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Overview of the 2018 CHEST Guidelines for Stroke Prevention in Patients with Atrial Fibrillation

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The CDC reports that 2.7-6.1 million Americans have atrial fibrillation (AF) and it is the most common type of cardiac arrhythmia. Risk factors for AF include, but are not limited to, advanced age, hypertension, obesity, European ancestry, diabetes, heart failure, ischemic heart disease, hyperthyroidism, chronic kidney disease, heavy alcohol use, and enlarged chambers on the left side of the heart. Hypertension is the most common cardiac disease and is associated with 14-22% of AF diagnoses.[1] AF increases a person's stroke risk by 4-5 times compared to a person without AF and is estimated to be associated with 15-20% of ischemic strokes.[1,2]

In patients evaluated to have a high stroke risk, using the CHA_2DS_2-VASc scoring system, it is imperative to initiate anticoagulation therapy. Anticoagulants include the vitamin K antagonist (e.g. warfarin), factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban), and direct thrombin inhibitor (dabigatran). All anticoagulants have a bleeding risk, and previously, there had been loose recommendations on the use of bleeding risk assessment tools for patients. However, it is now recommended that the HAS-BLED scoring tool be used to assess the risk of a major bleeding event occurring while being on anticoagulation therapy. CHEST released updated guideline recommendations in August 2018. The CHEST guidelines for anticoagulation serve as a supplement to aid in clinical decision-making processes. The updated recommendations provided in the guidelines are evidence-based and have been developed systematically. This overview will focus on these updated recommendations in regard to stroke preventions in patients with AF.

Vitamin K Antagonist

Warfarin (Coumadin®, Jantoven®) is a vitamin K antagonist that works by inhibiting the synthesis of vitamin-K dependent clotting factors (factors II, VII, IX, X, and proteins C and S).[3] Its onset of action is 24 to 72 hours with peak effects at 5 to 7 days. Warfarin is primarily metabolized hepatically via CYP2C9, but it is also metabolized, to a lesser extent, by CYP2C8, 2C18, 2C19, 1A2, and 3A4. Warfarin is a racemic mixture with the S-enantiomer displays 2 to 5 times more anticoagulant activity than the R-enantiomer. Warfarin is the preferred agent in patients with severe renal impairment because it has little to no renal elimination. Its dosing is variable, and adjusted periodically, to achieve a goal international normalized ratio (INR). The goal INR for most AF patients is 2-3; however, this goal can be adjusted based on other medical conditions or circumstances (e.g. mechanical mitral valve). There have been a few studies cited in the 2012 CHEST guidelines that have shown that an INR goal of 2.0-3.0 was effective without a clinically significant increase in bleeding risk.[4]

Factor Xa Inhibitors

Apixaban (Eliquis®), rivaroxaban (Xarelto®), and edoxaban (Savaysa®, Lixiana®) work by selectively inhibiting factor Xa, which inhibits platelet activation and fibrin clot formation. These medications are collectively referred to in the CHEST guidelines as direct oral anticoagulants (DOACs).[5-7] Apixaban's onset of action is 3 to 4 hours. It is metabolized primarily via CYP3A4/5, but is also metabolized by CYP1A2, 2C8, 2C9, 2C19, and 2J2. Apixaban has less renal elimination (about 27%) compared to the other DOACs. The dose is typically 5 mg twice daily however this is reduced to 2.5 mg twice daily if a patient has any two of the following conditions, > 80 years old, weight $\leq$ 60 kg, or serum creatinine > 1.5 mg/dL.

Rivaroxaban 20 mg once daily with the evening meal is the typical dose for stroke prevention in those with AF. The bioavailability of the 15 mg and 20 mg doses is 66% with the 10 mg strength reaching 80%-100%. Its bioavailability increases with food and therefore should be taken with meals. Rivaroxaban is metabolized by CYP3A4/5 and CYP2J2, is primarily excreted renally (66%), and has a half-life of 5 to 9 hours.

