North American Thrombosis Forum, AF Action Initiative Consensus Document

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ABSTRACT

The North American Thrombosis Forum Atrial Fibrillation Action Initiative consensus document is a comprehensive yet practical briefing document focusing on stroke and bleeding risk assessment in patients with atrial fibrillation, as well as recommendations regarding anticoagulation options and management. Despite the breadth of clinical trial data and guideline recommendation updates, many clinicians continue to struggle to synthesize the disparate information available. This problem slows the uptake and utilization of updated risk prediction tools and adoption of new oral anticoagulants. This document serves as a practical and educational reference for the entire medical community involved in the care of patients with atrial fibrillation.
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KEYWORDS: Anticoagulants; Antithrombotic management; Atrial fibrillation; Bleeding risk; Stroke

STROKE RISK STRATIFICATION

Atrial fibrillation (AF), the most frequently encountered sustained cardiac arrhythmia, is a major risk factor for ischemic stroke.[1,2] On average, patients with AF have a fivefold higher risk for stroke than the general population.[3] However, an individual patient's risk of stroke

varies depending on the presence or absence of various risk factors.

Stroke risk stratification scores rely on a combination of demographic and clinical characteristics. The most well-known and validated stroke-risk stratification score is the $CHADS_2$ score (**Table 1**).[4] $CHADS_2$ scores have been broadly categorized as low (0), intermediate (1), and high (2-6) risk of stroke.[5] In older guidelines, anticoagulant therapy was recommended for high-risk patients, whereas an anticoagulant or aspirin was recommended for moderate-risk patients, and aspirin alone for low-risk patients.[1,4,6-8]

However, the traditional stroke risk-stratification schemes, including the $CHADS_2$ risk score, are limited by not sufficiently identifying truly "low-risk" patients by excluding other known stroke risk factors such as vascular disease (myocardial infarction and peripheral vascular disease) and female sex,[5] as well as consideration of the increased stroke risk that exists in patients younger than 75 years of age. Such exclusions lead to underestimation of stroke risk and result in undertreatment with oral anticoagulants for stroke prevention.

The more recently developed and validated CHA_2DS_2-VASc risk-stratification score[9-14] (**Table 2**) is a modification and expansion of the $CHADS_2$ scheme that incorporates additional stroke risk factors.[5] It offers the main advantage of better identifying "truly low-risk" individuals that likely do not benefit from anticoagulation. The annual rate of thromboembolic events associated with CHA_2DS_2-VASc = 0 was 0%, compared with 1.40% with $CHADS_2$ = 0 in the same patients. In the updated guidelines, anticoagulation should be considered for AF patients with ≥1 stroke risk factors or a CHA_2DS_2-VASc ≥1 (**Table 3**).[4,5,15,16]

BLEEDING RISK STRATIFICATION

Anticoagulants reduce the risk of AF-related thromboembolism, but also increase the risk of bleeding. Scoring systems that use clinical characteristics to estimate a patient's annual risk for major bleeding can help clinicians who wish to compare the risks and benefits of anticoagulation. Several such scoring systems[17-21] have been derived and validated for patients with AF who are taking warfarin (**Table 4**), although all have only modest ability to predict bleeding.

The quantitative approximation of bleeding risk provided by these models may have less importance than a familiarity with the individual risk factors themselves. For example, an awareness that renal disease has repeatedly emerged as an independent risk factor for warfarin-associated major bleeding should prompt increased attention to the net clinical benefit of anticoagulation for a patient with AF, especially if the risk of ischemic stroke is low. More importantly, the knowledge that poorly controlled hypertension, concomitant antiplatelet therapy, and alcohol abuse each independently increases bleeding risk provides the potential opportunity to increase the safety of anticoagulation when one or more of these factors can be modified.

In practice, many AF patients with a high risk of ischemic stroke also have a high risk of bleeding, as the same risk factors predict both outcomes.[22] Providers and patients who use risk scores such as $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; **Table 5**) should be aware that the severity of the clinical outcomes they predict can vary significantly (**Table 6**).[23] For example, a stroke can be relatively minor (eg, transient or insignificant neurologic deficit) or result in neurologic devastation (a large cerebral infarct with dense, permanent hemiparesis). Similarly, a major bleed can range from a slow diverticular leak to a fatal intracranial hemorrhage. Clinicians should also be cautioned that the currently available bleeding risk calculators were developed for patients on warfarin and not novel oral anticoagulants (NOACs). Further research will be needed to determine how existing bleeding risk scoring systems will require modification if used to weigh the hazards of prescribing an oral direct factor Xa or thrombin inhibitor.

In summary, the vast majority of AF patients encountered in clinical practice have a net clinical benefit from anticoagulation as their risk of ischemic stroke without anticoagulation far outweighs their risk of serious bleeding if prescribed an anticoagulant. Bleeding risk scores should not be used to justify withholding anticoagulation if the calculated score is above some threshold, but rather to help clinicians identify modifiable factors (such as unnecessary concomitant antiplatelet medication use or poorly controlled hypertension) that, if addressed, may reduce the risk of anticoagulant-associated major bleeding.

THE FUTURE OF RISK STRATIFICATION— BIOMARKERS AND GENETICS

Development of AF

AF frequently goes clinically unrecognized and undiagnosed,[24,25] and may first present as a stroke.[26] Subclinical AF

CLINICAL SIGNIFICANCE

- The North American Thrombosis Forum Atrial Fibrillation Action Initiative consensus document is a comprehensive yet practical briefing document that provides a concise review of important clinical research and provides expert consensus recommendations regarding risk assessment and anticoagulation management.

- The document was developed to serve as a reference for both the medical community and patients.

- The document covers many management issues routinely encountered in clinical practice but not covered in conventional guideline recommendations.

Table 1   CHADS$_2$ Risk Score for Prediction of Stroke Risk in AF

Risk Factor	Points
CHF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke /TIA/embolism	2
Maximum score	6

AF = atrial fibrillation; CHF = congestive heart failure; TIA = transient ischemic attack.

Table 3   Adjusted Risk of Stroke for CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores

Score	CHADS$_2$ (%/y)[4]	CHA$_2$DS$_2$-VASc (%/y)[5]
0	1.9	0
1	2.8	1.3
2	4	2.2
3	5.9	3.2
4	8.5	4.0
5	12.5	6.7
6	18.2	9.8
7		9.6
8		6.7
9		15.2

associates with an increased risk of clinical[27] and silent[28] strokes. Furthermore, appreciation has increased that monitoring after ischemic stroke may reveal previously undiagnosed AF.[29-31] In a systematic review of studies of strokes of unknown origin, also known as cryptogenic strokes, the average rate of AF detection was 10.7% (95% confidence interval [CI], 7.9%-14.3%), with the detection rate increasing with longer length of monitoring.[32] Hence, the ability to predict incident AF has major public health import.

Several risk prediction scores for AF have been published, including from the Framingham Heart Study (FHS),[33,34] the Atherosclerosis Risk in Communities Study (ARIC),[35] and the Women's Health Study.[36] The CHARGE-AF group took individual-level data from 3 US cohort studies (FHS, ARIC, and the Cardiovascular Health Study) and developed a simple clinical model to predict 5-year risk of new-onset AF, and validated the model in 2 European cohorts (Age, Gene/Environment Susceptibility-Reykjavik Study [AGES] and Rotterdam Study [RS]).[37] A model including age, race, height, weight, systolic and diastolic blood pressure, current smoking, diabetes, use of antihypertensive medication, and history of myocardial infarction and heart failure had good discrimination (C-statistic, 0.765; 95% CI, 0.748-0.781) in the discovery cohorts, and adequate discrimination in the validation cohorts (AGES C-statistic, 0.664; 95% CI, 0.632-0.697; and RS C-statistic, 0.705; 95% CI, 0.664-0.747). Risk prediction models may serve as benchmarks to evaluate putative novel risk markers and to risk-stratify individuals for inclusion in trials of screening or preventive therapies for AF.

Table 2   CHA$_2$DS$_2$-VASc Risk Score for Prediction of Stroke Risk in AF

Risk Factor	Points
CHF/LV dysfunction	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/embolism	2
Vascular disease	1
Age 64-74 y	1
Sex category (female)	1
Maximum score	9

AF = atrial fibrillation; CHF = congestive heart failure; LV= left ventricular; TIA= transient ischemic attack.

Investigators have reported numerous novel biomarkers that may enhance risk stratification for new-onset or recurrent AF, and predict prognosis in individuals with established AF.[38] The American Heart Association has issued a Scientific Statement outlining a framework for the evaluation of novel biomarkers.[39] To be clinically useful, biomarkers should not only associate with disease, but should improve discrimination, provide incremental information over and above clinical factors, improve clinical outcomes, and be cost-effective.[39] Among the numerous biomarkers proposed, only the natriuretic peptides consistently improve risk reclassification for incident AF.[40,41]

Whereas AF in rare families with dense pedigree patterns of inheritance has long been appreciated,[42,43] more recent work has established the heritability of AF in the community.[44-46] Accounting for AF risk factors, a history of familial AF associates with a 40% higher risk of developing AF. Furthermore, a family history of AF modestly enhanced reclassification of risk.[45]

Genome-wide association studies have revealed 9 loci associated with an increased risk of AF.[47-51] Using a multimarker genetic risk score, which included the 12 nonredundant single nucleotide polymorphisms (SNPs) at the 9 AF risk loci (4 SNPs at *PITX2*), there was a fivefold higher risk in individuals of European ancestry with a high score compared with those with a low score; findings that were replicated in a Japanese cohort.[52] Investigators from the Malmö Diet and Cancer Prevention Study did not observe enhanced discrimination for the prediction of AF when analyzing 2 common SNPs.[53] Using a 12-SNP genetic risk score, investigators from the Women's Genome Health Study observed that the risk score enhanced discrimination, but not risk reclassification beyond clinical risk factors.[36]

In summary, clinical risk factors are reasonably good at risk-stratifying the onset of AF. While numerous biological and genetic markers associate with increased risk of AF, with the exception of natriuretic peptides, they have added little to our ability to reclassify risk of AF. Potential future directions for biomarker and genetic research in AF risk stratification include:

Table 4 Clinical Characteristics Included in 5 Models Designed to Predict the Risk of Warfarin-Associated Major Bleeding

Risk Score	Age	Prior Bleed	Hypertension	Renal or Hepatic Disease	Alcohol/ Drug	Antiplatelet Therapy	Anemia	Diabetes	Prior Stroke	Sex	INR Labile
OPBRI[17]	X	X		X			X	X	X		
HEMORRHAGES†[18]	X	X	X	X	X	X*	X				
Shireman et al[19]	X	X	X		X	X		X		X	
HAS-BLED[20]	X	X	X	X	X	X			X		X
ATRIA[21]	X	X	X	X			X				

HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol; INR = international normalized ratio; ATRIA = Anticoagulation Risk Factors in Atrial Fibrillation HEMORRHAGES: Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age > 75 years), Reduced platelet count or function, Rebleeding risk, Hypertension (uncontrolled), Anemia, Genetic factors (CYP 2C9 single-nucleotide polymorphisms), Excessive fall risk (including neuropsychiatric disease), and Stroke.
*Decreased number or function of platelets.
†This scoring system also included points for active cancer and high fall risk.

