0         | Low              |
| 1         | Moderate         |
| 2         |                  |
| 3         | High             |
| 4         |                  |
| 5         |                  |

INR: international normalized ratio

actually be at a moderate risk of stroke [37–39]. The CHA<sub>2</sub>D<sub>2</sub>-VASc considers additional risk factors, including Vascular disease (1 point) and Sex category (1 score point for female sex), and heightens the risk rendered by older age, assigning 2 points rather than 1 (as with CHADS<sub>2</sub>) for age ≥75 years, as well as 1 point for the risk factor of age 65–74 years [34]. With CHA<sub>2</sub>D<sub>2</sub>-VASc, patients with scores of 0, 1, or ≥2 are considered to be at low, moderate, or high risk of stroke, respectively [34]. In one study of the predictive value of risk classification schemes, when patients were categorized by CHA<sub>2</sub>D<sub>2</sub>-VASc score, 0 % of low-risk patients, 0.6 % of moderate-risk patients, and 3 % of high-risk patients experienced a thromboembolic event. In contrast, when the same cohort of patients was classified according to the CHADS<sub>2</sub> scoring system, 1.4 % of low-
score [7], the ACC/AHA/HRS, ASA, and ACCP do not endorse a specific scoring system, but do advise that an assessment of bleeding risk is needed [8, 11, 41]. The ESC guidelines recommend caution along with efforts to correct potentially reversible bleeding risk factors when prescribing antithrombotic therapy for patients with a HAS-BLED score ≥3. Importantly, the ESC guidelines emphasize that: whereas the HAS-BLED score should be used to identify modifiable bleeding risks, a high HAS-BLED score alone should not exclude patients from oral anticoagulant treatment [7].

NOACs have been included in the most recent updates to guidelines for stroke prevention in patients with AF (Table 2) [7–11]. It should be noted that edoxaban has not been included in the guideline recommendations because it was not approved at the time of publication. The ESC recommends the NOACs over warfarin based on their better efficacy, safety, and convenience [7], whereas the AHA/ASA recommend the NOACs as an alternative to warfarin in the presence of at least 1 additional risk factor for stroke [8]; neither guideline recommends one NOAC over another. While the ACC/AHA/HRS recommend any of the 3 NOACs (i.e., dabigatran, rivaroxaban, or apixaban) as an efficacious alternative to warfarin [10], the ACCP guidelines recommend dabigatran 150 mg twice daily in place of adjusted-dose VKA [11]. (The ACCP guidelines include dabigatran but not apixaban or rivaroxaban in their recommendations, as the latter 2 NOACs were not yet approved when the guidelines were drafted [11].) The ACCP guidelines favor oral anticoagulants over aspirin alone or, for patients at intermediate to high risk of stroke for whom warfarin is unsuitable, suggest aspirin given with clopidogrel; where oral anticoagulation is indicated, dabigatran is recommended over warfarin [11]. The AAN guideline update offers recommendations for specific NOACs in lieu of or as an alternative to warfarin based on type of stroke risk (i.e., general risk [dabigatran 150 mg], high risk of cerebral or systemic embolism [SE] [rivaroxaban], moderate risk of embolism [apixaban 5 mg twice daily]) [9]. Additionally, the AAN update recommends apixaban 5 mg bid over aspirin for reducing risk of stroke or SE [9], and the AAN guidelines include a recommendation for the addition of clopidogrel to aspirin as an alternative for patients with AF in whom warfarin is considered unsuitable [9]. It should be noted that while the ACC, ACCP, AHA, ASA, HRS, and ESC use the CHADS2, CHA2DS2-VASc, and/or HAS-BLED risk scores to determine their treatment recommendations, these risk scoring systems are based on the results of trials during the era in which patients were receiving warfarin, aspirin, or placebo, and not the new NOACs [10, 43–45]. The study that validated the CHADS2 score measured stroke risk among patients who were not receiving any form of anticoagulant therapy [33].

Performance and quality measures from the Joint Commission, a US healthcare accrediting organization formerly known as the Joint Commission on Accreditation of Healthcare Organizations, and from the ACC/AHA also provide guidance on the treatment of patients with NVAF [46, 47]. Published in 2008, the Joint Commission’s Stroke Performance Implementation Guide recommends warfarin (unless contraindicated) for patients with AF-related stroke [47]. ACC/AHA performance measures, also published in 2008, recommend antithrombotic therapy with aspirin or warfarin for patients with NVAF based on the patient’s stroke risk category [46].