Edoxaban 60 mg daily is recommended dose for stroke prophylaxis. The time to peak concentration is about 1 to 2 hours after administration with an oral bioavailability of 62%. Edoxaban is only minimally metabolized via hydrolysis, conjugation, and oxidation by CYP3A4. Edoxaban is eliminated mostly unchanged by kidneys (50%) and has a half-life of 10 to 14 hours. Edoxaban is not recommended in patients with CrCl >95 mL/min due to an increased risk of ischemic stroke.

Direct Thrombin Inhibitors

Dabigatran (Pradaxa®), another medication among the DOACs, works by inhibiting thrombin, which impedes the conversion of fibrinogen into fibrin, and thereby prevents the formation of a thrombus. Dabigatran reaches peak concentrations about 1 hour after administration and has an oral bioavailability of 3% to 7%.[8] It is metabolized by esterase-catalyzed hydrolysis to its active form. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is eliminated primary through the kidneys (80%) and has a half-life of about 12 to 17 hours. It is typically dosed 150 mg twice daily; however, it has been dosed 110 mg twice daily, off-label, in patients with an increased bleeding risk.

Comparing the Treatment Options for Stroke Prevention

There have been 12 studies comparing warfarin with antiplatelet therapy, all of which have shown that warfarin is associated with 39% relative risk reduction in strokes. The largest of these studies, the ACTIVE W trial, showed that warfarin was superior to dual antiplatelet therapy (clopidogrel with irbesartan) for stroke and a cardiovascular composite outcome. Both arms showed a similar rate of major bleeding.[9]

The DOACs have a faster onset and offset of action, compared to warfarin. Unlike warfarin, DOACs are not affected by dietary vitamin K intake. Also, DOACs have fewer drug interactions than warfarin. In their phase 3 trials, dabigatran, rivaroxaban, apixaban, and edoxaban proved to be just as safe and effective as warfarin in preventing stroke and systemic embolism. DOACs proved to have a 51% reduction in hemorrhagic stroke, 10% reduction in all-cause mortality, 14% reduction in major bleeding, and 52% reduction in intracranial hemorrhage, compared to warfarin. However, DOACs did have an increased incidence of gastrointestinal bleeding.

Apixaban is the only DOAC that has been compared with aspirin in AF patients. The AVERROES trial compared apixaban 5 mg twice daily to aspirin 81 – 324 mg daily in patients who could not take warfarin therapy.[10] Apixaban was more effective at reducing stroke risk and systemic embolism with no significant difference in major bleeding between apixaban and aspirin therapy.

Updated Recommendations

Stroke Risk Evaluation

The first updated recommendation in the CHEST guidelines for AF is to use the CHA_2DS_2-VASc score in atrial fibrillation patients to assess the risk of ischemic stroke and systemic embolism. A systematic review found that prior stroke or transient ischemic attack (15 of 16 studies positive; risk ratio [RR], 2.86), hypertension (11 of 20 studies positive; RR, 2.27), aging (9 of 12 studies positive; RR, 1.46 per decade increase), structural heart disease (9 of 13 studies positive; RR, 2.0), and diabetes (9 of 14 studies positive; RR, 1.62) are all independent predictors of stroke risk.[11] There was supportive evidence that sex (8 of 22 studies positive; RR, 1.67), vascular disease (6 of 17 studies positive; RR, 2.61), and heart failure (7 of 18 studies positive; RR, 1.85) also play a role in increasing the risk of stroke in those with AF. Also, because the relationship between aging and stroke risk is dynamic in nature, it is best to assess it at every patient contact. Chronic kidney disease is another predictor of stroke risk particularly those with eGFR < 60 ml/min are at an increased risk of stroke (RR, 1.62; 95% CI, 1.40-1.87; P < 0.001) and they are at an increased risk of bleeding.[12] This risk factor however is not included in the CHA_2DS_2-VASc scoring because patients with decreased GFR were excluded from the cohorts from which the clinical predictors were chosen. There is a new scoring system called the R_2CHADS_2 score that was recently studied, in 2015, which includes renal dysfunction, including CKD, in the risk evaluation however CHA_2DS_2-VASc is the recommended method at determining stroke risk.[13]