- Other races/ethnicities. The vast majority of studies have included individuals of European ancestry. Future studies should include other races/ethnicities.
- Biomarker/genetic study quality.[39] Future biomarker studies should adhere to American Heart Association recommendations and be adequate in size, and report absolute and relative risk estimates, CIs, and *P*-value, discrimination, reclassification, and accuracy metrics in models with standard AF risk factors compared with the bio-/genetic marker added.
- Reclassification. Bio-/genetic markers may provide potential pathophysiological insights, but only natriuretic peptides reliably reclassify risk for incident AF. Ideally, the discovery and validation of additional more specific markers that mechanistically link to AF risk will enhance reclassification.
- Test whether bio-/genetic markers are clinically useful and cost-effective.[39] Novel risk prediction models that incorporate clinical and bio-/genetic markers for incident AF will require rigorous evaluation of whether they clinically and cost-effectively improve the risk stratification of individuals for more intensive screening[25] or for trials to prevent AF.[39,54]

PREDICTING OUTCOMES IN PATIENTS WITH AF
Biomarkers and genetics hold the promise of improving prognostication and selection of therapies in the setting of AF.

For example, natriuretic peptides, which derive from cardiomyocytes that experience increased wall stress, associate with an increased risk of adverse cardiovascular events in this population. Specifically, within the RE-LY trial, patients in the highest N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) quartile as compared with those in the lowest quartile had an almost 2.5-fold increased risk of stroke and a 6.5-fold increased risk of vascular mortality, after adjustment for established risk factors.[55] Likewise, levels of NT-proBNP associated independently with the risk of stroke and mortality in the ARISTOTLE trial.[56] Furthermore, the addition of NT-proBNP to the CHA_2DS_2-VASc score improved the C-statistic from 0.62 to 0.65 for prediction of stroke or systemic embolism and from 0.59 to 0.69 for prediction of cardiovascular death, thus offering an additional tool that may prove useful in risk stratification.

Troponin, a marker of myocardial injury, also associates with elevated risk of adverse events in patients with AF. In RE-LY, troponin I added incremental prognostic information beyond traditional risk factors, and risk assessment was improved when troponin levels were added to models that included the CHA_2DS_2-VASc score.[55] Subsequently, within the ARISTOTLE trial, concentrations of troponin determined using a high-sensitivity assay (high-sensitivity troponin I), associated independently with stroke or systemic embolism (hazard ratio [HR] 1.98; 95% CI, 1.42-2.78), cardiac death (HR 4.52; 95% CI, 3.05-6.70), and major bleeding (HR 1.44; 95% CI, 1.11-1.86).[57] Once again, the use of troponin

Table 5 HAS-BLED Risk Score for Predicting Risk of Bleeding with Anticoagulation

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal liver or renal function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age >65)	1
D	Drugs or alcohol	1 or 2
	Maximum score	9

INR = international normalized ratio.

Table 6 Adjusted Risk of Major Bleeding for HAS-BLED Score[23]

HAS-BLED Score	Risk of Major Bleeding (%/y)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol.

levels improved the C-statistic. The use of a high-sensitivity troponin T assay in the ARISTOTLE population and in a registry of stable patients with AF yielded similar results.[58,59]

In patients with AF, markers of renal function, coagulation, and inflammation also have been evaluated. In terms of renal function, patients with low vs normal glomerular filtration rates had an increased risk of both stroke and bleeding.[60,61] Similarly, elevated levels of cystatin C associated independently with thromboembolic and bleeding events in both RE-LY and ARISTOTLE, and their inclusion improved risk models.[61,62] Markers of coagulation, such as D-dimer, also correlate significantly with adverse outcomes in the setting of AF.[63-65] Additionally, interleukin 6 and C-reactive protein associate with the risk of stroke, heart failure, and death, raising the possibility that markers of inflammation contribute to prognostication.[59,66,67] Demonstration of the clinical utility and cost-effectiveness of these and other markers requires continued study.

Several pharmacogenetic studies have addressed the selection of anticoagulant therapies in the context of warfarin therapy. Specifically, variants in the genes that encode an enzyme responsible for the metabolism of warfarin (*CYP2C9*) and the molecular target of warfarin (*VKCOR1*) influence warfarin dosing.[68] Studies have examined the use of genotype-guided algorithms on dosing of vitamin K antagonists (VKAs) and international normalized ratio (INR) management with somewhat variable results. Two trials showed that genotype-guided dosing of warfarin, acenocoumarol, or phenprocoumon improved the time in therapeutic range within the first 4 weeks of treatment, whereas a third trial did not.[69-72] These trials focused on average INR values, and they were not designed to have the statistical power to evaluate clinical events. More recent data from the large ENGAGE AF-TIMI 48 trial demonstrated that patients that were classified as sensitive responders to warfarin based on their CYP2C9 genotypes spent more time over-anticoagulated and had higher rates of bleeding than normal warfarin responders.[73] Data are also emerging on the potential importance of genetic variants with respect to the NOACs. A genome-wide association study in RE-LY found that carriage of the *CES1* rs2244613 minor allele occurred in approximately one-third of the patients and associated with lower exposure to the active dabigatran metabolite. This polymorphism affects an esterase that converts dabigatran etexilate to dabigatran. Furthermore, the presence of this polymorphism related to a lower risk of bleeding.[74] Moving forward, a better understanding of these relationships could move us closer to clinical application of genetics to optimize the selection of anticoagulant therapies.

VITAMIN K ANTAGONIST OVERVIEW

Warfarin has been the mainstay of treatment for the prevention of stroke in AF for decades. Compared with no therapy, warfarin reduces the risk of stroke by approximately 64%.[75] Warfarin achieves its anticoagulant effect by preventing the gamma-carboxylation of the vitamin-dependent coagulation factors II, VII, IX, and X. Warfarin achieves this therapeutic effect by maintaining the anticoagulation intensity, as measured by the INR, between 2.0 and 3.0.[76] The risk of ischemic stroke increases with INR levels <2, and the risk of major hemorrhage increases with INR levels >4.0.

The narrow therapeutic range of warfarin and the variability of its dose response mandates frequent monitoring of the INR to ensure maintenance of a therapeutic level and avoidance of supratherapeutic anticoagulation. Because its action involves the vitamin K cycle, dietary sources of vitamin K can interfere with its anticoagulant effect. Warfarin is metabolized by the liver, principally by the CYP enzyme 2C9, which renders it susceptible to interference by other drugs competing for these same pathways. Compared with men, women require lower doses of warfarin to achieve the same therapeutic levels. Warfarin dose requirements also decrease with older age.[77] The delayed onset of action of warfarin (72 to 96 hours) may necessitate bridging with parenteral anticoagulant therapy for those patients at highest risk of stroke. The long half-life of warfarin (40 hours) also complicates its management, particularly in the event of acute hemorrhage or urgent need for surgery.

The need for frequent monitoring and challenge of maintaining a therapeutic level are among the reasons most often cited for the underuse of warfarin in clinical practice. Recent data from the Global Anticoagulation Registry in the FIELD (GARFIELD) demonstrate the persistence of this trend, with approximately 40% of individuals receiving either aspirin or no therapy at all.[78] Among 138,319 individuals with AF receiving warfarin in the US, the mean time in therapeutic range was 53.7%, which increased to 57.5% after 6 months of therapy.[79]

These data highlight that although warfarin and other VKAs have been available for stroke prevention for over 60 years, many eligible AF patients remain untreated or have difficulty maintaining a consistently effective and safe level of anticoagulation. The development of NOACs as alternatives to VKAs helps to address this unmet need.

NOAC CLINICAL TRIAL DATA: DABIGATRAN, RIVAROXABAN, APIXABAN, AND EDOXABAN

The following sections discuss data from clinical trials for the individual NOACs. For side-by-side comparisons please see **Tables 7-10**.[3,80-93]

Clinical Trial Data: Dabigatran

The RE-LY trial, the first completed evaluation of a novel oral anticoagulant, recruited patients (n = 18,113) with AF (mean CHADS$_2$ score 2.1) to open-label warfarin or to 1 of 2 blinded doses of dabigatran, 110 mg or 150 mg twice daily. The 110-mg dose was similar to warfarin in reducing stroke or systemic embolism but reduced major bleeding by

Table 7 NOAC Features

	Dabigatran[80]	Rivaroxaban[80,81]	Apixaban[80,82]	Edoxaban[83-88]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	~25%	<4%
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	10-14 h
Renal elimination	80%	33%	27%	50%

BCRP = breast cancer resistant protein; CYP = cytochrome P450; NOAC = novel oral anticoagulant; P-gp = P-glycoprotein.

20%, whereas the 150-mg dose significantly reduced stroke or systemic embolism 35% compared with warfarin with similar major bleeding.[89,94] Dabigatran 150-mg dose also significantly reduced ischemic stroke 25% compared with warfarin. Both dabigatran doses markedly reduced intracranial bleeding by 60%-70% compared with warfarin. Dabigatran 150 mg was associated with a significant 50% increase in gastrointestinal bleeding compared with warfarin, whereas the 110-mg dose resulted in similar gastrointestinal bleeding. Dabigatran was discontinued more frequently than warfarin.[95] The only symptom leading to more frequent discontinuation of dabigatran was dyspepsia, with 2.1% of patients reporting dyspepsia as the cause of their stopping medication permanently.[89] Dyspepsia occurs in both the 110-mg and 150-mg groups (6.2% and 5.7% of subjects, respectively) compared with 1.4% per year in the warfarin group. For patients with a CHADS$_2$ score >3, excess major bleeding (mostly gastrointestinal in origin) was seen in the 150-mg dose but not in the 110-mg dose. A similar finding was seen when subjects were stratified by age. Patients aged <75 years had less major bleeding with the 110-mg dose compared with warfarin.[96]

The US Food and Drug Administration (FDA) reported that "real world" data in 134,414 Medicare patients closely reflect data reported from RE-LY for the dabigatran 150-mg twice-daily dose. In a general practice setting, dabigatran associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and death compared with warfarin, but an increased the risk of gastrointestinal bleeding.[97]

Dabigatran is dosed 150 mg twice daily for creatinine clearance >30 mL/min. The FDA approved dabigatran 75 mg twice daily for patients with a creatinine clearance of 15-30 mL/min for use in the US based on pharmacologic modeling, but the dose was never evaluated clinically.[98] In all other countries, dabigatran 110 mg twice daily is approved for patients at a higher bleeding risk and for those over the age of 80 years. Dabigatran may be taken with or without food.

