Anticoagulation for Atrial Fibrillation in the Elderly

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Abstract

Atrial fibrillation (AF) affects approximately 2.2 million patients in the United States (US). The median age of patients with AF is 75 years, with a prevalence of around 9% in the elderly [1]. In the US alone, it is projected that 5.6 million people will be diagnosed with non-valvular AF by 2050, of whom approximately 50% will be over 80 years of age [2]. The proportion of ischemic strokes attributable to AF rises significantly with age, from 1.5% in those aged 50-59 to 23.5% in those aged 80-89 [3]. Strokes in AF are associated with a higher mortality and disability than stroke from other causes [4]. Given the high prevalence of AF in the elderly, multiple comorbidities in many of these patients, and the greater risk of thromboembolism coupled with heightened concerns about bleeding, a specific review of the data and gaps in knowledge regarding anticoagulation for AF in older patients is in order.

Keywords: Atrial fibrillation, Anticoagulation, Hypertension

Stroke risk in the elderly

Older individuals with AF are at a higher risk of stroke compared to younger patients. The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines [5] recommend using the CHA_2DS_2-VASc (Congestive heart failure (CHF), Hypertension, Age ≥75 years, Diabetes, Stroke/Transient ischemic attack (TIA), Vascular disease, Age 65-74, Sex category (female)) score (**Table 1**) to assess stroke risk (Class I; Level of evidence B). These guidelines recommend oral anticoagulant (OAC) therapy for AF patients with a CHA_2DS_2-VASc ≥2 (Class I recommendation) with either warfarin (Level of evidence A), dabigatran, rivaroxaban or apixaban (Level of evidence: B) **(Table 2)** and no antithrombotic therapy, OAC or aspirin (ASA) in patients with a CHA_2DS_2-VASc score of 1.

The CHA_2DS_2-VASc score appropriately designates age ≥ 75 years as a major risk factor (2 points), equivalent to a history of previous stroke/TIA, making anticoagulant therapy a Class I indication for this group of patients even in the absence of other risk factors **(Figure 1)**.

How are we doing in terms of thromboprophylaxis in the elderly AF population?

Only about 46.5% of patients at a high risk for stroke are prescribed OAC therapy [9,10]. Reasons for under-prescription of OAC therapy include concerns about an increased risk of bleeding in the elderly, food-drug and drug-drug interactions, increased sensitivity to warfarin in the elderly, variable dose response, difficulty maintaining the target international normalized ratio (INR), cognitive and physical impairments in the elderly, and physicians' fears about the risk of falling in the geriatric population. There have been several studies to estimate the risk/benefit ratio of treating elderly AF patients with OAC, including the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study [9], which randomized individuals aged ≥75 years of age to aspirin or warfarin based on physician discretion. Stroke/systemic embolism (SE) occurred at a rate of 1.8%/year in warfarin-treated patients versus 3.8%/year in the aspirin group (hazard ratio [HR] 0.48; 95% confidence interval (CI), 0.28-0.80), with no difference in the rates of major hemorrhage (1.9 vs. 2.2%, respectively).

The target range for INR to reduce the risk of stroke/SE is 2-3, with levels below and above this range associated with an increase in thromboembolism and major bleeding respectively [11]. There have been several studies evaluating the use of lower targets for anticoagulation in elderly patients. A nested case-control study of the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) [12] population found that the risk of thromboembolism increased at INR levels <1.8 (odds ratio (OR), 3.72) while the odds of intracranial hemorrhage (ICH) increased at INR values above 3.5. A recent study by Cafolla et al. [13] enrolled 116 AF patients >80 years of age and divided them equally into two groups based on target INRs (target INR of 2.0 (1.5 to 2.5) versus 2.5 (2.0 to 3.0). Patients in the lower INR target group showed a significantly increased time in therapeutic range (TTR) compared to the latter group (72.59% versus 64.43%, P<0.01). Patients in the higher INR target group experienced more bleeding and thrombotic events than the lower target group. The lower incidence of thromboembolic events in the group with the lower target INR

Table I. CHADS$_2$, CHA$_2$DS$_2$-VASc, and HAS-BLED scores [8].

CHADS$_2$	Score	CHA$_2$DS$_2$-VASc	Score	HAS-BLED	Score
Congestive heart failure/ LV dysfunction	1	Congestive heart failure/ LV dysfunction	1	Hypertension	1
Hypertension	1	Hypertension	1	Abnormal renal/ liver function	1 or 2
Age ≥ 75 years of age	1	Age ≥ 75 years of age	2	Stroke	1
Diabetes Mellitus	1	Diabetes Mellitus	1	Bleeding tendency	1
Stroke/ TIA	2	Stroke/ TIA	2	Labile INRs	1
		Vascular disease (MI, PVD, or aortic plaque)	1	Age (> 65, frail)	1
		Age 65-74	1	Drugs (NSAIDs/ ASA) or alcohol abuse	1
		Sex category (female)	1		

CHADS$_2$: Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA; CHA$_2$DS$_2$- VASc : Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA, Vascular disease, Age 65-74, Sex category (female); HAS-BLED: Hypertension, Abnormal renal or liver function, Stroke, history of Bleeding, Labile INRs, Elderly, Drug or alcohol abuse; LV: Left Ventricular dysfunction; TIA: Transient Ischemic Attack; MI: Myocardial Infarction; PVD: Peripheral Vascular Disease; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

Table 2. ACCF/AHA/HRS [5], CCS [6], and ACCP [7] guidelines based on CHA$_2$DS$_2$ VASc scores.