Previously, a CHA_2DS_2-VASc score of 0 would not require anticoagulation therapy. The updated guidelines now recommend that females with a score of 1, based solely on their gender, also do not require anticoagulation since they are considered to have a low stroke risk. The change was made based on a study, by Neilson et al, which concluded that the female sex is only a relevant risk modifier if the patient is also over the age of 65 or has additional risk factors.[14] The results of this study found that females less than 65 years old, with no other risk factors (such as hypertension, diabetes, advanced age, history of stroke/TIA, or congestive heart failure) have a 1.78% stroke risk.[14] Recurrent ischemic strokes/TIA and deaths per 100 patient-years were 3.53 and 3.48 in women, and 4.49 and 3.98 in men, respectively. The female sex was not associated with increased risk for recurrent ischemic stroke/TIA (hazard ratio [HR] 1.15, 95% CI 0.84-1.58) or death (HR 1.35, 95% CI 0.97-1.86).[15] CHEST no longer recommends initiating anticoagulant therapy in female AF patients with a CHA_2DS_2-VASc $\geq$ 1 (adjusted stroke risk 1.3% per year), but rather, it should start in those with a score $\geq$ 2 (adjusted stroke risk 2.2% per year).

Choice of Anticoagulant

Oral anticoagulation is recommended over aspirin therapy or dual antiplatelet therapy in patients with nonvalvular AF who have a CHA_2DS_2-VASc score of $\geq$ 1 (not based on sex). The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) demonstrated that warfarin was superior to dual antiplatelet therapy for reduction of cardiovascular outcomes (RR = 1.50; 95% CI 1.19-1.89) with significantly lower risk of major bleeding in the oral anticoagulation therapy group (RR = 1.30; 95% CI 0.94-1.79).[16]

Additionally, the CHEST 2018 guidelines now suggest using a DOAC over warfarin therapy. In a meta-analysis published in 2014, DOACs were found to reduce the risk of stroke or systemic embolic events by 19% (RR = 0.81; 95% CI 0.73-0.91; P < 0.0001) and reduce the risk of hemorrhagic stroke by 51% (RR = 0.49; 95% CI 0.38-0.64; P < 0.0001).[17]

The updated guidelines also recommend that patients on warfarin therapy should aim to have their INR in therapeutic range more than 70% of the time. If the time in therapeutic range (TTR) with warfarin therapy is less than 65%, then interventions to improve control should be considered. These include more frequent INR testing, reviewing medication adherence and potential drug-drug interactions, and more patient friendly education and counseling. The GARFIELD-AF registry analyzed anticoagulation control with a focus on a patient's TTR.[18] This global, observational study revealed that 41.1% of anticoagulated patients had a TTR $\geq$ 65%. In total, only 51.4% of the INR values were in therapeutic range (INR 2-3) and 33.3% subtherapeutic. The results showed that the risk of stroke and systemic embolism (HR, 2.55; 95% CI, 1.61-4.03), all-cause mortality (HR, 2.39; 95% CI, 1.87-3.06), and major bleeding events (HR, 1.54; 95% CI, 1.04-2.26) were greater for a TTR < 65%.[19] Studies from Swedish registries, have concluded that there were significantly lower annual rates of thromboembolism (2.37% vs. 4.41%), all-cause mortality

Table 1 | Comparison of warfarin and DOAC Pharmacokinetics[3,5-8]