Clinical Trial Data: Rivaroxaban

Rivaroxaban has been evaluated in 2 studies of patients with AF. 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) trial[90] was a double-blind study of 14,264 patients with AF (mean CHADS$_2$ score 3.5) randomly assigned to rivaroxaban (20 mg once daily or 15 mg once daily for patients with a creatinine clearance ≤50 mL/min) or warfarin. Rivaroxaban was noninferior to warfarin in the reduction of stroke and systemic embolism (HR 0.88; 95% CI, 0.74 = 1.03; P <.001 for noninferiority; P = .12 for superiority), with similar major bleeding (HR 1.03; 95% CI, 0.96-1.11; P = .44). Intracranial hemorrhage fell significantly with rivaroxaban (HR 0.67; 95% CI, 0.47-0.93; P = .02). The Rivaroxaban vs Warfarin in Japanese Patients with Atrial Fibrillation (J-ROCKET) trial[99] included 1280 Japanese patients and showed similar bleeding outcomes and a

Table 8 Phase-3 AF Trials

	RE-LY[89]	ROCKET AF[90]	ARISTOTLE[91]	ENGAGE AF-TIMI 48[92]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
N	18,113	14,264	18,201	21,105
Dose (mg)	150, 110	20	5	60, 30
Frequency	Twice daily	Once daily	Twice daily	Once daily
Initial dose adj*	No	20 → 15 mg	5 → 2.5 mg	60 → 30 mg
Dose adj (%)	0	21	4.7	25.3
Dose adj* after randomization	No	No	No	Yes
Design	PROBE	2× blind	2× blind	2× blind

AF = atrial fibrillation; PROBE = prospective randomized, open-label, blinded endpoint evaluation.
*Dose adjusted in patients with ↓drug clearance.

Table 9   Baseline Characteristics

	RE-LY[89] (Dabigatran)	ROCKET AF[90] (Rivaroxaban)	ARISTOTLE[91] (Apixaban)	ENGAGE AF[92] (Edoxaban)
Randomized, n	18,113	14,264	18,201	21,105
Age, y	72 ± 9	73 (65-78)	70 (63-76)	72 (64-78)
Female, %	37	40	36	39
Mean CHADS$_2$ score	2.1	3.5	2.1	2.8
Paroxysmal AF, %	32	18	15	25
Prior stroke/TIA, %	20	55	19	28
VKA-naïve, %	50	38	43	41
Aspirin use, %	40	36	31	29
Median follow-up, y	2.0	1.9	1.8	2.8
Median TTR, %	64	58	66	68

CHADS$_2$: 0-1, 2, 3-6

AF = atrial fibrillation; TIA = transient ischemic attack; TTR = time spent in therapeutic range; VKA = vitamin K antagonist.
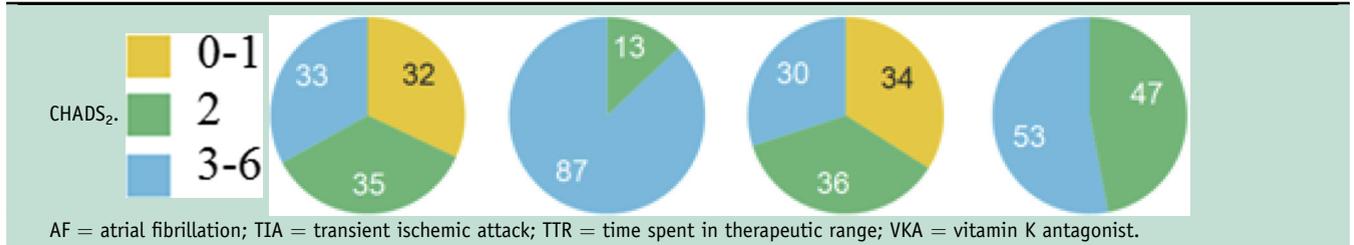
reduction in stroke and systemic embolism with rivaroxaban compared with warfarin.

Rivaroxaban is dosed 20 mg once daily for patients with creatinine clearance >50 mL/min, and 15 mg once daily for patients with creatinine clearance 15 to ≤50 mL/min. Rivaroxaban should be taken with the evening meal.

Clinical Trial Data: Apixaban

Two large trials have been conducted studying apixaban for stroke prevention in AF, one with aspirin and the other with warfarin as the comparator.[91,100] AVERROES included 5599 patients who were deemed "unsuitable" for warfarin and who were randomized to aspirin (mostly 81 mg per day) vs apixaban (5 mg twice a day, or 2.5 mg twice a day for patients with at least 2 of 3 criteria of age ≥80 years, creatinine ≥1.5 mg/dL, weight ≤60 kg). Apixaban yielded a 55% relative reduction in stroke or systemic embolism, a 13% nonsignificant increase in major bleeding, and numerically fewer intracranial hemorrhages (ICH; 11 vs 13) vs aspirin. Apixaban was well tolerated, as reflected by fewer patients prematurely stopping apixaban than aspirin.[100]

ARISTOTLE included 18,201 patients with AF and at least one additional risk factor for stroke (mean CHADS$_2$ score 2.1) who were randomized to warfarin (target INR 2.0 to 3.0) or apixaban. Apixaban significantly reduced stroke or systemic embolism by 21%, resulted in a 31% lower rate of major bleeding, and reduced all-cause mortality by 11%. Similar to the other direct-acting oral anticoagulants, apixaban showed a 50% relative risk reduction in hemorrhagic stroke.[91]

Apixaban is dosed 5 mg twice daily with a dose reduction to 2.5 mg twice daily for patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. Apixaban can be taken with or without food.

Clinical Trial Data: Edoxaban

ENGAGE AF-TIMI 48, a double-blind, double-dummy clinical trial, randomized 21,105 patients with moderate- to high-risk AF (mean CHADS$_2$ score 2.8) to 2 dosing regimens of once-daily edoxaban (60 mg and 30 mg) or to warfarin (goal INR 2.0 to 3.0). A dose reduction of 50% was performed for edoxaban patients who had at least one of the following criteria: creatinine clearance 30-50 mL/min, body weight <60 kg, or were taking selected strong P-glycoprotein inhibitors (quinidine, verapamil, or dronedarone).[101] Both edoxaban dose regimens proved noninferior to warfarin in prevention of stroke or systemic embolism during the on-treatment period (warfarin: 1.50%/year, edoxaban 60 mg: 1.18%/year [HR 0.79; 97.5% CI, 0.63-0.99; P <.001 for noninferiority], edoxaban 30 mg: 1.61%/year [HR 1.07; 97.5% CI, 0.87-1.31; P = .005 for noninferiority]). However, the lower dose regimen was less effective than warfarin in preventing ischemic stroke (HR 1.41; 95% CI, 1.19-1.67; P <.001), while the higher dose edoxaban regimen and warfarin showed similar prevention of ischemic stroke (HR 1.00; 95% CI, 0.83-1.19; P = .97). The annualized rates of major bleeding were 3.43% with warfarin, 2.75% with edoxaban 60 mg (HR 0.80; 95% CI, 0.71-0.91; P <.001), and 1.61% (HR 0.47; 95% CI, 0.41-0.55; P <.001) with edoxaban 30 mg. The corresponding annualized rates of cardiovascular death were 3.17%, 2.74% (HR 0.86, P = .013), and 2.71% (HR 0.85, P = .008). Both regimens of edoxaban showed significantly better net outcomes across a variety of combinations of cardiovascular

Table 10 Phase-3 AF Trials: Summary of Key Efficacy and Safety Results

| Outcome | RE-LY[89] | | | ROCKET AF[90,93] | | ARISTOTLE[91] | | ENGAGE AF-TIMI 48[3] | | |
	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	Rivaroxaban 20/15 mg	Warfarin	Apixaban 5/2.5 mg	Warfarin	Edoxaban 60/30 mg	Edoxaban 30/15 mg	Warfarin
Efficacy										
Stroke/SEE										
Event rate (%/y)	1.11	1.54	1.71	2.1	2.4	1.27	1.60	1.57	2.04	1.80
HR (95% CI)	0.72 (0.58-0.90)	0.90 (0.74-1.10)	NA	0.88 (0.75-1.03)	NA	0.79 (0.65-0.95)	NA	0.87 (0.73-1.04)	1.13 (0.96-1.34)	NA
P-value	.004	.29	NA	.12	NA	.01	NA	.08	.10	NA
Ischemic stroke										
Event rate (%/y)	0.92	1.34	1.22	1.34	1.42	0.97	1.05	1.25	1.77	1.25
HR (95% CI)	0.76 (0.59-0.97)	1.11 (0.88-1.39)	NA	0.94 (0.75-1.17)	NA	0.92 (0.74-1.13)	NA	1.00 (0.83-1.19)	1.41 (1.19-1.67)	NA
P-value	.03	.35	NA	.58	NA	.42	NA	.97	<.001	NA
Hemorrhagic stroke										
Event rate (%/y)	0.10	0.12	0.38	0.26	0.44	0.24	0.47	0.26	0.16	0.47
HR (95% CI)	0.26 (0.14-0.49)	0.31 (0.17-0.56)	NA	0.59 (0.37-0.93)	NA	0.51 (0.35-0.75)	NA	0.54 (0.38-0.77)	0.33 (0.22-0.50)	NA
P-value	<.001	<.001	NA	.02	NA	<.001	NA	<.001	<.001	NA
MI										
Event rate (%/y)	0.81	0.82	0.64	0.91	1.12	0.53	0.61	0.70	0.89	0.75
HR (95% CI)	1.27 (0.94-1.71)	1.29 (0.96-1.75)	NA	0.81 (0.63-1.06)	NA	0.88 (0.66-1.17)	NA	0.94 (0.74-1.19)	1.19 (0.95-1.49)	NA
P-value	.12	.09	NA	.12	NA	.37	NA	.60	.13	NA
All-cause death										
Event rate (%/y)	3.64	3.75	4.13	1.87	2.21	3.52	3.94	3.99	3.80	4.35
HR (95% CI)	0.88 (0.77-1.00)	0.91 (0.80-1.03)	NA	0.85 (0.70-1.02)	NA	0.89 (0.80-1.0)	NA	0.92 (0.83-1.01)	0.87 (0.79-0.96)	NA
P-value	.05	.13	NA	.07	NA	.047	NA	.08	.006	NA
Safety										
Major bleeding										
Event rate (%/y)	3.32	2.87	3.57	3.6	3.4	2.13	3.09	2.75	1.61	3.43
HR (95% CI)	0.93 (0.81-1.07)	0.80 (0.70-0.93)	NA	1.04 (0.90-1.20)	NA	0.69 (0.60-0.80)	NA	0.80 (0.71-0.91)	0.47 (0.41-0.55)	NA
P-value	.31	.003	NA	.58	NA	<.001	NA	<.001	<.001	NA
ICH										
Event rate (%/y)	0.32	0.23	0.76	0.5	0.7	0.33	0.80	0.39	0.26	0.85
HR (95% CI)	0.41 (0.28-0.60)	0.30 (0.19-0.45)	NA	0.67 (0.47-0.93)	NA	0.42 (0.30-0.58)	NA	0.47 (0.34-0.63)	0.30 (0.21-0.43)	NA
P-value	<.001	<.001	NA	.02	NA	<.001	NA	<.001	<.001	NA
GI bleeding										
Event rate (%/y)	1.56	1.15	1.07	2.0	1.24	0.76	0.86	1.51	0.82	1.23
HR (95% CI)	1.48 (1.18-1.85)	1.08 (0.85-1.38)	NA	1.66 (1.34-2.05)	NA	0.89 (0.70-1.15)	NA	1.23 (1.02-1.50)	0.67 (0.53-0.83)	NA
P-value	.001	.52	NA	<.001	NA	.37	NA	.03	<.001	NA

AF = atrial fibrillation; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; SEE = stroke or systemic embolism.

events, bleeding, and death. There were no excesses in adverse events, hepatic events, or malignancies with edoxaban.