More recently, the Stroke and Stroke Rehabilitation Work Group provided guidance in 2012 with quality measures to improve outcomes in stroke, TIA, and stroke rehabilitation. Composed of the AAN, American College of Radiology, National Committee for Quality Assurance, and the American Medical Association–convened Physician Consortium for Performance Improvement (PCPI®), the Stroke and Stroke Rehabilitation Work Group advocates anticoagulant therapy with dabigatran, rivaroxaban, warfarin, or low-molecular-weight heparin at discharge for patients with AF [48].

Application of treatment guidelines to clinical practice

With multiple oral anticoagulants now available to reduce the risk of stroke in patients with NVAF, guidelines and treatment paradigms will continue to evolve to reflect findings from clinical trials and emerging clinical experience. The hypothetical cases that follow explore how clinicians might apply guidelines and clinical trial data to treatment decisions for the patient throughout the clinical course of NVAF.

Hypothetical patient case 1: Balancing the benefit of thromboprophylaxis with the risk of bleeding

BL is a 64-year-old white woman who presents to the emergency room with cellulitis of the left forearm that has not responded to outpatient antibiotic treatment. BL takes metoprolol for hypertension, but no other medications. She has no history of diabetes. She is a nonsmoker who exercises regularly and occasionally has a glass of wine with dinner. Physical examination reveals the following: heart rate, 78 bpm, irregular; temperature, 101°F. On electrocardiogram (ECG), an irregularly irregular rhythm is noted with no ST-elevation and a normal axis. Apart from moderate cellulitis of the left forearm and associated signs of infection, no other abnormal findings are noted during the physical examination.

BL is admitted to the hospital and the cellulitis responds to intravenous antibiotics. She asks if her irregular heart rhythm will require additional treatment or a repeat of
treatment she had taken for it previously. Upon further inquiry, her hospitalist notes that 2 years ago BL had been examined for complaints of breathlessness and a rapid heart rate. After a complete cardiac workup at that time, she had been diagnosed with paroxysmal NVAF and was prescribed warfarin. BL states she didn’t like the frequent blood tests that were associated with warfarin and often found it difficult to get to the anticoagulant clinic due to her work schedule. During a follow-up visit approximately 2 months after BL had started taking warfarin, her physician found that she was still in AF, although her heart rate had returned to normal, and although he recommended that she continue taking warfarin, she chose to stop it at that time.

Case discussion

Due to her history of hypertension, BL has a HAS-BLED score of 1, a CHADS2 score of 1, and a CHA2DS2-VASc score of 2. Her HAS-BLED score indicates a low risk of bleeding. Her CHADS2 score indicates a moderate risk of stroke, which is associated with a stroke rate of 2.8 % per year [33]. In contrast, her CHA2DS2-VASc score places her in the high-risk category, although the rate of stroke associated with a CHA2DS2-VASc score of 2 is 2.2 % per year, similar to that associated with her CHADS2 score [10]. Her moderate to high stroke risk (depending on the scoring system used) suggests the importance of stroke prevention in this patient.

Treatment guidelines provide various recommendations for patients with a CHADS2 score of 1 (or a CHA2DS2-VASc score of ≥2), ranging from daily aspirin to oral anticoagulation with warfarin or a NOAC (Table 2) [7–11]. In the present case, however, an effective treatment choice for BL must also consider her low risk of bleeding and her past noncompliance with warfarin therapy. Based on BL’s history of difficulty maintaining a therapeutic INR while on warfarin and adhering to monitoring requirements, warfarin would not be the ideal first choice for this patient. Instead, one of the NOACs may provide a safe, efficacious, and convenient alternative.

Consideration of pharmacologic properties and patient-specific characteristics, such as comorbidities, may help in the identification of a specific NOAC for stroke prevention (Table 5) [23–31, 49–58]. However, in this case, BL’s medical history and concomitant medication (metoprolol) do not rule out any of the NOACs. Given a CHADS2 score of 1, one might consider aspirin versus a NOAC. In contrast, her CHA2DS2-VASc score of 2 would suggest that an anticoagulant is a more appropriate choice. As noted previously, aspirin is less effective than warfarin in preventing stroke in patients with NVAF [21]. Of the NOACs, only apixaban has been studied head-to-head versus aspirin (AVERROES trial) [32]. The AVERROES trial demonstrated greater efficacy with apixaban in significantly reducing the risk of stroke and SE compared with aspirin (hazard ratio 0.45; 95 % confidence interval, 0.32, 0.62; p < 0.001; Table 1) [32]. For example, the annual rate of stroke or SE was 1.6 % (51/2808) with apixaban versus 3.7 % (113/2791) with aspirin, with no significant difference between treatments in rates of major (p = 0.57), gastrointestinal (GI; p = 0.71), or intracranial (p = 0.69) bleeding [31]. Based on the results of the AVERROES trial, and given the low risk of bleeding anticipated for BL based on her HAS-BLED score of 1, using an oral anticoagulant instead of aspirin on balance appears to be the better choice, considering that complications of stroke can be life-debilitating.