Parameter	Warfarin	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Dosing	QD; Dose individualized to INR (e.g. 2-3)	5 mg BID	20 mg QD with a food	60 mg QD	-Label: 150 mg BID -Off label: 110 mg BID if increased bleeding risk
Renal Dose Adjustments	None	2.5 mg twice daily if 2 of the following: • ≥ 80 years old • weight ≤ 60 kg • serum creatinine > 1.5 mg/dL	• CrCl 15-50 mL/min: 15 mg QD with food • CrCl < 15 mL/min: avoid	• CrCl > 95 mL/min: contraindicated • CrCl 15-50 mL/min: 30 mg QD • CrCl < 15 mL/min: contraindicated	CrCl 30-50 mL/min: 75 mg BID if dronedarone or ketoconazole CrCl 15-30 mL/minute: 75 mg BID; avoid if concomitant P-gp inhibitor CrCl ≤ 30 mL/min: contraindicated per the American College of Chest Physicians
Targets	Factors II, VII, IX, X, proteins C and S	Factor Xa	Factor Xa	Factor Xa	Factor IIa
Bioavailability	Almost completed absorbed	50%	10 mg dose: 80-100% 20 mg dose: 66% (greater with food)	62%	3-7%
Vd	0.14 L/kg	21 L	50 L	107 L	50-70 L
Onset of Action (hours)	24-72	3-4	-	-	-
Peak Effect	5-7 days	3—4 hours	2—4 hours	1—2 hours	1—2 hours
Protein Binding	99%	87%	92—95% (primarily albumin)	55%	35%
Metabolism	CYP2C9 (primary), CYP2C8, 2C18, 2C19, 1A2, and 3A4	CYP3A4/5 (primary), CYP1A2, 2C8, 2C9, 2C19, and 2J2	CYP3A4/5, CYP2J2	Minimal via hydrolysis, conjugation and oxidation by CYP3A4	Esterase-catalyzed hydrolysis
Half-life (hours)	40	12	5-9	10-14	12-17
Renal Elimination	Minimal	27%	66%	50%	80%

Pharmacokinetic values represent mean data from healthy individuals.
CPY450 = cytochrome P450; L = liter; kg = kilogram; mg = milligram; QD = daily; Vd = volume of distribution

(1.29% vs. 4.35%), and major bleeding (1.61% vs. 3.81%) when a patient's TTR was ≥ 70% versus < 70%.[20]

There is a clinical scoring system called the SAMe-TT_2R_2 (**Table 2**), that is used to assess if a patient is a good candidate for warfarin therapy, meaning that he or she will have a TTR ≥ 65%. A score of 0-2 indicates that a patient is likely to achieve a good TTR with warfarin. A score of >2 indicates that a patient is less likely to achieve a good INR and they might need more frequent INR checks/follow ups and education/counseling. Given that some of the factors included in the score may also be associated with decreased DOAC adherence, it is not clear if a patient would do better on DOAC therapy vs warfarin therapy. The crux of the scoring system is that AF patients should not have to fail warfarin therapy before they are offered a DOAC since this is now the preferred treatment option for this patient population.

Bleeding Risk Assessment

CHEST recommends assessing a patient's bleeding risk at each patient interaction which is different than the previous recommendation of just assessing this risk a couple of times a year. A systematic review concluded that HAS-BLED has greater sensitivity compared with other scoring systems and is easy to apply, and therefore should be used to assess a patient's bleeding risk.[21] The HAS-BLED score out performs the CHA_2DS_2-VASc and CHA_2DS_2 score for predicting serious bleeding.[22] A study published in 2015 concluded that the HAS-BLED may even underestimate bleeding risks in moderate and high risk patients.[23] However, this is still the preferred method of assessing bleeding risk per the CHEST guidelines. It is important to note that a high HAS-BLED score (score ≥ 3) is rarely a reason to avoid anticoagulation. Assessing the bleeding risk gives providers the opportunity to address any modifiable risk factors that might increase a patient's bleeding risk. These include uncontrolled hypertension, labile INRs, concomitant use of aspirin or NSAIDs, and excess alcohol use. Studies have shown that addressing and potentially modifying any bleeding risk factors, will decrease a patient's risk for bleeding complications.[24] Other risk scoring studies include ABC, ORBIT, ATRIA, and $HEMORR_2HAGES$ (**Table 3**).

For patients with previous unprovoked bleeding events, bleeding on warfarin therapy, or at high risk for bleeding, the CHEST 2018 guidelines suggest using apixaban, edoxaban, or dabigatran 110 mg. Apixaban, backed by the results of the ARISTOTLE, and dabigatran, based on the RE-LY trial, are the only DOACs without an increased risk of gastrointestinal bleeding compared with warfarin. Dabigatran 150 mg every 12 hours is preferred in patients with a high risk of ischemic stroke because it is the only DOAC that has shown to be superior in efficacy compared to warfarin. The ENGAGE AF-TIMI trial supports the use of edoxaban.[25-27]

In AF patients who have survived intracranial hemorrhage and are at high risk of recurrence (e.g., probable cerebral amyloid angiopathy), guidelines suggest a left atrial appendage occlusion (LAAO). Randomized trials have shown that LAAO has similar efficacy compared to oral anticoagulants in patients with AF.[28] This is a good option to consider for patients because it reduces the risk of ischemic stroke and systemic embolism without needing to put patients on long term anticoagulation.