Only the higher-dose regimen of edoxaban was put forward for regulatory approval. Edoxaban is approved in the US for patients with a calculated creatinine clearance ≤95 mL/min based on a post hoc subgroup analysis that demonstrated reduced efficacy in patients with creatinine clearance >95 mL/min. Edoxaban is dosed 60 mg once daily for patients with a creatinine clearance >50 and ≤95 mL/min with a dose reduction to 30 mg once daily for patients with a creatinine clearance 15 to 50 mL/min. For the AF population, a dose adjustment is not recommended for patients with body weight ≤60 kg or patients taking concomitant P-glycoprotein inhibitors. Edoxaban can be taken with or without food. Throughout the rest of the world, there is no restriction in the use of edoxaban in patients with creatinine clearance >95 mL/min, and a dose reduction to 30 mg is recommended for patients with body weight <60 kg and in patients taking concomitant strong P-glycoprotein inhibitors in addition to creatinine clearance 15-50 mL/min.

USE AND UTILITY OF LABORATORY COAGULATION TESTS

Because of the potential risks of bleeding with overdose and thrombosis with underdose, the use of anticoagulants requires care and understanding by both physician and patient. Patients prescribed warfarin require routine monitoring with the prothrombin time test (PT)/INR due to the variable effects of the drug.[1,102] Monitoring can occur in the physician's office/clinic or the patient's home. Anticoagulation clinics afford an excellent option for expert care as well as an ongoing opportunity for education and reinforcement of instructions. Because results vary between tests performed by a central lab and by point-of-care testing, monitoring is best done consistently at one site.

The new oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) do not require routine laboratory monitoring. However, there are clinical circumstances in which laboratory assessment of the anticoagulant effect would assist in clinical decision-making: evaluations at times of surgical or invasive procedures, after bleeding events, suspected noncompliance, altered drug effect due to renal dysfunction or extremes of body weight, concomitant drug use, and unstable medical conditions.[103-109] In 2014 the Institute for Safe Medication Practices strongly suggested use of plasma-level tests that can identify patients with excessive or suboptimal effects of the NOAC. However, laboratory assays to assess the anticoagulant effect of NOACs require further optimization to determine an anticoagulant effect, a drug level, or the risk of bleeding/thrombosis. Single-center and multicenter studies are underway to address these issues.

The NOACs respond differently from warfarin and heparin with regard to the conventional PT, activated partial thromboplastin time (aPTT), thrombin clotting time, and chromogenic anti-FXa assays.[105,106,109-114] Furthermore,

each NOAC displays its own characteristic effect in each assay. Importantly, different manufacturer's reagents within an assay group display variable effects at therapeutic concentrations for each NOAC.[106,110-114] The INR should not be used for the NOACs because erroneous results have been identified.[105,109,115] Dedicated assays using calibrators and controls to quantitate each NOAC are in development, but none are validated or US FDA approved for clinical use at this time. **Table 11** lists currently available assays that can be considered for either qualitative (drug present/absent) or quantitative (blood concentration) laboratory assessment of each NOAC.[106,108,109,111,112,116-119]

Clinical laboratories can follow these practical guidelines at this time.[105,107,118-120]

- Know the sensitivity of your lab's PT and aPTT reagent−instrument combination to each NOAC; if responsiveness is adequate, use for determining presence/absence of drug.
- Do not use the INR.
- Do not rely on a normal PT or aPTT to exclude a clinically relevant NOAC anticoagulant effect.
- A normal thrombin clotting time test can rule out clinically relevant dabigatran concentrations.[112]
- The chromogenic anti-FXa heparin assay may be used to screen for the presence/absence of rivaroxaban, apixaban, and edoxaban, but only if assay sensitivity is adequate; without calibrators, quantitation is not possible.
- Be aware of interferences of NOAC "contamination" in other lab tests. NOACs will behave as a circulating inhibitor, not as a factor deficiency, as occurs with warfarin.
- Lab results depend highly on time of blood sample collection; the peak effect of each NOAC is ~2 hours postingestion.

Laboratory staff need to stay current for the release and US FDA approval of new assays, calibrators, controls, and defined therapeutic ranges (threshold values for bleeding and thrombosis) for NOAC assessment.

Individual tests will need to be selected for each anticoagulant. When choosing an assay, consider the advantages of chromogenic rather than clot-based assays. Clot-based assays are affected by numerous preanalytical variables (eg, specimen type, sample handling, high levels of factor VIII and fibrin degradation products) and underlying patient factors (eg, lupus anticoagulant, paraproteins, hypoalbuminemia, fibrinolytic disorders), and thus will not be specific for the drug effect. Thrombin generation tests may be useful to monitor reversal of a bleeding state due to good sensitivity and relevance to clinical coagulation,[111] but validation is needed. Expressing results in terms of drug concentration may improve the quality of testing.[110,117]

MANAGEMENT OF BLEEDING AND REVERSAL AGENTS

Bleeding is the most common side effect of all anticoagulants. Consequently, health care professionals and emergency

Table 11   Laboratory Assays to Assess NOACs

Assays	Clinical Use Status in USA	Assay Performance	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Clot-based assays						
PT	FDA approved	Widely available; fast TAT	Not useful	Useful for qualitative assessment; know sensitivity of the reagent to rivaroxaban	Not useful	Not useful
aPTT	FDA approved	Widely available; fast TAT	Useful for qualitative assessment; know sensitivity of the reagent to dabigatran	Not useful	Not useful	Not useful
TT	FDA approved	Availability varies; fast TAT	Useful for qualitative assessment; very sensitive and may be abnormal at clinically insignificant concentrations	Not useful	Not useful	Not useful
Dilute TT*	RUO	Not widely available; TAT quick if automated	Useful for quantitative assessment if calibrators used	Not useful	Not useful	Not useful
Ecarin assay*	RUO	Not widely available; TAT quick if automated	Useful for quantitative assessment if calibrators used	Not useful	Not useful	Not useful
Anti-FXa assay*	RUO	Not widely available; TAT quick if automated	Not useful	Useful for quantitative assessment if calibrators used	Useful for quantitative assessment if calibrators used	Useful for quantitative assessment if calibrators used
Chromogenic assays						
Anti-FXa assay*	RUO	Availability varies; TAT quick if automated	Not useful	Useful for quantitative assessment if calibrators used	Useful for quantitative assessment if calibrators used	Useful for quantitative assessment if calibrators used
Anti-FIIa assay*	RUO	Not Widely available; TAT quick if automated	Useful for quantitative assessment if calibrators used	Not useful	Not useful	Not useful
Ecarin assay*	RUO	Not widely available; TAT quick if automated	Useful for quantitative assessment if calibrators used	Not useful	Not useful	Not useful

aPTT = activated partial thromboplastin time test; FDA = US Food and Drug Administration; NOAC = novel oral anticoagulant; PT = prothrombin time test; RUO = research use only (not US FDA approved for clinical use); TAT = turn-around time from initiation of test to result reporting; TT = thrombin clotting time test.

*Assay requires calibrators and controls specific to the drug to be tested.

departments require a systematic and rational approach to its management. To provide this information, we review the (a) steps to minimizing anticoagulant-related bleeding, (b) clinical evaluation of the bleeding patient, (c) supportive therapy for patients with anticoagulant-related bleeding, (d) specialized interventions, and (e) prospects for the future.

Minimizing the Risk of Anticoagulant-related Bleeding

Management of bleeding with oral anticoagulants starts with prevention. Patients should receive the appropriate anticoagulants at the correct dose for the recommended duration. Concomitant administration of antiplatelet drugs, such as aspirin or clopidogrel, increases the risk of bleeding, and these drugs should be avoided if possible.

Assessment of renal function is critical before prescription of NOACs because clearance of these agents depends at least in part on the kidneys. Patients with a creatinine clearance <30 mL/min should not take NOACs because of the potential for drug accumulation. Impaired renal function affects dabigatran more than the other NOACs because 80% of the drug is eliminated unchanged by the kidneys. In contrast, renal elimination is responsible for 33%, 27%, and 50% of the clearance of rivaroxaban, apixaban and edoxaban, respectively. During NOAC therapy, renal function should be monitored at least once a year to evaluate deterioration, and more frequently if the baseline creatinine clearance is <50 mL/min.

The risk of bleeding increases if patients with hepatic dysfunction receive anticoagulants. The NOACs are metabolized, at least in part, by the liver, and their use should be avoided in patients with liver disease with baseline elevation of the prothrombin time.

Anticoagulants increase the risk of bleeding at the time of surgery or interventions. To reduce this risk, anticoagulants must be withheld prior to elective procedures associated with a moderate to high risk of bleeding. Warfarin is usually stopped for at least 5 days to ensure that the INR has returned to normal. Because of their shorter half-lives, NOACs can be withheld for 24 to 48 hours, but may need to be omitted longer in patients with impaired renal function. Assessment of residual anticoagulant activity (eg, thrombin time or aPTT for dabigatran and chromogenic anti-FXa assay for rivaroxaban, apixaban, and edoxaban) may be prudent before surgical procedures associated with a high risk of bleeding (see previous section: Use and Utility of Laboratory Coagulation Tests), although further optimization and validation of these tests are needed.

Approach to the Bleeding Patient

The first step is to identify the site of bleeding and severity of the bleeding.[121-125] Bleeding can be minor, moderate, or severe/life-threatening on the basis of whether it is localized or diffuse, associated with tachycardia, hypotension, and a decrease in hemoglobin, or involves a critical organ, such as the brain, pericardium, or retroperitoneal space. The section below discusses briefly the approach for different severities of bleeding.

Minor Bleeding. Localized bleeding, such as ecchymosis, epistaxis, or bleeding from minor wounds, can usually be managed symptomatically and, if necessary, by omitting 1 or 2 doses of anticoagulant. Symptomatic measures may include nasal packing or cautery, or both, for epistaxis, and pressure dressings for wounds.

Moderate Bleeding. Moderate bleeding, such as bleeding from the upper or lower gastrointestinal tract, can be managed by stopping the anticoagulant. If the hemoglobin has fallen, long-acting antiplatelet drugs, such as aspirin or clopidogrel, should also be temporarily withheld if it is safe to do so. Blood transfusion can be given if needed, but definitive treatment depends on the etiology of the bleeding.