CHA$_2$ DS$_2$ VASc score	ACCF/AHA/HRS	ACCP	CCS
0	No antithrombotic therapy	No antithrombotic therapy or ASA or ASA + Clopidogrel. Preferably no therapy.	No anti thrombotic therapy
1	No antithrombotic therapy or ASA or OAC based on assessment of bleeding risk, and patient preference.	OAC recommended over no therapy/ ASA/ ASA+ Clopidogrel. For patients who are unsuitable for or choose not to take OAC (for reasons other than a high risk for major bleeding) combination therapy with ASA + Clopidogrel is recommended over ASA alone.	Oral anticoagulation therapy. One of the newer anticoagulants recommended in preference to warfarin. ASA may be considered based on individual risk/ benefit assessment.
≥2	OAC	OAC, with Dabigatran 150 mg bid preferred over warfarin therapy	Oral anticoagulation therapy. One of the newer anticoagulants is recommended in preference to warfarin (except in patients already on warfarin, with stable INR's and no bleeding complications).

CHADS$_2$: Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA. The updated ESC guidelines recommend using the CHA$_2$DS$_2$-VASc score to evaluate the risk for stroke in AF patients; ACCF/ AHA/ HRS: American College of Cardiology/ American Heart Association/ Heart Rhythm Society; ACCP: American College of Chest Physicians; CCS: Canadian Cardiovascular Society; OAC: Oral Anticoagulation

could potentially be explained by the lower INR target mean deviation, and better tolerance of the drug in this group of patients. However, it should be kept in mind that the benefit of using a lower INR targets was seen in fragile, elderly (>80 years of age) patients with previously documented unstable INRs and frequent INR values above 5.

Challenges associated with warfarin therapy in the elderly

Quality of anticoagulation

In patients treated with warfarin for AF, improved survival was seen in those patients with a TTR>40%. However, the risk
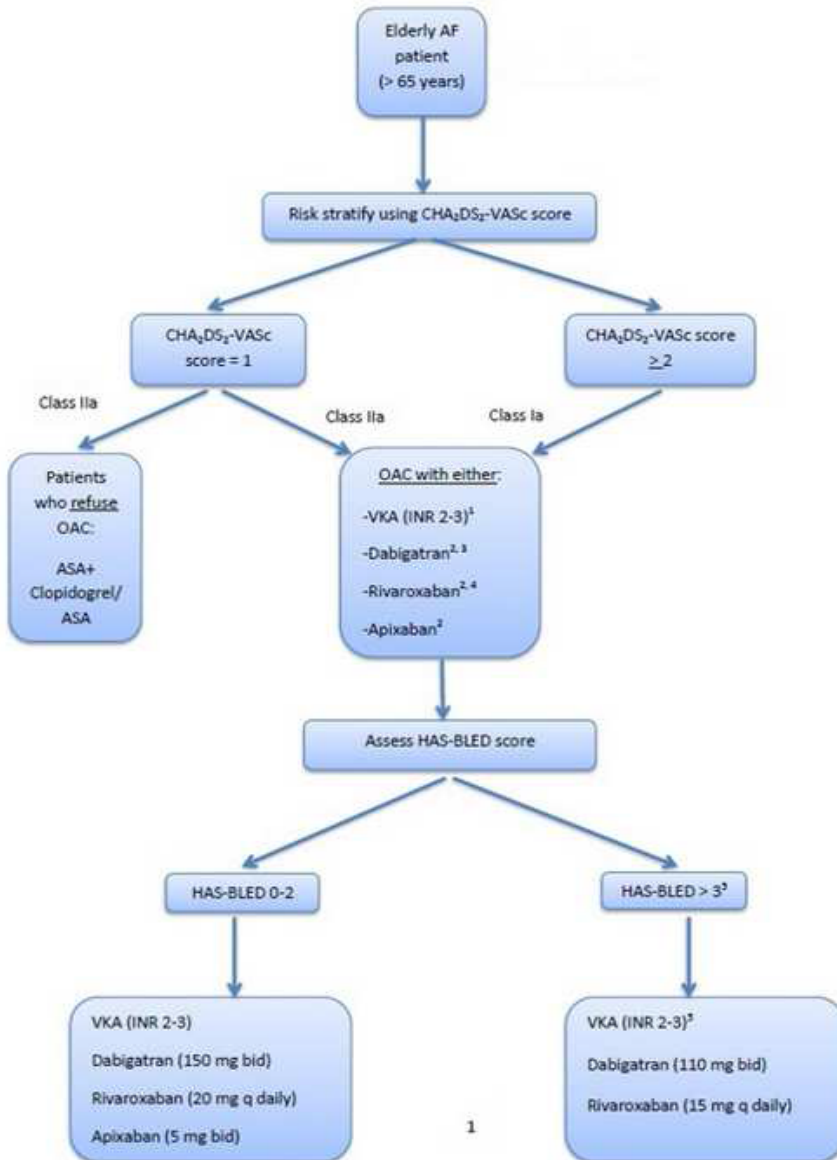
Figure 1 ESC guidelines incorporating the CHA2DS2- VASc and HAS-BLED scores [8].

CHA2DS2- VASc : Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA, Vascular disease, Age 65-74, Sex category (female); HAS-BLED: Hypertension , Abnormal renal or liver function , Stroke , history of Bleeding , Labile INRs, Elderly, Drug or alcohol abuse.

1 If VKA therapy cannot be used secondary to difficulty maintaining therapeutic INRs, or severe side effects to VKA, or inability of the patient to undergo regular INR monitoring one of the newer anticoagulants may be used as an alternative (Class IB).

2 When OAC is recommended, one of the newer anticoagulants (dabigatran, rivaroxaban, or apixaban) should be considered for patients over VKA therapy (Class IIA).

3 Dabigatran 150 mg bid should be used for all patients, except in these situations where the 110 mg dose should be used instead

a. Age > 80

b. HAS-BLED > 3

c. Concomitant use of a P-gp inhibitor (verapamil, amiodarone)

d) Renal impairment (CrCl 30-49 ml/ min)

4 Rivaroxaban 20 mg once daily should be considered for most patients except in these situations where the 15 mg once daily dose may be used-

a.High bleeding risk (HAS-BLED score >3)

b. Renal impairment (CrCl 30-49 mL/min).