Anticoagulation and Cardioversion

Patients that have atrial fibrillation for more than 48 hours in duration or of unknown duration, the guidelines recommend therapeutic anticoagulation for at least three weeks or undergoing transesophageal echocardiogram (TEE) prior to cardioversion. These patients should remain on anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm, regardless of baseline stroke risk. A systematic review of 18 observational studies supports the use of VKA therapy in the context of elective electrical or pharmacologic cardioversion, to lower the risk of stroke or thromboembolism with peri-cardioversion anticoagulation compared to placebo. The recommendation of 3 weeks of therapeutic anticoagulation with VKA prior to cardioversion and a minimum of 4 weeks post cardioversion is based on observational data. This data has also shown that thromboembolism is significantly more common at an INR of 1.5-2.4 before cardioversion than an INR of 2.5. Studies also have shown that the highest risk of stroke and thromboembolism is in the first 72 hours post-cardioversion and most thromboembolic complications occur within 10 days of cardioversion. A recent study concluded that most post-cardioversion strokes are associated with patients not being properly anticoagulated.[29]

While there is evidence supporting the use of DOACs in cardioversion, it is important to note that many of the evaluated trials were underpowered to show true efficacy, so the quality of evidence is low. A systematic review of 6 studies, comparing DOACs vs. VKA in cardioversion, reported the risk ratios (relative risk reductions) were 0.82 (0.38-1.75) for stroke/systemic embolism, 0.72 (0.27-1.90) for mortality, and 0.72 (0.19-2.71) for MI;

Table 2 | The SAMe-TT_2R_2 Score

Acronym	Risk Factor	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history (≥2): hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease	1
T	Treatment (interacting drugs)	1
T	Tobacco use (within 2 years)	1
R	Race (non-Caucasian)	1
Maximum Score		8[a]

Low risk: 0-1 points indicates patient is a candidate for warfarin therapy and estimates an INR time in therapeutic range >65%.

High risk: ≥2 points indicates patients who are at high risk of suboptimal anticoagulation control with warfarin.

thus, concluding that DOACs were at least comparable to efficacy compared to VKA.[30] The EMANATE trial found the incidence of stroke or systemic embolism was 0% in patients given apixaban versus 0.8% in patients given warfarin/heparin (p = 0.016).[31] However, another systematic review found that the relative risk ratio for stroke/thromboembolism was 0.33 (0.016-1.68) for all DOACs compared to warfarin.[21]

For patients with a known left atrial appendage (LAA) thrombus detected on a TEE, the guidelines recommend postponing cardioversion and continuing anticoagulation for another 4-12 weeks to allow thrombus resolution or endothelialization. The updated guidelines reference the ACUTE RCT as the best data for the use of VKA in the TEE-guided approach. In AF patients undergoing a TEE, 10% have a LAA thrombus, which puts them at a 3.5-fold risk of stroke or thromboembolism.[32]

Anticoagulation and Coronary Artery Disease

For patients with AF undergoing coronary stenting, the use of multiple antithrombotics should be based on the risk of bleeding and the clinical presentation needing coronary stenting. Results from a systematic review and meta-analysis showed that triple therapy (DAPT [dual antiplatelet therapy] + OAC [oral anticoagulation]) was associated with an increased risk of bleeding compared to DAPT alone. There were no differences between triple therapy and dual therapy for all-cause death, cardiovascular death, or thrombotic complications (e.g. ACS, stent thrombosis, thromboembolism/stroke, and major adverse cardiac and cerebrovascular events).[33]