Because the gut lumen is an open space, gastrointestinal bleeding is rarely life threatening. Consequently, urgent anticoagulant reversal is unnecessary provided that the patient is hemodynamically stable. Nonetheless, anticoagulant activity should be assessed to determine whether excessive anticoagulation contributes to the bleeding. This involves INR determination for warfarin and can start with evaluation of the aPTT and thrombin time for dabigatran and the PT for rivaroxaban and edoxaban, and, to a lesser extent, for apixaban. Whereas warfarin has a half-life of several days, the half-life of the NOACs is about 12 hours. Consequently, evaluating the anticoagulant effect of the NOACs requires knowing the time of the last dose. Bleeding patients taking NOACs should have determination of creatinine clearance to permit estimation of the elimination half-life.

Severe or Life-threatening Bleeding. Severe or life-threatening bleeding includes patients with hemodynamic instability and bleeding into a critical organ or bleeding in the setting of major trauma. Anticoagulant and antiplatelet drugs should be stopped in patients who present with severe or life-threatening bleeding. In addition to the supportive measures described below, advanced therapies should be considered. These include vitamin K and 4-factor prothrombin complex concentrate (PCC) for reversal of warfarin, idarucizumab (5 g as an intravenous bolus) for reversal of dabigatran,[126] and administration of procoagulants, such as 4-factor PCC, activated PCC, or recombinant activated factor VII for reversal of rivaroxaban, apixaban, or edoxaban. Once andexanet alfa is licensed, it can be used as a specific reversal agent for the oral factor Xa inhibitors.[127]

Supportive Measures

Supportive measures in patients with anticoagulant-related major bleeding include (a) prompt identification and management of the source of bleeding, (b) restoration of hemodynamic stability and tissue perfusion, and (c) provision of coagulation support.

Identification and Management of the Source of Bleeding. Early identification of the source of bleeding directs the adoption of appropriate measures to minimize further blood loss. If the source of bleeding is not immediately obvious, imaging tests, endoscopy, or surgery may help to identify it. The hemoglobin should be monitored on an ongoing basis and maintained at a level of at least 7 to 9 g/dL.

Restoration of Hemodynamic Stability and Tissue Perfusion. To ensure adequate tissue perfusion, the systolic blood pressure should be maintained at 80 to 90 mm Hg by administration of fluids and crystalloid. If the blood pressure fails to respond to fluid resuscitation, vasopressors and inotropic agents should be considered. Optimal body temperature, a normal blood pH, and electrolyte balance should be maintained.

Provision of Coagulation Support. Bleeding patients should have frequent monitoring of the coagulation status and platelet count and receive measures to support coagulation as soon as possible if needed. Those with massive bleeding should get plasma along with packed red blood cells in a ratio of at least 1:2; patients without substantial bleeding should not routinely receive plasma. Cryoprecipitate should be given if the fibrinogen concentration falls below 1.5 to 2 g/dL. Platelets should be transfused to maintain the platelet count over 50,000/μL, or over 100,000/μL in patients with bleeding into a critical organ. Patients who were taking long-acting antiplatelet drugs, such as aspirin or P2Y12 antagonists, should also have consideration of platelet transfusion.

Advanced Interventions

Advanced interventions for patients with anticoagulant-related bleeding include (a) reversal of warfarin, (b) oral activated charcoal to reduce absorption of recently consumed NOACs, (c) idarucizumab for dabigatran reversal and procoagulants for reversal of the oral factor Xa inhibitors, and (d) dialysis for removal of dabigatran if idarucizumab is unavailable.

Reversal of Warfarin. Patients receiving warfarin should receive intravenous vitamin K (5 to 10 mg) and prothrombin complex concentrate (25 to 50 units/kg) if the INR is elevated and bleeding is severe or involving a critical organ. Four-factor prothrombin complex concentrates, which contain factors II, VII, IX, and X, are preferable to 3-factor concentrates, which contain little or no factor VII. Fresh frozen plasma or low-dose factor VIIa can be given in conjunction with 3-factor prothrombin complex concentrate as sources of factor VII. If prothrombin complex concentrate is unavailable, fresh frozen plasma (15 mL/kg) can be given.

Oral Activated Charcoal. In cases of overdose with NOACs or in patients who took their last dose within the past 2 to 4 hours, oral activated charcoal may attenuate absorption of the drug from the stomach or duodenum.

Procoagulant Reversal of NOACs. The anticoagulant activity of the NOACs usually disappears over the course of about 12 hours in patients with normal renal function. Therefore, reversal is rarely necessary. Dabigatran-treated patients who present with life-threatening bleeding should receive idarucizumab. Until andexanet alfa is licensed, procoagulants should be considered for patients taking rivaroxaban, apixaban, or edoxaban who present with life-threatening bleeds. These procoagulants include 4-factor PCC (50 units/kg), activated prothrombin complex concentrate (50 units/kg), or recombinant factor VIIa (90 μg/kg).

Hemodialysis for Removal of Dabigatran. If idarucizumab is unavailable, hemodialysis can be considered for removal of dabigatran in patients who have massive bleeding and renal failure. Although a 4- to 6-hour dialysis session removes up to 60% of circulating dabigatran, patients with very high dabigatran levels may require several sessions. Because they are highly protein-bound, rivaroxaban, apixaban, and edoxaban cannot be removed by dialysis.

CONCLUSIONS AND FUTURE DIRECTIONS

Management of serious or life-threatening anticoagulant-related bleeding requires a multidisciplinary team approach. Patients should have rapid evaluation of the source of bleeding and management. Assessment of the risks associated with temporary discontinuation of antiplatelet agents or anticoagulant reversal in patients with newly implanted coronary stents or mechanical heart valves and in those with atrial fibrillation that are at high risk for stroke may require consultation with a cardiologist. The gastroenterology or surgical service should be consulted early in patients with ongoing gastrointestinal bleeding, and the hematology service should be contacted for advice about reversal strategies in patients with major or life-threatening bleeding.

In patients taking NOACs, the time elapsed since the last dose of anticoagulant should be determined and the contribution of the anticoagulant to the bleeding determined by appropriate coagulation testing for the specific drug. Although the antidote for warfarin is vitamin K, reversal with vitamin K is delayed. However, 4-factor prothrombin complex concentrate can restore the INR to near normal levels within minutes of administration.

The relatively short half-life of the NOACs renders antidotes unnecessary in most situations. Nonetheless, rapid reversal may be necessary in patients with life-threatening bleeding, bleeding into a critical organ, bleeding that continues despite supportive measures, and in patients requiring urgent surgery or intervention. Idarucizumab is licensed for reversal of dabigatran. This dabigatran-directed antibody fragment will not reverse warfarin or the oral factor Xa inhibitors. Andexanet alfa is under development for reversal of rivaroxaban, apixaban, and edoxaban. Until it is licensed, 4-factor PCC, activated PCC, or recombinant factor VIIa can be considered for reversal of these agents in life-threatening situations.

The current lack of antidotes for the oral factor Xa inhibitors should not dissuade patients or physicians from

using them because compared with warfarin, these agents reduce the risk of intracranial bleeding by 50%. Furthermore, despite the lack of antidotes, the outcome of patients with major bleeds is no worse with the oral factor Xa inhibitors than it is with warfarin and may be better. These considerations underlie recent guidelines that give preference to the NOACs over warfarin for stroke prevention in most patients with atrial fibrillation.

Periprocedural Management of NOACs Cardioversion and Ablation

The standard approach to anticoagulation in individuals undergoing cardioversion for AF of >48 hours duration is to treat for at least 3 weeks with warfarin to achieve a consistently therapeutic INR (>2.0) prior to elective cardioversion (either electrical or pharmacologic).[14,102,128] In clinical situations in which cardioversion is necessary before completing 3 weeks of anticoagulation with warfarin, performing a transesophageal echocardiogram (TEE) to assess left atrial appendage thrombus offers an alternative. With either approach, anticoagulation with warfarin is recommended for a minimum of 4 weeks after cardioversion.[14,102,128]

The evidence related to the use of the NOACs in the pericardioversion period is growing but remains less robust than for warfarin.[89-91,98,129,130] The RE-LY trial compared dabigatran, a direct thrombin inhibitor, with warfarin in patients with nonvalvular AF. A post hoc analysis of 1983 cardioversions (85% electrical) in 1270 trial participants demonstrated that there was no significant difference in thromboembolism and stroke within 30 days in those who received dabigatran 110 or 150 mg twice daily or warfarin leading up to cardioversion. This result applied to both the conventional and expedited TEE approach.[98]

A post hoc analysis of a total of 743 cardioversions performed in 540 patients in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study included 265 first cardioversions in patients assigned to apixaban and 275 in those assigned to warfarin.[129] This analysis concluded that major thromboembolic events after cardioversion of atrial fibrillation are rare and comparable between warfarin and apixaban.[129]

In a prospective randomized trial of rivaroxaban in patients with atrial fibrillation undergoing electrical cardioversion, 1504 patients were randomized to rivaroxaban or dose-adjusted warfarin in a 2:1 ratio.[130] The investigators selected either an early (target period of 1-5 days after randomization) or delayed (3-8 weeks) cardioversion strategy. The primary efficacy outcome was the composite of stroke, transient ischemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 5 (2 strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (2 strokes) of 492 patients (1.02%) in the VKA group (risk ratio 0.50; 95%

CI, 0.15-1.73). In the rivaroxaban group, 4 patients experienced primary efficacy events following early cardioversion (0.71%) and one following delayed cardioversion (0.24%). In the VKA group, 3 patients had primary efficacy events following early cardioversion (1.08%) and 2 following delayed cardioversion (0.93%). Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs (P <.001). Major bleeding occurred in 6 patients (0.6%) in the rivaroxaban group and 4 patients (0.8%) in the VKA group (risk ratio 0.76; 95% CI, 0.21-2.67).[130] The authors concluded that rivaroxaban is an effective and safe alternative to VKAs and may allow prompt cardioversion.[130] Based on these data, dabigatran, apixaban, and rivaroxaban offer reasonable alternatives to warfarin for patients who require anticoagulation prior to and after cardioversion.

During and after AF ablation, the increase in risk for embolic events has led to the use of continuous or nearly continuous anticoagulation in the periprocedural period. The standard of care for anticoagulation in the early years of AF ablation was continuous anticoagulation with heparin during and immediately after the procedure. This regimen of continuous heparin during the procedure was usually followed by anticoagulation of a period of at least 3 months with warfarin. Two strategies evolved related to periprocedural warfarin management. With the interrupted strategy, warfarin would be withheld for 5 days before the procedure. Many centers would bridge with subcutaneous or low-molecular-weight heparin. Warfarin was then restarted after the ablation. However, observational data indicated that thromboembolic risk was reduced without an increase in bleeding rates using an uninterrupted strategy with continuous oral anticoagulation with warfarin before, during, and after the procedure.[131,132]

A recent prospective, open-label, randomized, parallel-group, multicenter study assessed the role of continuous warfarin therapy in preventing periprocedural thromboembolic and hemorrhagic events after radiofrequency catheter ablation provides additional support for the uninterrupted approach.[133] The investigators demonstrated that performing catheter ablation of AF without warfarin discontinuation reduces the occurrence of periprocedural stroke and minor bleeding complications compared with bridging with low-molecular-weight heparin in a prospective study. Thus, uninterrupted warfarin appears to be more effective and safer than interrupted therapy with heparin or low-molecular heparin bridging.