Hypothetical patient case 2: Identifying and managing stroke risk in the midst of comorbidities and a high risk of bleeding

AS is a 73-year-old black man with type 2 diabetes, hypertension, and persistent NVAF who presents to the emergency room with complaints of occasional palpitations, lightheadedness, and a productive cough. He takes metformin for diabetes, valsartan with chlorthalidone for hypertension, and a daily aspirin tablet for his AF. He is a nonsmoker and leads a generally sedentary lifestyle. On physical examination, AS has a BMI of 34 kg/m² (height 5’10’’; weight, 237 lbs); blood pressure, 154/90 mm Hg; pulse, 100 bpm; and temperature, 102 °F. His lab and test results were consistent with a diagnosis of acute pneumonia.

AS is admitted to the hospital and treated for pneumonia. Past history reveals that he was diagnosed 2 years ago with AF and treated at that time with warfarin, which was stopped 1 year ago due to a GI bleed. Subsequently, he was put on an aspirin regimen of 75 mg per day. During the current visit AS expresses concern to the hospitalist about his persistent AF, diabetes, and high blood pressure, all of which increase his risk of stroke. He says he wants to resume oral anticoagulant treatment, which he thinks may be better for him than aspirin.

Case discussion

This patient’s age and history of hypertension and diabetes give him a CHADS2 score of 2 (and CHA2DS2-VASc score of 3), which indicates an increased risk of stroke and is associated with a stroke rate of 4.0 % per year based on his CHADS2 score, or 3.2 % per year based on his CHA2DS2-VASc score [10, 33]. His age (≥65 years), past history of GI bleeding, and hypertension add up to a HAS-BLED score of 3, which is linked to an increased risk of bleeding, and data show it to be associated with a bleeding rate of 3.74 % per year [42]. The high risk of both stroke and bleeding call for immediate stroke prevention. Guideline recommendations for patients with a CHADS2 score of 2...
Table 5: Clinical and pharmacologic properties of apixaban, rivaroxaban, dabigatran, and edoxaban