5 HAS-BLED score of >3 signifies a very high risk of bleeding and should prompt regular follow-up of such patients, and careful monitoring of INR if on VKA. Efforts should be made to control reversible risk factors such as uncontrolled BP, concomitant use of NSAIDS etc.

for stroke in these patients decreased significantly only when the TTR was >70% [14]. Maintaining an adequate INR can be challenging in elderly patients owing to various factors. Older age is associated with an exaggerated response to OAC, with lower doses of warfarin providing adequate and sometimes excess anticoagulation. Moreover, the prevalence of polypharmacy rises with age, and this can cause large fluctuations in INR. However, age alone should not be a deterrent to maintaining good quality anticoagulation [15]. Frequent and close anticoagulation monitoring of dose-adjusted warfarin is crucial to prevent bleeding events in elderly patients on warfarin.

Other factors

Declining renal function is one of the most important factors affecting the pharmacokinetics of OACs in the elderly. Elderly patients with a normal serum creatinine can still have significantly impaired renal function. The AHA/ACC/HRS guidelines recommend evaluating renal function prior to initiation of the newer OACs, and at least once a year. The 2012 CCS focused update recommends that all AF patients should have an annual assessment of their renal function and undergo regular assessments for drug/dose changes based on their estimated glomerular filtration rate (eGFR). Patients with chronic kidney disease and a creatinine clearance (CrCl)>30 ml/min should be treated with antithrombotic therapy based on their CHA_2DS_2-VASc score as in patients with normal renal function. Those with a CrCl of 15-30 ml/min should receive antithrombotic therapy based on their CHA_2DS_2-VASc score, but the preferred agent is warfarin. Warfarin is recommended for patients with end stage renal disease (CrCl <15 ml/min) or on hemodialysis (Class IIa recommendation). Multiple co-morbidities, polypharmacy, risk for falls, and declining cognitive function can further complicate the management of elderly AF patients on anticoagulation.

Bleeding with warfarin therapy

What is the actual risk?

The risk for bleeding with warfarin therapy in patients >80 years of age has been estimated to range anywhere from 1.63% to 13.1% per year [15,16]. The risk for hemorrhage increases with an INR ≥ 4.0, older age and in the first 90 days of therapy **(Figure 2).** Recently, Gomes et al. [17] studied the rates of major bleeding in 125,195 AF patients on warfarin, >66 years of age. The overall risk of bleeding in this study was 3.8% per year, somewhat higher than that seen in clinical trials (1-3%). The risk of major bleeding
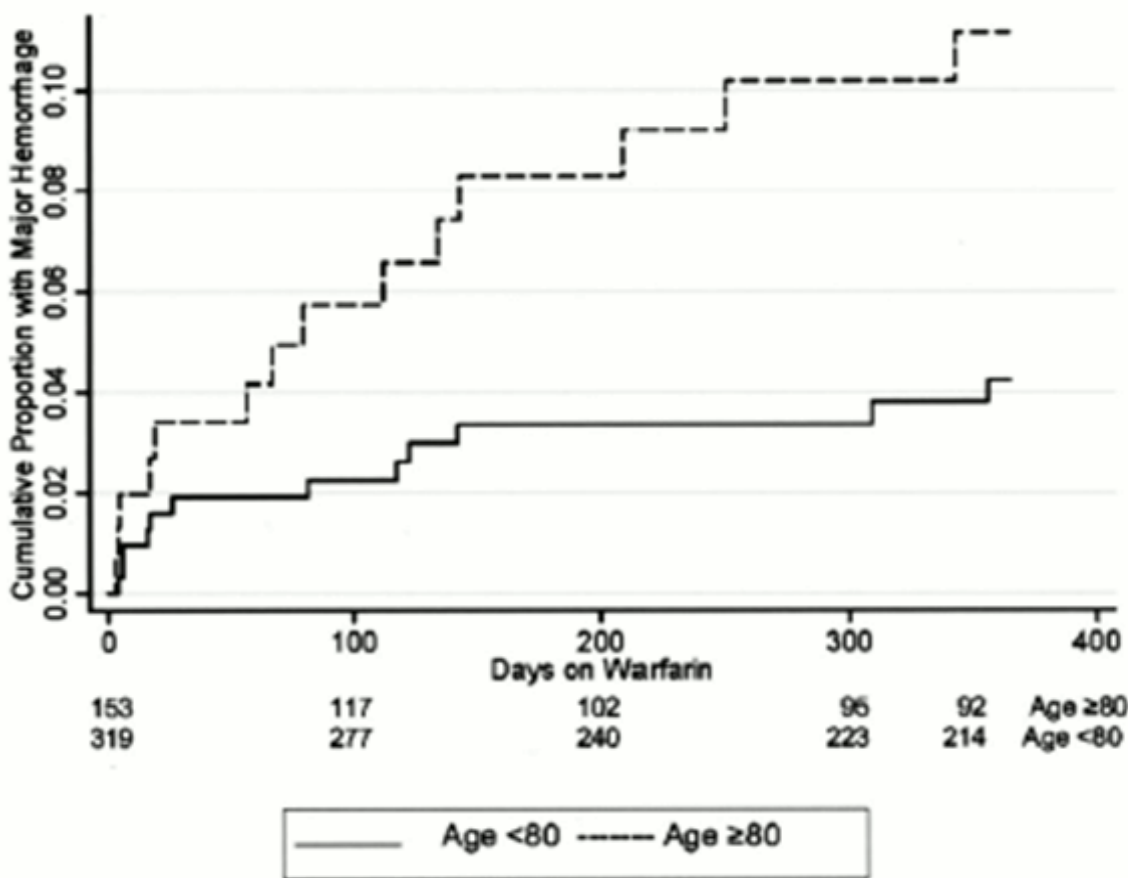

153	117	102	95	92	Age ≥80
319	277	240	223	214	Age <80

Figure 2 Cumulative incidence of major bleeding among patients aged <80 years and >80 years [17]. Numbers below graph are the number of patients without bleeding who continued on warfarin at that time point (P0.009, log-rank test). (Reprinted with permission).

in patients >75 years was 4.6% versus 2.9% in those <75 years of age.