The strategies used for warfarin have been extrapolated to the NOACs and now include an interrupted, minimally interrupted, or uninterrupted approach. While there is considerably less information about the efficacy and safety of NOACs in patients undergoing ablation compared with warfarin, data are emerging.[134] Anticoagulation with dabigatran has been evaluated in this setting, with some studies showing comparable outcomes compared with warfarin, while one reported an increased bleeding risk.[135,136] A

Table 12   Outcomes with Short-Term Interruption of NOACs

Study	Medication	30-d Rate (Postprocedure)		Comment
		Stroke/Systemic Embolism	Major Bleeding*	
RE-LY[107]	dabigatran	0.5%	5.1%	All patients in this analysis interrupted dabigatran *preprocedure*. Among patients taking dabigatran 150 mg twice daily, 1021 interrupted for 72 h or less; 468 interrupted for more than 72 h. 15% of patients with dabigatran 110 mg and 17% of dabigatran 150 mg received heparin bridging therapy
ROCKET AF[148]	rivaroxaban	0.3%	0.99%	Only 6% of patients received heparin bridging therapy. Most patients interrupted rivaroxaban ≥3 d prior to procedure
ARISTOTLE†	apixaban	0.35%	1.6%	Approximately 1/3 of patients on apixaban did not interrupt medication preprocedure. Among those who *did* interrupt, 70% held apixaban for ≥3 d pre-procedure.

NOAC = novel oral anticoagulant.

*The values in this column should not be used to draw conclusions about relative safety because the types of procedures performed and the timing of anticoagulation re-start may have been different in the 2 trials.

†Abstract by Garcia et al.[149]

recent meta-analysis of minimally interrupted dabigatran concluded that the risks of thromboembolic and bleeding complications with minimally interrupted dabigatran are similar to those with minimally interrupted warfarin.[137] Based on the best available but incomplete data, it may also be safe to perform AF ablation with rivaroxaban.[137,138] If used, it is reasonable to omit the NOAC 24 to 36 hours before the procedure and resume them the morning after the procedure with a bridge of intravenous unfractionated heparin starting 6 hours after hemostasis has been achieved. Recently, the strategies of resuming NOACs 6 hours after hemostasis without heparin bridging[139] and uninterrupted NOACs have been evaluated.[140] Both clinical approaches have shown periprocedural safety and efficacy comparable with warfarin.[139,140]

Periprocedural Management of NOACs — non-eP Procedures

The management of patients with AF who take warfarin and require a procedure often requires difficult decisions. Some procedures involve a minor bleeding risk (eg, cataract surgery, tooth extraction) can be done safely on therapeutic oral anticoagulant therapy. Other procedures (such as same-day office procedures and many biopsies) carry low bleed risk, but many invasive procedures and surgeries carry a high bleed risk and lead to temporary oral anticoagulant interruption due to concerns about bleeding. Patients at low risk for thromboembolism (eg, CHADS$_2$ score ≤1) can simply hold warfarin for 4-5 days before the procedure and resume it soon after the procedure is completed. For patients at high risk of AF-related stroke (eg, CHADS$_2$ score >3), many clinicians prescribe perioperative bridging therapy with

unfractionated heparin or low-molecular-weight heparin on the pre- and postoperative days when little or no warfarin effect persists.[141] The administration of this "bridging anticoagulation" is complex, has uncertain benefit, and increases the risk of postprocedure bleeding.[142] The BRUISE study revealed that temporary interruption of warfarin with therapeutic dose-bridging therapy was associated with an 80% increase in pocket hematomas during implantable cardioverter defibrillator or pacemaker surgery compared with a strategy of continuing warfarin.[143] Recent evidence from a large meta-analysis of bridging therapy during temporary interruption of VKA for an elective procedure or surgery, as well as a large cohort study of bridging therapy after mechanical heart valve implantation, suggests a three- to fourfold increase in major bleeding with heparin-bridging therapy without any reduction in stroke or systemic embolism in the postprocedural period.[142,144] A randomized, placebo-controlled trial indicates that, for warfarin-treated AF patients at low to moderate risk for stroke, perioperative dalteparin increases the risk of major bleeding but does not reduce the risk of arterial thrombosis. Among the 950 patients assigned to receive placebo (ie, no bridging therapy) perioperatively, the rate of arterial thromboembolism within 30 days after the procedure was 0.4% (vs 0.3% among patients who received dalteparin, $P = .01$ for noninferiority).[145] In addition, the RE-ALIGN trial, which compared dabigatran with warfarin for the prevention of thromboembolism in patients with mechanical heart valves, highlights the risks of early postoperative anticoagulation. In RE-ALIGN, the 199 postoperative patients received their study medication, on average, 6 days after open-heart surgery, and 9 (4.5%) experienced major pericardial hemorrhage.[146]

Table 13   Preoperative Interruption of New Oral Anticoagulants: A Suggested Management Approach[147]

Drug (Dose)	Patient Renal Function	Low Bleeding Risk Surgery* (2-3 Drug Half-Lives Between Last Dose and Surgery)	High Bleeding Risk Surgery† (4-5 Drug Half-Lives Between Last Dose and Surgery)
Dabigatran	Normal or mild impairment (CrCl >50 mL/min)	*Last dose*: 2 d before surgery (skip 2 doses)	*Last dose*: 3 d before surgery (skip 4 doses)
	Moderate impairment (CrCl 30-50 mL/min)	*Last dose*: 3 d before surgery (skip 4 doses)	*Last dose*: 4-5 d before surgery (skip 6-8 doses)
Rivaroxaban	Normal or mild impairment (CrCl >50 mL/min)	*Last dose*: 2 d before surgery (skip 1 dose)	*Last dose*: 3 d before surgery (skip 2 doses)
	Moderate impairment (CrCl 30-50 mL/min)	*Last dose*: 2 d before surgery (skip 1 dose)	*Last dose*: 3 d before surgery (skip 2 doses)
	Severe impairment (CrCl 15-29.9 mL/min)	*Last dose*: 3 d before surgery (skip 2 doses)	*Last dose*: 4 d before surgery (skip 3 doses)
Apixaban	Normal or mild impairment (CrCl >50 mL/min)	*Last dose*: 2 d before surgery (skip 2 doses)	*Last dose*: 3 d before surgery (skip 4 doses)
	Moderate impairment (CrCl 30-50 mL/min)	*Last dose*: 2 d before surgery (skip 2 doses)	*Last dose*: 4 d before surgery (skip 4 doses)
Edoxaban	Normal or mild impairment (CrCl >50 mL/min to ≤95 mL/min‡)	*Last dose*: 2 d before surgery (skip 1 dose)	*Last dose*: 3 d before surgery (skip 2 doses)
	Moderate impairment (CrCl 30-50 mL/min)	*Last dose*: 2 d before surgery (skip 1 dose)	*Last dose*: 3 d before surgery (skip 2 doses)
	Severe impairment (CrCl 15-29.9 mL/min)	*Last dose*: 3 d before surgery (skip 2 doses)	*Last dose*: 4 d before surgery (skip 3 doses)

CrCl = creatinine clearance.
*Aiming for mild-to-moderate residual anticoagulant effect at surgery (<12%-25%).
†Aiming for no or minimal residual anticoagulant effect (<3%-6%) at surgery.
‡Edoxaban not approved for patients with CrCl >95 mL/min.

The rapid onset and relatively short half-life of the NOACs should simplify the perioperative management of AF patients taking these medications.[147] Consistent data from all of the large phase-3 registration trials of NOACs in AF indicate that short-term interruption of a NOAC associates with a low (<1%) risk of stroke or systemic embolism and similar to those of the warfarin-treated groups (**Table 12**).[107,148-150] Postprocedure major bleeding rates vary more between the trials, likely due to differences in patients or procedures because, within each trial, the NOAC-related bleeding risk was comparable with the corresponding risk seen among the patients randomized to warfarin. The published experience with temporary interruptions from the ROCKET AF trial suggested a very low thromboembolic (<1.0%) and major bleed rate (~1.0%) in the rivaroxaban arm, and the majority of interruptions were done without bridging therapy (<92%).[148] By contrast, a substudy of the RE-LY study with the open-label dabigatran trial in which 15% to 17% of patients in both dabigatran groups received mostly treatment-dose heparin-bridging therapy revealed a 6.5% major bleed in bridged groups vs 1.8% major bleed rate in the nonbridged groups (odds ratio 3.68; 95% CI 2.24-6.04, *P* <.001).[151] Two large placebo-controlled randomized trials on heparin-bridging therapy should give definitive answers on the efficacy and safety of heparin-bridging therapy during temporary interruption of patients on chronic warfarin therapy for an elective procedure or surgery (Cite PERIOP-2[152] and BRIDGE[153]). However, it does appear that bridging therapy offers no benefit in terms of reduction of postprocedural stroke/systemic embolism and is associated with a three- to fourfold increased risk of major bleeding.

The best guidance we have on periprocedural interruption of patients on the NOACs suggests excellent periprocedural outcomes when considering 3 factors: 1) the pharmacokinetic characteristics of each NOAC; 2) the procedural bleeding risk to allow 2-3 drug half-lives between the last dose and the procedure for low bleed-risk procedures, and 4-5 drug half-lives for procedures at high bleed risk; and 3) the patient's renal function (**Table 13**).[147] In this fashion, the last dose of each NOAC would be approximately 1-2 days before surgery for patients with normal renal function and 3-5 days before surgery for patients with moderate renal insufficiency.[147] Patients taking dabigatran would likely need further interruption time depending upon their renal function. In the postprocedural phase, the NOACs could likely be safely resumed within 24 hours for low bleeding risk procedures, and within 2-3 days for major surgeries or procedures with high bleeding risk.[147] One can also consider a step-wise increase in the NOAC dose postprocedure, with prophylactic doses for the first 24-48 hours (**Table 14**). Lastly, heparin therapy should be avoided except in prophylactic doses post procedure when patients cannot tolerate oral medications. A recently initiated

Table 14 Postoperative Resumption of New Oral Anticoagulants: A Suggested Management Approach

Drug	Low Bleeding Risk Surgery	High Bleeding Risk Surgery*
Dabigatran	Resume on day after surgery (24 h postoperative), 150 mg twice daily	Resume 2-3 d after surgery (4-72 h postoperative), 150 mg twice daily†
Rivaroxaban	Resume on day after surgery (24 h postoperative), 20 mg once daily	Resume 2-3 d after surgery (48-72 h postoperative), 20 mg once daily
Apixaban	Resume on day after surgery (24 h postoperative), 5 mg twice daily.	Resume 2-3 d after surgery (48-72 h postoperative), 5 mg twice daily†
Edoxaban	After the surgical or other procedure as soon as adequate hemostasis has been established noting that the time to onset of pharmacodynamic effect is 1-2 h	

*Aiming for no or minimal residual anticoagulant effect (<3%-6%) at surgery.