Results from another meta-analysis found that triple therapy with DOACs was more effective (outcome stroke/systemic embolism HR 0.78 [95% CI 0.76-0.93] and vascular death HR 0.85 [95% CI 0.76-0.93]) and as safe as VKA with respect to major bleeding (HR 0.83 [95% CI 0.69-1.01]). This analysis also reported that DOACs were safer with respect to intracerebral hemorrhage (ICH) (HR 0.38 [95% CI 0.26-0.56]). Thus, it might be more effective and safe to use DOACs over VKA to treat patients with nonvalvular AF who are on aspirin therapy.[34]

In a large observational cohort study, there was no increased risk of recurrent coronary events for OAC + clopidogrel (HR 0.69 [95% CI 0.48-1.00]), OAC + ASA (HR 0.96 [95% CI 0.96-1.42]), or ASA + clopidogrel (HR 1.17 [95% CI 1.03-2.20]) relative to triple therapy.[35] The WOEST randomized trial found that 19.4% of patients receiving OAC + clopidogrel and 44.4% of patients receiving OAC + clopidogrel + ASA had "any bleeding" (HR 0.36 [95% CI 0.26-0.50]); this trial was underpowered for efficacy and safety endpoints.[36] The RE-DUAL PCI trial found that 15.4% of patients on dual therapy (dabigatran 110 mg + clopidogrel or ticagrelor) had major or clinically relevant nonmajor bleeding compared to 26.9% of patients on triple therapy (warfarin + clopidogrel or ticagrelor + aspirin) (HR 0.52 [95% CI 0.42-0.63]).[37] Major or clinically relevant nonmajor bleeding was seen in 20.2% of patients on dabigatran 150 mg + clopidogrel or ticagrelor and 25.7% of patients on triple therapy (HR 0.72 [95% CI 0.58-0.88]). The composite efficacy of thromboembolic events (MI, stroke, or systemic embolism), death, or unplanned revascularization was 13.7% in the dual therapy groups compared with 13.4% in the triple therapy group (HR 1.04 [95% CI 0.84-1.29]).[37]

Anticoagulation and antiplatelet therapy post PCI recommendations are stratified based on bleeding risk. Patients with low bleeding risk (HAS-BLED < 2) should be treated with triple therapy for 1 to 3 months, followed by dual therapy with anticoagulation and clopidogrel for 12 months. However, patients with a high thrombotic risk, defined as CHA_2DS_2-VASc $\geq$ 1 (adjusted stroke risk 1.3% per year) for men and score $\geq$ 2 (adjusted stroke risk 2.2% per year) for females, may receive triple therapy for up to 6 months. Patients with high bleeding risk (HAS-BLED score $\geq$ 3) should receive dual therapy with an anticoagulant and clopidogrel for 12 months post-stent. Regardless of thrombotic and bleeding risk, patients should be treated with anticoagulation monotherapy without antiplatelets after 12 months of therapy. The recommended anticoagulants post PCI are warfarin (with TTR > 65-70%), dabigatran, or rivaroxaban.

Clinical Implications

In practice, the new recommendations have the potential to improve patient care and improve clinical outcomes for patients. However, the new recommendation is to provide anticoagulation to all patients with a CHA_2DS_2-VASc score of $\geq$ 1 in males or $\geq$ 2 in females. Additionally, completing a HAS-BLED score at every visit will require providers to update current notes and to ensure that it is documented appropriately for atrial fibrillation. As mentioned previously, the HAS-BLED score is a decision-making aid. It will not be a final determinant in choosing an appropriate anticoagulant therapy and safety of triple therapy if needed.

The cost of DOACs may be a prohibitive factor in some patient populations while the products are still available brand-only. However, many insurances cover at least one of the DO-

Table 3 | The HAS-BLED Score[23]

Acronym	Risk Factor	Points
H	Hypertension (>160 mmHg systolic)	1
A	Abnormal lab values: • SCr >2.26 mg/dL • Bilirubin >2x upper normal limit • AST/ALT/AP >3x upper normal limit	1
S	Stroke history	1
B	Prior major bleeding or predisposition to bleeding	1
L	Labile INR (time in therapeutic range <60%)	1
E	Elderly (age >65 years)	
D	Drug use: medications that increase bleeding risk (antiplatelets, NSAIDs), or illicits (eg, cocaine) -Alcohol use: ≥8 drinks/week	1

Score associated bleeds per 100 patient years: 0 = 1.13; 1 = 1.02; 2 = 1.88; 3 = 3.74; 4 = 8.70; 5 = 12.5. Scores ≥3 indicate high yearly bleed risk.