Intracranial hemorrhage

Intracranial hemorrhage (ICH) is the most dreaded type of hemorrhage in any patient on OAC. Though the risk of ICH increases with age, the absolute risk of warfarin-associated ICH is relatively low at around 0.2% to 0.6% per year [18]. However, a post-hoc analysis of the ATRIA study by Fang et al. [19] showed that warfarin-associated ICH had a very high mortality rate (60% in the first 30 days).

McGrath et al. [20] evaluated 3,197 patients with AF and an acute stroke from the Registry of the Canadian Stroke Network to assess risk factors for ICH. The odds ratios for age (OR, 1.19; 95% CI, 1.06–1.34 per decade), and prior stroke or TIA (OR, 1.45; 95% CI, 1.12–1.87) were higher for ischemic stroke compared to ICH. An elevated INR at the time of admission was more strongly associated with ICH than ischemic stroke (INR>3.0 versus <1.4, OR, 0.07; 95% CI, 0.04–0.10). The Stroke Prevention in Atrial Fibrillation investigators (SPAF) [21] found that a systolic BP of >160 mm Hg and a diastolic BP of >90 mm Hg increases the risk of ICH in patients on anticoagulation (RR of 4). Head trauma in a patient on anticoagulation therapy can increase the likelihood of ICH (subdural hematoma). Despite this risk, a recent study [22] found that persons taking warfarin must fall around 295 times in one year for the risk of warfarin therapy to outweigh the potential benefit. Nevertheless, elderly patients with a supra-therapeutic INR (INR>3) and/or a history of previous stroke/TIA are at a very high risk for ICH. Falls in this population can result in serious consequences, including, but not limited to, ICH. The highest incidence of ICH is seen in elderly patients with evidence of cerebral amyloid deposition with microbleeds. Several studies have evaluated the use of MRI imaging of the brain and cerebrospinal fluid antibodies and total tau levels to identify patients at risk. However, further research is needed in this regard before any practical application of these tests can be adopted to assess patients at the highest risk for ICH [23].

Assessment of bleeding risk

Several bleeding risk scores have been developed to stratify risk of hemorrhage, including the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol abuse), RIETE (Computerized Registry of Patients With Venous Thromboembolism), HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation). Although HAS-BLED discriminates bleeding risk better than the rest, all of these scoring systems have a modest predictive ability for bleeding (c-statistic ≈ 0.6) [24].

The 2014 AHA/ACC/HRS guideline states that, although these scoring systems may be useful in determining bleeding risk, given that all these scoring systems have poor predictive capabilities and a low C-index, there is insufficient evidence to provide recommendations for their use in clinical practice. The HAS-

BLED score has been validated in a prospective study where 'real world' patients with AF were followed for one year and the predictive capability compared to rates of major bleeding [25]. Thus, HAS-BLED has been recommended by the ESC and CCS as the scoring system of choice, as it is much simpler to use than the other systems. A patient with a HAS-BLED score >3 is considered to be at a high risk for bleeding and requires regular monitoring and caution while initiating OAC. A high HAS-BLED score in itself does not preclude an elderly patient from OAC therapy; rather, efforts should be made to control reversible risk factors such as uncontrolled BP, use of non-steroidal anti-inflammatory drugs, labile INRs etc.

Improving efficacy of warfarin therapy in the geriatric population

Older patients are more sensitive to small changes in warfarin dosing, and therefore should be started on lower initial doses as recommended in the American College of Chest Physicians (ACCP) guidelines. Algorithm-consistent dosing is a strong predictor of TTR, as shown in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial (10% increase in algorithm-consistent dosing predicted a 6.12% increase in TTR) [26]. Patient education, identifying patient-level barriers to adherence to warfarin therapy, and prompt follow-up when INR values are out of range are other ways to improve the efficacy of warfarin therapy.

Use of antiplatelet therapy for prevention of stroke in elderly AF patients

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE)-W, and ACTIVE-A trials [27,28] showed that warfarin was superior to the combination of clopidogrel and ASA for preventing strokes. The ACTIVE A (Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation) trial [29] enrolled 7554 AF patients (mean age 71 years) who were considered unsuitable for warfarin therapy and assigned patients to ASA+clopidogrel versus ASA. ASA+clopidogrel decreased the risk of stroke (RR 0.72, P<0.001), and increased the risk of major hemorrhage (RR 1.57, P<0.001) compared to ASA alone. The reasons for patients being deemed unfit for warfarin therapy included physician judgment (50.4%), patient's preference not to take warfarin (26%), and specific risk for bleeding (23%).

The 2012 European Society of Cardiology (ESC) focused update [30] recommended that combination antiplatelet therapy should be limited only to patients who refuse OAC. The Canadian Cardiovascular Society (CCS) guidelines recommend using dabigatran in those considered unsuitable for warfarin **(Table 2)**. Except for the Stroke Prevention in Atrial Fibrillation-1 (SPAF) study, no other studies have demonstrated any significant reduction in stroke risk with ASA. Moreover, in the SPAF-1 study, ASA did not decrease the risk of stroke in patients >75 years of age. In addition, there was an increased rate of adverse events, including bleeding, with ASA in patients aged 80-89 years in the Warfarin versus Aspirin for Stroke Prevention in Octogenarians

(WASPO) trial [31]. Accordingly, the 2014 ACCF/AHA/HRS guidelines do not offer any specific recommendations regarding the use of antiplatelet therapy for stroke prevention in AF.