†For patients at high risk for thromboembolism, consider administering a reduced dose of dabigatran (eg, 110-150 mg once daily) on evening after surgery and on following day (first postoperative day) after surgery.

cohort study will examine 30-day periprocedural outcomes in patients treated with NOACs who are following a standardized protocol similar to the one above (PAUSE trial).[154]

Starting NOACs in VKA-naive vs -experienced Patients

The relative efficacy and safety of NOACs compared with warfarin differs depending on whether patients have been on prior VKA therapy, and has engendered considerable interest. Studies have shown that individuals who are naive to VKA therapy have a higher risk of stroke when initiated on anticoagulant therapy as compared with those who are VKA experienced.[155] On the other side of the spectrum, there is concern that VKA-experienced patients might not derive the same benefits from NOAC therapy because they have proven they can "tolerate" VKA therapy and generally have lower stroke and bleeding rates. To address this issue, all of the phase-3 NOAC trials examined the performance of NOACs vs warfarin in VKA-naive and -experienced patients (Figure 1).[156]

In the RE-LY (dabigatran), ROCKET AF (rivaroxaban), and ARISTOTLE (apixaban) studies, the efficacy of NOACs compared with warfarin in preventing stroke or systemic embolism were generally consistent in warfarin-experienced vs -naive patients.[157-159] In the ENGAGE AF-TIMI 48 trial, however, edoxaban showed greater efficacy in individuals who were VKA naive, as compared with those with prior VKA exposure.[92] Edoxaban's apparent larger benefit in VKA-naive patients appeared to result primarily from an increased incidence of ischemic stroke in VKA-naive patients compared with
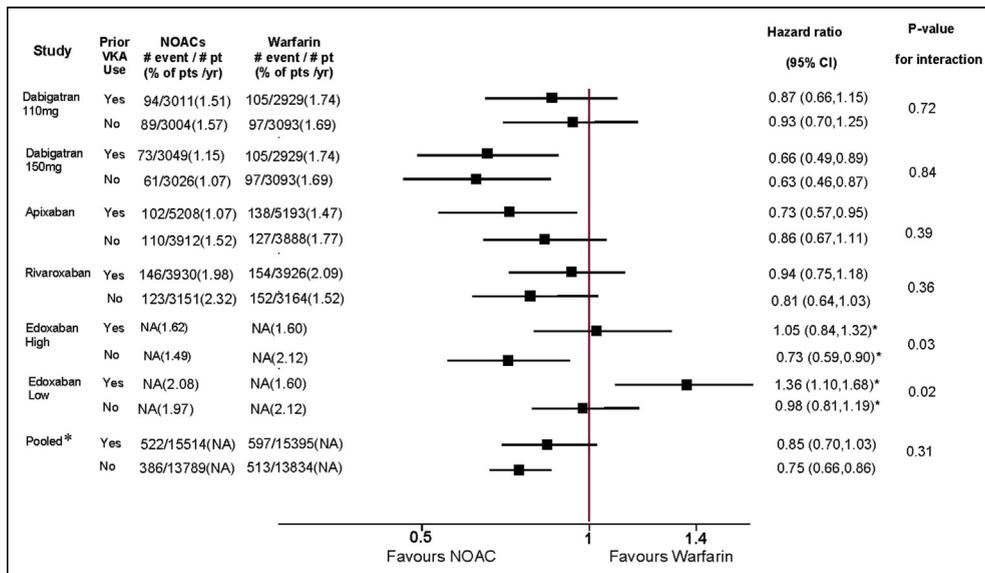
VKA-experienced patients. With respect to bleeding, the relative safety of all the NOACs compared with warfarin did not differ between VKA experienced vs naive patients (Figure 2).[156]

When deciding to start an anticoagulant in a patient, the NOACs may have particular advantage with regards to efficacy in the short term. Patients starting warfarin may have an increased risk of stroke for the several weeks to months it takes them to get into a stable therapeutic range. It is important to highlight, however, that NOACs remain effective and safe compared with warfarin, even in patients who have significant prior VKA experience.

High Risk Populations: Elderly and Patients with Impaired Renal Function

Elderly patients have a high risk of stroke and bleeding, with a 1.5-fold increase in ischemic stroke risk with every 10 years of age and 40% increase in the risk of bleeding on anticoagulant therapy.[160,161] The modest overall benefit of aspirin for stroke prevention among patients with AF decreases in patients over age 70-75 years, while the risk of bleeding increases substantially. When looking at the clinical trials data for NOACs, the proportion of patients older than 75 years ranges from 30% to 40%, which allows for robust subgroup analyses.

In the RE-LY trial, the superiority for prevention of stroke of dabigatran as compared with warfarin therapy was preserved in patients 75 years of age or older when compared with younger patients at both the 150-mg twice a day (bid) dose and the 110-mg dose.[162] However, there were higher rates of major bleeding for both doses of dabigatran when compared with warfarin therapy in the elderly patients (age ≥75 years) (HR 1.18; 95% CI, 0.98-1.42 for 150 mg bid, and HR 1.01; 95% CI, 0.83-1.23 for 110 mg bid) than in younger patients (HR 0.70; 95% CI, 0.57-0.86 for 150 mg bid, P-interaction <.001, and HR 0.62; 95% CI 0.50-0.77 for 110 mg bid, P-interaction <.001). In contrast, the reduction in intracranial hemorrhage of dabigatran compared with warfarin was preserved in the elderly population. Similar findings were seen in the very elderly patients (age >80 years) in the RE-LY population.[163] Rivaroxaban in the ROCKET AF trial was noninferior to warfarin therapy for prevention of stroke or systemic embolism for patients older than 75 years of age and for younger patients.[164] Major bleeding was similar for patients ages ≤65 years, <75 years, and >75 years, with no difference in intracranial hemorrhage when looking at age and treatment effect.[165] In the ARISTOTLE trial with apixaban, the superiority of apixaban compared with warfarin in reducing stroke or systemic embolism, in causing less major bleeding, and in decreasing all-cause mortality was preserved irrespective of age.[91] In fact, when compared with warfarin, there is a trend to an even more favorable net clinical benefit of apixaban in patients older than 75 years of age. In the ENGAGE AF trial, both doses of edoxaban (60 mg and 30 mg once daily) were shown to be noninferior to warfarin in the prevention of stroke or systemic embolism,

Study	Prior VKA Use	NOACs # event / # pt (% of pts /yr)	Warfarin # event / # pt (% of pts /yr)		Hazard ratio (95% CI)	P-value for interaction
Dabigatran 110mg	Yes	94/3011(1.51)	105/2929(1.74)		0.87 (0.66,1.15)	0.72
	No	89/3004(1.57)	97/3093(1.69)		0.93 (0.70,1.25)	
Dabigatran 150mg	Yes	73/3049(1.15)	105/2929(1.74)		0.66 (0.49,0.89)	0.84
	No	61/3026(1.07)	97/3093(1.69)		0.63 (0.46,0.87)	
Apixaban	Yes	102/5208(1.07)	138/5193(1.47)		0.73 (0.57,0.95)	0.39
	No	110/3912(1.52)	127/3888(1.77)		0.86 (0.67,1.11)	
Rivaroxaban	Yes	146/3930(1.98)	154/3926(2.09)		0.94 (0.75,1.18)	0.36
	No	123/3151(2.32)	152/3164(1.52)		0.81 (0.64,1.03)	
Edoxaban High	Yes	NA(1.62)	NA(1.60)		1.05 (0.84,1.32)*	0.03
	No	NA(1.49)	NA(2.12)		0.73 (0.59,0.90)*	
Edoxaban Low	Yes	NA(2.08)	NA(1.60)		1.36 (1.10,1.68)*	0.02
	No	NA(1.97)	NA(2.12)		0.98 (0.81,1.19)*	
Pooled*	Yes	522/15514(NA)	597/15395(NA)		0.85 (0.70,1.03)	0.31
	No	386/13789(NA)	513/13834(NA)		0.75 (0.66,0.86)	

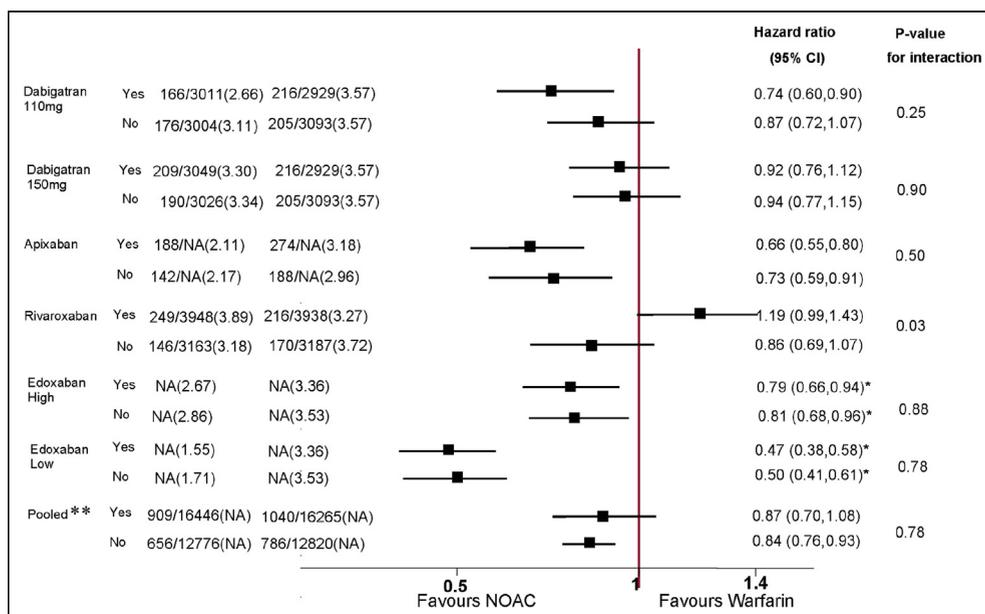0.5 Favours NOAC   1   1.4 Favours Warfarin

Figure 1   Subgroup analysis of primary efficacy outcome (stroke and systemic embolism) of novel oral anticoagulants (NOACs) compared with warfarin in the presence or absence of long-term therapy with a VKA. *The pooled finding in Figure 1 is reported by Ruff et al.[156]

regardless of age.[166] Edoxaban was safer than warfarin, causing less major bleeding as well as less intracranial hemorrhage than warfarin, irrespective of age. Edoxaban had a greater absolute net clinical benefit in the elderly. In summary, the risk of stroke and bleeding increases with age, and the advantages of the NOACs when compared with warfarin, particularly with respect to serious bleeding, are preserved. Caution should be noted with dabigatran 150 mg, which has a higher risk of extracranial bleeding compared with warfarin therapy in the elderly.