| Criteria                  | Dabigatran [28] | Rivaroxaban [30] | Apixaban [29] | Edoxaban [27] |
|---------------------------|-----------------|------------------|---------------|---------------|
| Anemia                    | Contraindicated  | Contraindicated in patients with hemoglobin <10 g/dL | Contraindicated in patients with hemoglobin <9 g/dL | NA            |
| Bleeding risk             | Contraindicated in patients with hemoglobin <10 g/dL and patients with active pathologic bleeding | Concomitant drugs affecting hemostasis can increase bleeding risk, including NSAIDs, heparin, aspirin, platelet aggregation inhibitors, and chronic use of NSAIDs | Concomitant drugs affecting hemostasis can increase bleeding risk, including platelet aggregation inhibitors, other antithrombotic drugs, heparin, thrombolytic agents, SSRIs, SNRIs, and chronic use of NSAIDs | Concomitant use of drugs affecting hemostasis may increase the risk of bleeding, including aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of NSAIDs |
| Intermittent use of drugs affecting hemostasis can increase bleeding risk, including platelet aggregation inhibitors, heparin, fibrinolytic therapy, and chronic use of NSAIDs | Concomitant drugs affecting hemostasis can increase bleeding risk, including NSAIDs, heparin, aspirin, platelet aggregation inhibitors, and other antithrombotic drugs, and fibrinolytic therapy | Concomitant drugs affecting hemostasis can increase bleeding risk, including platelet aggregation inhibitors, other antithrombotic drugs, heparin, thrombolytic agents, SSRIs, SNRIs, and chronic use of NSAIDs | Concomitant use of drugs affecting hemostasis may increase the risk of bleeding, including aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of NSAIDs | Concomitant use of drugs affecting hemostasis may increase the risk of bleeding, including aspirin and other antiplatelet agents, other antithrombotic agents, fibrinolytic therapy, and chronic use of NSAIDs |
| Interruption for surgery/procedures | To reduce risk of bleeding, discontinue dabigatran 1–2 d (CrCl ≥50 mL/min) or 3–5 d (CrCl <50 mL/min) before invasive or surgical procedures | To reduce risk of bleeding, discontinue rivaroxaban at least 24 h prior to surgical or other invasive procedures | To reduce risk of bleeding, discontinue apixaban at least 48 h prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding, and at least 24 h prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled | To reduce the risk of bleeding, discontinue edoxaban at least 24 hours before invasive or surgical procedure |
| Drug interactions         | Avoid concomitant use with P-gp inducers (e.g., rifampin) | Avoid concomitant use with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) or inducers (carbamazepine, phenytointin, rifampin, St. John’s wort) | Reduce apixaban dosage to 2.5 mg bid or avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) | Co-administration with anticoagulants, antplatelet drugs and thrombolytics may increase the risk of bleeding |
| For patients with moderate renal impairment (CrCl 30–50 mL/min) | For patients with CrCl 15–50 mL/min, rivaroxaban may be used concomitantly with combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) only if the potential benefit justifies the potential risk | Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytointin, St. John’s wort) because such drugs will decrease exposure to apixaban | Avoid concomitant use with rifampin | No dose reduction is recommended in patients taking concomitant P-gp inhibitors |
| Hepatic impairment        | Large intersubject variability but no evident consistent change in exposure or PD in patients with moderate hepatic impairment | Avoid use in moderate and severe hepatic impairment or with any hepatic disease associated with coagulopathy | No dose adjustment necessary in patients with mild hepatic impairment | Use of edoxaban in patients with moderate or severe hepatic impairment is not recommended as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment |
| Renal elimination         | 80 % [69]       | 36 % [68]       | 27 % [29, 66] | 50 % [57]    |
| Renal impairment | Contraindicated in patients with CrCl <15 mL/min; reduce dosage to 75 mg bid if CrCl 15–30 mL/min | Avoid use in patients with CrCl <15 mL/min | Reduce dosage to 2.5 mg bid in patients with serum creatinine ≥1.5 mg/dL and either age ≥80 years or body weight ≤60 kg | Reduce edoxaban dose to 30 mg qd in patients with CrCl 15-50 mL/min. Not recommended in patients with CrCl <15 mL/min |
|------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Reversal antidote | In progress; none approved for use | In progress; none approved for use | In progress; none approved for use | In progress; none approved for use |
| Tested reversal strategiesa | Dialysis [54] | PCC (Cofact) [50] | rFVIIa [51] | rFVIIa [56] |
| | aPCC (FEIBA®) [55] | aPCC (FEIBA®) [53] | aPCC (FEIBA®) [51] | aPCC (FEIBA®) [56] |
| | PER977 (when available) [76] | Andexanet alfa (when available) [52] | Activated charcoal [71] | PPSB-HT [56] |
| | | PER977 (when available) [76] | Andexanet alfa (when available) [49, 52] | |

aPCC activated prothrombin complex concentrate; bid twice daily, CrCl creatinine clearance, CYP3A4 cytochrome P450 3A4, ESRD end-stage renal disease, FEIBA® factor VIII inhibitor bypass activity, NA not available, NSAID nonsteroidal anti-inflammatory drug, PCC prothrombin complex concentrate, PD pharmacodynamics, P-gp P-glycoprotein, PPSB-HT prothrombin complex concentrate, rFVIIa recombinant activated factor VIIa, SNRI serotonin/norepinephrine reuptake inhibitor, SSRI selective serotonin reuptake inhibitor
has the least renal elimination (~27 %) compared with rivaroxaban (~36 %) and dabigatran (~80 %), and is also eliminated via biliary and possibly direct intestinal excretion (Table 5) [27–29, 64–71]. Apixaban also demonstrated superiority over warfarin in reducing risk of stroke/SE, major bleeding, and mortality, irrespective of renal function [72]. Apixaban 5 mg twice daily may be a good NOAC option for this patient who is at high risk of bleeding and with comorbidities [7, 8, 10].