ACs. The first DOAC that is anticipated to be available as generic is Pradaxa®, which loses its patent protection in 2021. The patent for Xarelto® expires in 2021, Eliquis® in 2022 or 2023, and Savaysa® in 2023, all reliant on no patent extensions by the drug manufacturers. With DOACs, patients are not required to be on a special restrictive diet and do not require as frequent monitoring as warfarin. However, patients will need to be counseled on the importance of adherence which involves strict time frames and medication compliance. It is also important to note that there are certain patient populations that will continue to need warfarin therapy over DOACs. These include patients with chronic kidney disease, valvular atrial fibrillation (with valve replacements such as mechanical prosthetic valves and with concomitant moderate or severe mitral stenosis), and genetic clotting disorders (such as factor V leiden and antiphospholipid Syndrome).

Recommendations Summary

CHEST has updated their guidelines for the treatment of atrial fibrillation. Firstly, they now recommend using the CHA_2DS_2-VASc score in AF patients to assess stroke risk; only patients who have a score of $\geq$ 1 for men or $\geq$ 2 for women, should receive antithrombotic therapy. Additionally, nonvalvular AF patients, with the appropriate CHA_2DS_2-VASc score, should receive oral anticoagulation rather than no therapy, aspirin therapy, or dual antiplatelet therapy. For eligible patients, DOACs are recommended over warfarin. With that said, patients with prior bleeding events (unprovoked or while on warfarin) or at a high risk of bleeding, apixaban, edoxaban or dabigatran 110 mg are recommended agents. Patients with a high bleeding risk (HAS-BLED $\geq$ 3) should be monitored frequently. If a patient needs to be on warfarin, the guidelines recommend aiming to have a TTR > 70% and an INR goal of 2-3. If the TTR < 65%, then improvement interventions should be implemented (frequent INR testing, assessing medication adherence, reviewing possible drug interactions, and educating patients). All patients on antithrombotic therapy should have modifiable risk factors (e.g. uncontrolled hypertension, labile INRs, NSAID use, and alcohol use) assessed.

Patients with AF > 48 hours or an unknown duration, should have anticoagulation for $\geq$ 3 weeks or to have a TEE prior to cardioversion. Regardless of stroke risk, patients should stay on anticoagulation for $\geq$ 4 weeks after successful cardioversion to sinus rhythm. If a patient has a known left atrial appendage thrombus, detected on the TEE, then cardioversion should be postponed and anticoagulation should continue for another 4-12 weeks. AF patients, with a low bleeding risk (HAS-BLED 0-2), having elective coronary stent procedures should receive triple therapy for 1-3 months followed by dual therapy (anticoagulation + clopidogrel) until 12 months, and then anticoagulation monotherapy. AF patients, with a high bleeding risk (HAS-BLED $\geq$ 3), having elective coronary stent procedures, should receive triple therapy for 1 month followed by dual therapy for 6 months, followed by oral anticoagulation therapy. For those having coronary stent procedures for an acute coronary syndrome, a patient should receive triple therapy for 6 months followed by dual therapy until 12 months, followed by anticoagulation monotherapy for patients with a low bleeding risk. For those having coronary stent procedures for an acute coronary syndrome, the recommended regimen is triple therapy for 1-3 months followed by dual therapy until 12 months, followed by anticoagulation should be given to patients with a high bleeding risk. Finally, a left atrial appendage occlusion is recommended in AF patients who survived an intracranial hemorrhage and are at a high risk of recurrence.

Conclusion

Anticoagulation is required in patients with AF with a high risk of developing a stroke. Options of oral anticoagulation include the vitamin K antagonists (e.g. warfarin) and direct oral anticoagulants (DOACs). Factor Xa inhibitors and the direct thrombin inhibitor are DOACs. Aspirin monotherapy or aspirin in combination with other antiplatelets such as clopidogrel are no longer recommended for stroke prevention in AF patients. DOACs are preferred over warfarin therapy.