Triple anti-thrombotic therapy and bleeding risk

The prevalence of coronary artery disease (CAD) rises with age, and managing elderly AF patients with CAD can be challenging, especially if they have to undergo percutaneous coronary intervention (PCI). Sorenson et al. [32] reported bleeding rates of 5.1% for aspirin plus warfarin, 12.3% for clopidogrel plus warfarin, and 12.0% for triple therapy in a cohort of 40,812 patients from a National Danish patient registry. Ruiz-Nodar et al. [33] studied 590 patients with AF with CHA_2DS_2-VASc scores of >1 undergoing PCI. Of the study cohort, 420 (71%) patients had a HAS-BLED score >3. In these patients, OAC use at discharge (as part of combination therapy) had a significantly lower mortality rate but a much higher bleeding rate. The risks for stroke, major bleeding, and stent thrombosis have to be weighed before making a decision regarding combination therapy. The AHA/ACC/HRS guideline recommends the use of clopidogrel with OACs but without aspirin following coronary revascularization. Various societies have proposed guidelines regarding the use of triple therapy in AF patients, the key points of which have been summarized in **Table 3.**

Newer Anticoagulants

Dabigatran

Dabigatran is a direct thrombin inhibitor approved in 2010 by the U. S. Food and Drug Administration (FDA). It undergoes 80% renal elimination and must be used cautiously in renal impairment. The RE-LY trial [34] randomized 18,113 patients to dabigatran

Table 3. The ACCF/AHA/HRS [5], ACCP [7], ESC [8], and CCS [6] guidelines for antithrombotic therapy in AF patients with CAD.

ACCF/AHA/HRS guidelines	ESC guidelines	ACCP guidelines	CCS guidelines
1. Stable CAD: No specific recommendations.	1. Stable CAD: In patients with stable CAD and no acute events for $\geq$ 1 year, warfarin monotherapy is recommended (Class IIB. If elective PCI is carried out, a BMS should preferably be used over DES unless a significant benefit is expected with a DES (Class IIA).	1. Stable CAD: In AF patients with stable CAD, warfarin therapy alone is recommended over combination therapy.	1.Stable CAD: In AF patients with - $CHADS_2$ score =0, ASA may be used. $CHADS_2$ score $\geq$1, OAC monotherapy.
2. Following PCI : a)BMS : Warfarin + Clopidogrel for at least 1 month. b) DES: Warfarin + Clopidogrel for 3 months after a sirolimus eluting stent, and 6 months after a paclitaxel eluting stent. Warfarin + Clopidogrel may be continued for longer duration (12 months) in selected patients, followed by VKA monotherapy.	2. Following PCI: a) BMS- Triple therapy[1] may be used for a minimum of one month. b)DES- Triple therapy for 3 months for a sirolimus eluting stent, and 6 months for a paclitaxel eluting stent should be considered. Following this dual therapy with warfarin + Clopidogrel or ASA (75-100 mg daily + PPI/ H2 blockers) for up to 1 year may be considered after assessing individual bleeding risks.	2.Following PCI: AF patients with a $CHADS_2$ score of $\geq$2 a) BMS: Triple therapy for 1 month. b) DES: Triple therapy for 3-6 months. After this initial period dual therapy (warfarin + ASA/ Clopidogrel) may be used for upto 12 months.	2. Following PCI: BMS/ DES- In AF patients with- $CHADS_2\leq$ 1, ASA + Clopidogrel. $CHADS_2$ score $\geq$2, triple therapy may be considered.
3. Following PCI, warfarin + ASA and/ or Clopidogrel may be given keeping in mind that these strategies are associated with an increased risk for bleeding.	3. Following an ACS: Triple therapy for 3-6 months (longer in a patient with low bleeding risk), followed by long term dual therapy with warfarin + Clopidogrel or ASA + gastric protection (Class IIA).	3. For AF patients with a CHADS2 score < 2, dual therapy may be used for the first 12 months after placement of either a BMS or a DES.	3. The CCS guidelines do not specify the duration of therapy after PCI, however they state that the decision should be based on assessment of the relative risks of stroke, stent thrombosis, and hemorrhage.
	4. When warfarin + Clopidogrel or ASA is prescribed a carefully regulated INR range of 2.0-2.5 may be appropriate.		4. In AF patients with CAD at a high risk for coronary events warfarin may be preferred over dabigatran.

AF: Atrial fibrillation; ACCF/ AHA/ HRS: American College of Cardiology/ American Heart Association/ Heart Rhythm Society; ACCP : American College of Chest Physicians; ASA: Aspirin; BMS: Bare metal stent; CAD: Coronary artery disease; CCS : Canadian Cardiovascular Society; $CHADS_2$: Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA; DES: Drug eluting stent; ESC : European Society of Cardiology; OAC: Oral Anticoagulation; PCI : Percutaneous coronary intervention; PPI: Proton pump inhibitor; VKA: Vitamin K Antagonists; Triple therapy – VKA + ASA+ Clopidogrel.

Table 4. Newer anticoagulants.

Patient and drug characteristics	Dabigatran (RE-LY trial) [34]	Rivaroxaban (ROCKET-AF trial) [41]	Apixaban (ARISTOTLE trial) [44]	Edoxaban (ENGAGE-AF TIMI 48) [46]
Total patients enrolled	18,111	14,264	18,201	21,105
Mean age (years)	71.5 ± 8.7	73 (65-78)	70 (63-76)	72 (64-78)
Percentage of patients ≥ 75 years of age (%)	40	38	31	40
Average body weight (kg)	82.5 ± 19	BMI (Body Mass Index): : 28.3 ± 4	82 ± 14	> 60 kg in 90% of the patients
Mean CHADS2 score	2.1	3.5	2.1	2.8
Dose	150 mg bid	20 mg once daily	5 mg bid	30-60 mg daily
Dose adjusted for renal impairment	75 mg bid for CrCl 15-30 ml/min (US only)	15 mg once daily	2.5 mg bid	Dose halved for CrCl 30-50 ml/ min
Dose under special circumstances	110 mg bid (ESC and CCS) in patients > 80 years of age, HAS-BLED ≥ 3, use of interacting drugs, renal impairment.	15 mg once daily in patients with HAS-BLED score ≥ 3, and renal impairment.	2.5-mg in patients with two or more of the following criteria: ≥ 80 years, body weight ≤60 kg, or renal impairment	Dose halved for CrCl of 30 - 50 ml/min, a body weight of ≤ 60 kg or concomitant use of verapamil,quinidine or dronedarone
Half-life (hours)	12-17 (CrCl 50-80 ml/ min) 18-24 (CrCl 30-49 ml/ min) >24 (CrCl <30 ml/min)	5-13	9-14	6-10
Excretion	Renal (80%)	Renal (1/3), liver (2/3)	Renal (25%), fecal (75%)	Renal (35%), fecal (65%)
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa

CHADS$_2$: Congestive heart failure, Hypertension, Age > 75, Diabetes Mellitus, Stroke/ TIA; CrCl: Creatinine Clearance; ESC: European Society of Cardiology; CCS: Canadian Cardiovascular Society; HAS-BLED: Hypertension, Abnormal renal or liver function , Stroke , history of Bleeding , Labile INRs, Elderly, Drug or alcohol abuse; OAC: Oral Anticoagulation therapy; ACCF/ AHA/ HRS: American College of Cardiology/ American Heart Association/ Heart Rhythm Society; ACCP: American College of Chest Physicians; FDA: Food and Drug Administration.

150 mg (D150) twice daily, dabigatran 110 mg (D110) twice daily, or open-label warfarin. The mean age, CHADS$_2$ score, and TTR of the patients were 70 years, 2.1, and 64% respectively **(Table 4).** Eighty-two percent of patients were aged >65 years and 40% were aged >75 years. The rates of stroke/SE were 1.53%/year for D110, 1.11% per year for D150, and 1.69% per year for warfarin [35]. Both doses of dabigatran were non-inferior to warfarin, and the 150 mg dose of dabigatran was superior to warfarin (RR, 0.66; 95% [CI], 0.53 to 0.82; P<0.001). Both doses of dabigatran were associated with a lower risk for ICH when compared to warfarin, across all age groups. However, in patients >75 years of age, both doses of dabigatran were associated with a higher risk for extracranial bleeding, particularly gastrointestinal (GI) bleeding (RR 1.39 (P=0.02) and 1.79 (P=0.06) for D110 and D150 dabigatran respectively) [36].

In particular, Graham et al. [37] studied elderly patients (>65 years) on oral anticoagulants for AF and found a decreased risk for ischemic stroke (HR: 0.80; 95% CI: 0.67-0.96) and ICH (HR: 0.34; 94% CI: 0.26-0.46) in patients on dabigatran as compared to a propensity-matched cohort of patients on warfarin. The investigators also found an increased risk for major GI bleeding (HR: 1.28; 95% CI: 1.14-1.44) with dabigatran as compared to warfarin. However, the study did not take into account the concomitant use of aspirin and over the counter non-steroidal anti-inflammatory drugs. Also, the time in therapeutic range (TTR) with warfarin could not be ascertained, although the TTR probably reflected that seen in general practice.

A higher incidence of dyspepsia was noted in patients on dabigatran as compared to warfarin in the RE-LY trial. Dabigatran requires a low pH for good absorption, and in order to achieve this, the capsules contain tartaric acid cores coated on the outside with dabigatran, which has been postulated as the cause for increased dyspepsia and possibly GI bleeding.

There have been concerns regarding the increased risk of myocardial infarction (MI) associated with the use of dabigatran. A meta-analysis [38] evaluated this risk and found that dabigatran use was associated with a statistically significant higher risk of MI compared to warfarin. With the 150 mg BID dosage the odds ratio for MI when compared with warfarin was 1.43 (95% CI 1.08 to 1.89; P= 0.152), and with the 110 mg BID dosage it was 1.33 (95% CI 0.99 to 1.77; P=0.760).

Dosing with older age and impaired renal function

The 150 mg dose of dabigatran was approved by the FDA, [39] but not the 110 mg dose. Prior to arriving at this decision, the FDA analyzed high risk groups in the RE-LY study (elderly, patients with renal insufficiency) and found that among patients >75 years of age (40% of the total cohort), the rate of stroke/SE was lower with D150 (1.4%/year) than with D110 (1.9%/year), though the rate of major bleeding was higher with the D150 dose (5.1 vs. 4.4 %/patient/year). Based on this analysis, the D150 dose was found to be more efficacious across all groups of patients. The FDA was concerned that the D110 dose might be preferred

more often by physicians concerned more about prevention of bleeding in elderly patients than prevention of TE events. Reilly et al. [40] studied the effects of dabigatran plasma concentration and age on the incidence of ischemic stroke and major bleeds. They found that in patients with major bleeding events, the median trough and post-dose concentrations were 55% and 36% higher, respectively, than in those without bleeding events. Renal function (CrCl) and age were found to be the two most important determinants of the plasma concentration of dabigatran, with a 68% higher trough concentration in patients >75 years of age as compared to those <65 years of age. In addition, low body weight and female sex were associated with higher plasma concentrations of dabigatran. This substudy showed that across the 10th to 90th percentiles of plasma trough concentrations, the risk of major bleeding ranged from 2-7%, with increasing age as an important contributing factor. The risk for ischemic stroke across the same concentrations ranged from ~1.5% in patients <75 years of age to ~2.1% for patients ≥80. In frail elderly patients, especially in those with impaired renal function, a lower daily dose might be more ideal, given the decreased risk of major bleeds without loss of efficacy in terms of preventing embolic stroke.