**Discussion and conclusions**

Conventional treatment options for reducing the risk of stroke in patients with NVAF, including VKAs and aspirin, have limitations that currently leave many patients undertreated or untreated, and thus, suboptimally protected from stroke. The NOACs provide an additional treatment pathway that may help address this trend by offering treatment options with equivalent or improved efficacy and safety compared with warfarin. Current treatment guidelines have begun to incorporate recommendations for use of the available NOACs, and as additional data emerge and guidelines are further updated, these recommendations will likely evolve. In the interim, clinicians may need to consider the recommendations of published guidelines while also weighing results of clinical trials on NOACs. Furthermore, real-world experience will provide clinicians with additional insight into their treatment decisions. The challenge, however, will be for clinicians to assess the benefits and risks of treatment within the framework of the individual characteristics that define each patient case scenario. Use of scoring systems to assess stroke and bleeding risk; consideration of patient characteristics such as concomitant medications, age, and renal failure; and an understanding of relevant pharmacologic characteristics of the NOACs will all assist in these treatment decisions (Table 5).

When comparing the results of clinical trials of each NOAC versus warfarin, subtle differences in clinical outcomes become evident, such as rates of stroke, SE, all-cause mortality, major bleeding, and intracranial hemorrhage. For example, compared with warfarin, dabigatran 150 mg provided greater risk reduction for stroke and SE in the RE-LY trial than did apixaban, rivaroxaban, or edoxaban in the ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 trials, respectively (Table 1) [23–28]. However, edoxaban and apixaban had a greater risk reduction for major bleeding versus warfarin than did dabigatran, as well as greater risk reduction for stroke and SE versus warfarin than did rivaroxaban. Apixaban and dabigatran 150 mg had a similar risk reduction for intracranial hemorrhage, but less than edoxaban 30 mg and dabigatran 110 mg and more than rivaroxaban. Rivaroxaban, apixaban, dabigatran 150 mg, and edoxaban provided comparable risk reduction versus warfarin for all-cause mortality [23–28].
indirect comparisons of the ARISTOTLE, RE-LY, and ROCKET-AF trials confirm these observations with regard to rivaroxaban, apixaban, and dabigatran [73–75]. One study quantified the benefits and risks of the NOACs with the following odds ratios (ORs) for stroke or SE: rivaroxaban versus dabigatran 150 mg, OR 1.35 ($p = 0.04$); rivaroxaban versus dabigatran 110 mg, OR 0.97 ($p = 0.81$); apixaban versus dabigatran 150 mg, OR 1.22 ($p = 0.18$); apixaban versus dabigatran 110 mg, OR 0.88 ($p = 0.34$); apixaban versus rivaroxaban, OR 0.90 ($p = 0.43$). For major bleeding, the estimated ORs were: rivaroxaban versus dabigatran 150 mg, OR 1.10 ($p = 0.36$); rivaroxaban versus dabigatran 110 mg, OR 1.28 ($p = 0.02$); apixaban versus dabigatran 150 mg, OR 0.74 ($p = 0.004$); apixaban versus dabigatran 110 mg, OR 0.87 ($p = 0.17$); apixaban versus rivaroxaban, OR 0.68 ($p < 0.0011$) [74]. Indirect comparisons like these must be considered with caution because of differences in trial design and patient populations.

With the availability of the NOACs, success in reducing the risk of stroke among patients with NVAF no longer has to pivot on the suitability of warfarin for patients. Until treatment guidelines are updated to incorporate all available data on the NOACs, clinicians would be well advised to consider recent clinical trial data for these agents alongside current treatment guidelines for stroke prevention in AF. Such attentiveness may help render treatment decisions that accurately address the constellation of characteristics composing each individual case and result in safe, high-quality, and cost-effective patient care.

**Abbreviations**

AEs: Adverse events; ACC: American College of Cardiology; ACCP: American College of Chest Physicians; AF: Atrial fibrillation; AHA: American Heart Association; AAN: American Academy of Neurology; AS: American Stroke Association; BMI: Body mass index; ESC: European Society of Cardiology; GI: Gastrointestinal; HRS: Heart Rhythm Society; NVAF: Nonvalvular AF; NOACs: Novel oral anticoagulants; OR: Odds ratio; PCPT: Physician Consortium for Performance Improvement; SE: Systemic embolism; TIA: Transient ischemic attack; VKA: Vitamin K antagonist.

**Competing interests**

AA reports research or speaking for Bristol-Myers Squibb/Pfizer, Johnson & Johnson, and Boehringer Ingelheim. SD reports research, speaking, or consulting for Bristol-Myers Squibb/Pfizer, Johnson & Johnson, and Boehringer Ingelheim. The authors did not receive any payment for working on this manuscript.

**Authors’ contributions**

AA and SD made substantial contributions to the conception of the manuscript, revised the manuscript critically for important intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Both authors read and approved the final manuscript.

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