The updated CHEST guideline recommendations have taken the recent trials and evidence and formulated them into a comprehensive guide to preventing stroke and other complications, such as bleeding, in patients with atrial fibrillation. The provider and patient should work together to formulate a therapy plan to ensure a safe a appropriate treatment is selected. This includes keeping an eye on the patient's CHA_2DS_2-VASc scores and HAS-BLED, and adjusting therapies and lifestyle modifications as needed at every patient interaction.

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Personalized Medicine Corner

Using Pharmacogenetics to Guide Proton Pump Inhibitor Dosing: A Patient Case

Proton pump inhibitors (PPIs) are predominantly metabolized by the cytochrome P450 2C19 (CYP2C19) enzyme. *CYP2C19* genotype can affect plasma concentration of PPIs and their therapeutic effects and/or toxicity.[1,2] Approximately 5-30% of the general population have a *CYP2C19* genotype associated with increased metabolism of PPIs (referred to as rapid or ultra-rapid metabolizers) and are at increased risk for treatment failure because of lower drug concentrations. Conversely, about 20-60% of patients have a genotype that can lead to loss of or significant reductions in CYP2C19 activity (poor or intermediate metabolizers) and are at increased risk for adverse drug effects because of higher PPI plasma levels.[1,2]

The UF Health Precision Medicine Program (PMP) implemented *CYP2C19* genotyping for PPIs in 2018. Current literature supports a 50-100% PPI dose increase for CYP2C19 rapid and ultra-rapid metabolizers and a 25-50% dose decrease for intermediate and poor metabolizers.[1,2] Non-genotype clinical factors, such as drug interactions or comorbid conditions, can alter the activity of CYP2C19.[3] The presence of a strong CYP2C19 inhibitor (e.g., fluoxetine) can cause a patient with a normal genotype to resemble a poor metabolizer while taking the interacting drug (also known as "phenoconversion").[3,4] In this article, we present a case for a patient who underwent *CYP2C19* genotyping after failing multiple PPI regimens.

Patient Presentation

A 45 year-old female with a history of gastroesophageal reflux disease (GERD) presented with complaints of intractable nausea and vomiting. The patient had tried multiple PPI regimens, including dexlansoprazole 60 mg daily and esomeprazole 40 mg daily, without significant relief. Her relevant medications at presentation included esomeprazole 40 mg twice daily, fluoxetine 40 mg once daily, ondansetron 8 mg every 6 hours as needed, olanzapine 10 mg nightly, and promethazine 25 mg every 6 hours as needed. The UF Health PMP was consulted to assist in providing an interpretation and accompanying recommendation for her *CYP2C19* genotype result and related medications.

Pharmacogenetic Test Result

*CYP2C19*1/*2*; intermediate metabolizer phenotype (decreased CYP2C19 activity)[±]

[±]Note: Because of a drug interaction with fluoxetine, a strong CYP2C19 inhibitor, the patient may resemble a CYP2C19 poor metabolizer while taking fluoxetine.

Drug Therapy Recommendation provided by the PMP Team

This patient's *CYP2C19* poor metabolizer status is associated with little to no CYP2C19 activity and increased risk for adverse effects with PPIs. We recommended decreasing her esomeprazole dose from 40 mg twice daily to 40 mg once daily or discontinuing esomeprazole altogether because of her *CYP2C19* metabolism status and documented lack of benefit from multiple PPI trials.

Discussion

At the time of presentation this patient was experiencing significant nausea and vomiting with no other GERD symptoms. Increased plasma levels of esomeprazole caused by her *CYP2C19* poor metabolizer status (based on her genotype and concomitant CYP2C19 inhibitor therapy) could have contributed to her nausea and vomiting, which has been reported in 1-2% of patients taking esomeprazole.[5] Given this patient's CYP2C19 status and lack of previous PPI response, an esomeprazole dose increase would likely not have improved her symptoms and may have exacerbated them because of higher drug exposure.

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