Prior to initiating therapy with dabigatran, the risk-benefit ratio should be assessed for all patients, especially the elderly. The mean age and weight of patients enrolled in the RE-LY trial was 70 years and 82 kg respectively, and in frail elderly patients, especially those >80 years of age with some degree of renal insufficiency, the D150 dose may pose an increased risk of bleeding. This risk may also be exacerbated by concomitant medications like verapamil and amiodarone (P-glyprotein inhibitors). As described above, a subset of geriatric patients may be at a higher bleeding risk with both the D150 dose as well as warfarin therapy. In such patients, other dosing options might warrant further study. The latest guidelines by the ACCF/AHA/HRS, ACCP, ESC, and CCS in regards to the newer anticoagulants are summarized in **Table 4.**

Rivaroxaban

Rivaroxaban is a direct factor Xa inhibitor predominantly metabolized by the liver, with one-third of the drug undergoing renal elimination. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [41] randomized 14,264 patients with AF and a CHADS$_2$ score of ≥ 2 to rivaroxaban (20 mg daily or 15 mg daily in patients with a CrCl of 30-49 ml per minute) or warfarin. ROCKET-AF had a significantly sicker population than RE-LY and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) (ARISTOLE) trial [42]. The mean age of the patients was 73 years, with a mean CHADS$_2$ score of 3.5. It should be noted that the TTR for the ROCKET-AF trial overall was lower as compared to other randomized controlled trials at 55%. In the primary analysis, the rivaroxaban group had a lower rate of stroke/SE (1.7% per year) than those in the warfarin group (2.2% per year) (HR 0.79; 95% CI; 0.66-0.96; P<0.001 for non-inferiority). Rates of major bleeding were similar for rivaroxaban and warfarin (14.9% vs. 14.5%, HR: 1.03, CI 0.96-1.11; P=0.44), although major bleeding from a gastrointestinal site was higher in the rivaroxaban group (3.2 vs 2.2%, P<0.001). Rates of ICH were lower in the rivaroxaban

group than in the warfarin group (0.5% vs. 0.7% per year, P=0.02). The ROCKET-AF trial had a higher rate of early treatment discontinuation (around 14.3% in the first year), which was higher compared to the other major trials (around 10-11%). Halperin et al. [43] studied 6,229 elderly patients (≥75 years of age) as a part of a pre-specified secondary analysis of the ROCKET-AF trial and found no difference in the primary efficacy outcome (stroke/ SE) between warfarin therapy and rivaroxaban. Similarly, there were no differences in major bleeding events between the warfarin and rivaroxaban groups. However, the incidence of GI bleeding was higher in patients treated with rivaroxaban compared to warfarin.

Apixaban

Apixaban is a direct factor Xa inhibitor recently approved by the FDA for stroke prevention in AF. The ARISTOTLE trial [44] randomized 18,201 patients with AF and one additional risk factor for stroke to apixaban or dose-adjusted warfarin. The median age of the population was 70 years with 31% of the population >75 years of age. The mean CHADS$_2$ score was 2.1, and the mean TTR of the warfarin cohort was 66%. The primary outcome of stroke/SE occurred in 1.27% patients/year in the apixaban group versus 1.60% per year in the warfarin group (HR for apixaban 0.79; 95% CI, 0.66 to 0.95; P<0.001 for non-inferiority and P = 0.01 for superiority). The rate of ICH was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (HR, 0.42; P<0.001). The clinical benefit of apixaban over warfarin was consistent across all patients irrespective of their CHADS$_2$, CHA$_2$DS$_2$-VASc, and HAS-BLED scores. In addition, apixaban decreased all-cause mortality when compared to warfarin.

The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial [45] showed greater efficacy for apixaban in preventing stroke/SE events and similar rates of bleeding compared to ASA, making this a good option in elderly patients considered unsuitable for warfarin therapy.

Dosing with older age and impaired renal function

Apixaban was given 5 mg twice daily in the ARISTOTLE study, although 2.5 mg twice daily was used in a subset of patients with two or more of the following criteria: ≥80 years, body weight ≤ 60 kg, or a serum creatinine level of ≥ 1.5 mg/dL. The superiority of apixaban relative to warfarin for preventing stroke was consistent, irrespective of the degree of renal impairment [44].

Edoxaban

The Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 [46] (ENGAGE-AF TIMI 48) randomized 21,105 patients to warfarin, high dose or low dose edoxaban. Patients received low dose edoxaban if any one of the following was present: estimated CrCl of 30- 50 ml/ minute, weight of ≤ 60 kg, or the concomitant use of verapamil, dronedarone or quinidine. Both doses of edoxaban were found to be non-inferior to warfarin for the prevention of stroke and systemic embolism (rate of stroke or systemic embolic event for warfarin vs high dose edoxaban was

Table 5. Peri-operative/pre-procedural protocol in patients on OAC therapy.

Warfarin [47]	Newer OACsNewer OACs							
1. Warfarin therapy should be stopped approximately five days prior to surgery 2. Warfarin therapy may be started 12 to 24 hours after surgery, when there is adequate hemostasis. 3. Bridging therapy with low molecular weight (LMW) heparin is recommended for patients with a mechanical heart valve, atrial fibrillation, or VTE at a high risk for thromboembolism.	1. The optimal timing prior to surgery for stopping the newer OACs depends on the patient's renal function, and the risk of bleeding associated with the procedure. Optimal timing prior to surgery to stop newer OACs [48]							
	CrCl	> 80		50-79		30-49		15-29	
	Risk of bleeding	L	H	L	H	L	H	L	H
	Dabigatran (duration in hours)	>24	>48	>36	>72	>48	>96	CI	CI
	Rivaroxaban (duration in hours)	>24	>48	>24	>48	>24	>48	>36	>48
	Apixaban (duration in hours)	>24	>48	>24	>48	>24	>48	>36	>48
	Newer OACs are contraindicated in patients with CrCl < 15 ml/min [50].								
CI: Contraindicated; CrCl: Creatinine Clearance; L: Low; H: High; OAC: Oral Anticoagulation therapy; VTE: Venous Thromboembolism									

Table 6. Management of bleeding events in patients on oral anticoagulation.

Management of major bleeding in a patient on oral anticoagulation [50,51]
Supportive therapy in the form of fluid resuscitation, blood transfusion, investigation for the source of bleeding, mechanical compression and where appropriate surgical hemostasis should be undertaken.
Fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC) can be used to reverse the effect of warfarin in case of a major bleed. Vitamin K can be administered concomitantly, though it takes a longer time to reverse the anticoagulant effect.
There are no specific antidotes available in the market for the newer anticoagulants although a reversal agent for dabigatran is being studied currently. However these agents have shorter half-lives, and their anticoagulant action does not last long after discontinuation of the drug.
In cases of life threatening bleeding in a patient on Dabigatran, prothrombin complex concentrates (PCC) or recombinant activated factor VIIa may be considered though the clinical utility of these agents has not been established.
Adequate diuresis should be maintained as Dabigatran is predominantly renally excreted.
In cases of severe bleeding, or overdose of Dabigatran, when rapid reversal is required hemodialysis can be carried out to facilitate plasma clearance of Dabigatran.

1.50% vs 1.18% per year, HR: 0.79; 97.5% CI, 0.63 to 0.99; P<0.001 for non-inferiority). The rates of major bleeding, including ICH, were lower for edoxaban versus warfarin, except that the rate of major GI bleeding was higher with high dose edoxaban compared to warfarin. The mean age of the study group was 72 years, with around 40% of the population ≥ 75 years of age. However, there was a higher risk of ischemic stroke with edoxaban in patients with a CrCl > 95 ml/ min compared with warfarin leading to the current labeling that edoxaban should not be used in this subgroup of patients.

Advantages of newer anticoagulants over warfarin

Advantages of the newer OACs include predictable pharmacodynamic effects, good efficacy and safety profiles without the need for anticoagulation monitoring, rapid onset of action (2-4 hours vs ~ 72 hours for warfarin), and shorter half-lives that make the use of these agents in the peri-procedural period much easier **(Table 5)**. The newer anticoagulants have also been consistently found to reduce the risk of ICH as compared to warfarin irrespective of age.

Risks with newer anticoagulants

Warfarin has been in use as an anticoagulant for several decades now. Though there are problems associated with warfarin use, these are well known, and they have been studied extensively both in clinical trials and in real world practice. Many patients started on OACs require these medications for an extended period of time, often lifelong. We do not have long-term data for the newer anticoagulants. Only one-third of the patients enrolled

in the newer anticoagulant clinical trials were >75 years of age. Moreover, 'frail' elderly patients and patients with significant renal disease were not included in these trials. There is a risk for major bleeding even with the newer anticoagulants, especially in the frail elderly. In a recent study [49] analyzing the risk of major bleeding with dabigatran in real world practice in New Zealand over a two month period, the predictors of bleeding were incorrect prescription, impaired renal function, and patient age. Currently, the newer anticoagulants do not have FDA-approved antidotes to reverse bleeding. However, a fully humanized antibody fragment called idarucizumab was recently shown to reverse the anticoagulant effects of dabigatran in healthy volunteers, and further large scale studies are underway [51,52]. The management of bleeding with the newer anticoagulants is mainly supportive, as described in **Table 6.** High cost may also be a limiting factor for the newer anticoagulants, although D150 was found to be cost effective in patients with high $CHADS_2$ scores and an inability to maintain stable INRs [53].

Although these drugs are recommended in patients with unstable and difficult to maintain INRs, it is important to determine the reason for the unstable INRs. If the problem is poor compliance with medications, and the patient cannot be trusted to take the drug regularly, the newer OACs may not be a better choice in these patients, as they have a much shorter half-life and missing a dose or two can result in an increased thromboembolic risk.

Further Research

While many studies have been done comparing newer OACs to warfarin, there are no head-to-head comparisons of any of the newer OACs with each other. Patients with renal impairment have a very high risk for both stroke and major bleeding and the incidence of renal dysfunction is higher in the elderly than in the younger population. Patients with advanced renal failure and/ or on dialysis were not included in any of the major newer OAC trials and as of now warfarin is the only option available for these patients. Also, as noted above, triple antithrombotic therapy in elderly patients with AF and acute coronary syndrome is problematic, as it confers a high risk of major bleeding. With the advent of newer antiplatelet agents such as ticagrelor and prasugrel, further studies with these agents in patients with AF and ACS requiring triple therapy are warranted.

Conclusions

Elderly patients with AF are at a particularly high risk for TE complications. With a large fraction of such patients not receiving anticoagulation, the recent introduction of newer anticoagulants may improve rates of treatment by providing different options for management. For an elderly patient who has been on warfarin for a long time with good TTRs, no major complications, and ensured compliance with regular testing, it may be appropriate to continue with warfarin based on the patient's preference. On the other hand, the newer OACs have convenient dosing, no need for blood testing for efficacy, and may be particularly attractive in patients at high risk for stroke in whom the TTR is sub-optimal [54].

Patients place a greater emphasis on stroke prevention and a lower value on avoiding bleeding than do physicians who treat AF [55]. It is very important to take into account patient preference before making a decision regarding starting or deferring anticoagulant therapy for a patient. The risk of stroke, risk of major bleeding, and the need for regular INR monitoring if on warfarin should be explained clearly. The addition of the newer OACs to the therapeutic options available for stroke prevention in AF has provided patients and clinicians with an attractive alternative choice of therapy which does not require regular monitoring, has a similar or better safety profile with respect to major bleeding (especially ICH), and can be conveniently dosed. At the same time as these newer OACs have only been around for a short time, their long term performance data is yet to be fully evaluated. It has been shown in several studies [56] that AF patients with similar risk profiles choose different stroke prevention strategies, and it is only appropriate that patient preferences are included when making this important decision.

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