Use of the NOACs requires caution in patients with renal dysfunction because these drugs are all partially cleared by the kidneys (dabigatran 80%, rivaroxaban 33%, apixaban 25%, and edoxaban 50%) and therefore have higher

		NOACs	Warfarin		Hazard ratio (95% CI)	P-value for interaction
Dabigatran 110mg	Yes	166/3011(2.66)	216/2929(3.57)		0.74 (0.60,0.90)	0.25
	No	176/3004(3.11)	205/3093(3.57)		0.87 (0.72,1.07)	
Dabigatran 150mg	Yes	209/3049(3.30)	216/2929(3.57)		0.92 (0.76,1.12)	0.90
	No	190/3026(3.34)	205/3093(3.57)		0.94 (0.77,1.15)	
Apixaban	Yes	188/NA(2.11)	274/NA(3.18)		0.66 (0.55,0.80)	0.50
	No	142/NA(2.17)	188/NA(2.96)		0.73 (0.59,0.91)	
Rivaroxaban	Yes	249/3948(3.89)	216/3938(3.27)		1.19 (0.99,1.43)	0.03
	No	146/3163(3.18)	170/3187(3.72)		0.86 (0.69,1.07)	
Edoxaban High	Yes	NA(2.67)	NA(3.36)		0.79 (0.66,0.94)*	0.88
	No	NA(2.86)	NA(3.53)		0.81 (0.68,0.96)*	
Edoxaban Low	Yes	NA(1.55)	NA(3.36)		0.47 (0.38,0.58)*	0.78
	No	NA(1.71)	NA(3.53)		0.50 (0.41,0.61)*	
Pooled**	Yes	909/16446(NA)	1040/16265(NA)		0.87 (0.70,1.08)	0.78
	No	656/12776(NA)	786/12820(NA)		0.84 (0.76,0.93)	

0.5 Favours NOAC   1   1.4 Favours Warfarin

Figure 2   Subgroup analysis of primary safety outcome (International Society on Thrombosis and Haemostasis scale major bleeding) of NOACs compared with warfarin in the presence or absence of long-term therapy with a VKA. *Estimated. **The pooled finding in Figure 2 is reported by Ruff et al.[156]

bioavailability with decreased renal excretion. Because dabigatran has the highest renal clearance of 80%, apixaban, rivaroxaban, and edoxaban are potentially safer options in patients with significant renal dysfunction.[167] In the RE-LY trial, dabigatran 150 mg and dabigatran 110 mg had consistent efficacy results compared with warfarin across the range of renal function. However, both doses of dabigatran were associated with higher rates of major bleeding compared with warfarin among patients with moderate renal dysfunction (glomerular filtration rate [GFR] <50 mL/min).[168] It is important to note that no dose adjustment was made for renal dysfunction in the RE-LY trial. Dosing for rivaroxaban for patients with a GFR ≥50 mL/min was 20 mg daily and 15 mg for GFR 30-49 mL/min in ROCKET AF.[169] Patients with a GFR ≥50 mL/min and the higher dose of rivaroxaban had lower rates of intracranial hemorrhage when compared with warfarin therapy. The lower dose of rivaroxaban in patients with moderate renal impairment showed noninferiority to warfarin therapy for prevention of stroke, with similar rates of intracranial hemorrhage.[170] In ARISTOTLE, patients with 2 of the following criteria were given a decreased dose of 2.5 mg of apixaban twice daily: age >80 years, creatinine >1.5 mg/dL, and weight <60 kg.[91] The treatment effect of apixaban was preserved in patients with normal renal function (GFR >80 mL/min), mild renal dysfunction (GFR 50-80 mL/min), and moderate renal dysfunction (GFR <50 mL/min), when looking at stroke, systemic embolism, and all-cause mortality.[61] In addition, patients treated with apixaban had significantly less major bleeding when compared with warfarin, regardless of renal function. Importantly, patients with renal impairment had the greatest reduction in major bleeding with apixaban. In ENGAGE AF, patients with at least one of the following criteria were given half of the initial dose of edoxaban (30 mg or 15 mg) once daily: GFR 30-50 mL/min, weight <60 kg, and concomitant use of specific P-glycoprotein inhibitors.[92] In the patient's dose reduced for renal impairment (90% of patients who qualified for dose reduction), edoxaban preserved efficacy in prevention of stroke with even greater reductions in major bleeding.[171]

Finally, given that patients with a GFR <30 mL/min were excluded from RE-LY, ROCKET AF, and ENGAGE AF, these new agents should not be used in those patients.[90,91,169] Interestingly, despite the fact that patients with a GFR of <25 mL/min or a creatinine >2.5 mg/dL were excluded from ARISTOTLE, apixaban 5 mg bid has an FDA label for patients with a creatinine clearance <15 mL/min or on dialysis based on available pharmacokinetic and pharmacodynamic data.[86]

It is important to note that there was a general lack of racial diversity in all of these trials, and there remain questions about the translation of trial results to different racial minorities who often are undertreated, have higher risk of adverse events, and may have differential responses to the therapies.[172-174]

Antithrombotic Management in Patients with AF and Coronary Artery Disease

The benefit of platelet-directed therapy for individuals with coronary artery disease (CAD) risk factors and those with documented disease correlates directly with the risk of ischemic and thrombotic events.[175,176] Patients with established CAD, including those with prior myocardial infarction or coronary artery bypass grafting should receive aspirin. Patients with an acute coronary syndrome (ACS), with or without an existing coronary artery stent within the past year, should take dual platelet-directed therapy, including aspirin plus clopidogrel, prasugrel, or ticagrelor.[177,178]

The antithrombotic management of patients with AF *and* CAD requires a thorough risk assessment that takes into consideration both conditions and diseases and their optimal treatment.[179] Patients with AF who have very low risk for systemic embolism and stroke may not require antithrombotic therapy.[180] In contrast, those at low-to-moderate, moderate, and high risk should receive an anticoagulant, unless they have a prohibitive risk for life-threatening bleeding.[181] The addition of platelet-directed therapy increases the risk of bleeding for all anticoagulants, including the NOACs, and dual platelet-directed therapy increases the risk to a greater degree than monotherapy.[182] Triple therapy, defined currently as a VKA, titrated to a target INR of 2.0 to 2.5, aspirin (≤100 mg daily), and clopidogrel (75 mg daily) are recommended for patients with AF and a CHA$_2$DS$_2$-VASc score of 2 or greater who also have a high risk for coronary arterial events — particularly acute stent thrombosis. Dual therapy, defined currently as a VKA plus clopidogrel, should be considered in patients with a concomitantly moderate-to-high risk for bleeding.[183] Platelet-directed therapy, whether mono or dual, should be continued for 6 to 12 months or longer as determined by the risk for coronary arterial events and the type of stent. Patients with AF and stable CAD, including those with a myocardial infarction or percutaneous coronary intervention (PCI) more than a year ago, may be adequately treated with anticoagulant therapy (VKA or NOAC) alone; however, additional study is needed.

Several studies have addressed the use of NOACs after ACS, although AF patients were not included. The APPRAISE-2 trial found that the addition of apixaban to antiplatelet therapy (16% aspirin only, 81% on dual therapy with aspirin and clopidogrel) substantially increased major bleeding (HR 2.59; 95% CI, 1.50-4.46) compared with placebo.[184] The ATLAS ACS 2-TIMI 51 trial found that rivaroxaban at a low dose of 2.5 mg twice daily, in addition to antiplatelet therapy (99% on aspirin and 93% on clopidogrel), produced a 16% reduction in a composite endpoint of cardiovascular death, myocardial infarction, and stroke when compared with placebo.[185] Both doses (2.5 mg and 5 mg twice daily) however, yielded increased major and intracranial bleeding. Note that these doses are much lower than the 20-mg (or 15-mg) daily dose of rivaroxaban currently recommended for stroke prevention in AF patients.

Additionally, these 2 trials did not provide an opportunity to define outcomes for the use of NOACs in combination with contemporary P2Y12 receptor inhibitors such as prasugrel or ticagrelor among patients with AF after ACS or PCI. Therefore, triple antithrombotic therapy on a background of NOAC (dabigatran, rivaroxaban, or apixaban) or third- or fourth-generation platelet P2Y12 receptor antagonist (prasugrel and ticagrelor, respectively) cannot be recommended until further investigation is undertaken.[167]

Several ongoing clinical trials are investigating varying combinations of anticoagulants and platelet antagonists among patients with AF undergoing PCI. The PIONEER AF-PCI Study (NCT01830543) will randomize 2169 patients to either rivaroxaban (2.5 mg twice daily) plus aspirin and clopidogrel, prasugrel, or ticagrelor, followed by rivaroxaban and low-dose aspirin; a VKA (INR range 2.0-3.0), low-dose aspirin and clopidogrel, prasugrel, or ticagrelor, followed by a VKA plus low-dose aspirin or rivaroxaban 15 mg daily (10 mg daily in patients with moderate renal impairment) plus clopidogrel, prasugrel, or ticagrelor for up to 12 months. The primary outcome measure is bleeding.

The REDUAL-PCI Study (NCT02164864) will randomize 8520 patients with AF undergoing PCI to dabigatran 110 mg twice daily plus clopidogrel or ticagrelor; dabigatran 150 mg twice daily plus clopidogrel or ticagrelor; or warfarin plus aspirin and clopidogrel or ticagrelor. The primary outcome measures are: death or a thrombotic event and International Society on Thrombosis and Haemostasis scale major bleeding up to 30 months from treatment initiation.

Several small-scale studies are investigating the combination of apixaban plus aspirin and ticagrelor or apixaban plus ticagrelor with primary endpoint measures of thrombosis- related biomarkers and bleeding complications.

In the Dual Antiplatelet Therapy Trial (DAPT), a total of 9961 patients who had undergone PCI with a drug-eluting stent and completed a 1-year course of DAPT without ischemic, thrombotic, or bleeding events were randomly assigned to continue thienopyridine treatment or to receive placebo. All patients received aspirin. Patients requiring an oral anticoagulant were excluded from study participation. Continued DAPT with a thienopyridine, as compared with placebo (aspirin monotherapy), reduced the rates of stent thrombosis (0.4% vs 1.4%; HR 0.29; 95% CI, 0.17-0.48; P <.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs 5.9%; HR 0.71; 95% CI, 0.59-0.85; P <.001). The rate of myocardial infarction was lower with DAPT than with aspirin alone (2.1% vs 4.1%; HR 0.47; P <.001). The rate of death from any cause was 2.0% in the DAPT group and 1.5% in the aspirin-alone group (HR 1.36; 95% CI, 1.00-1.85; P = .05). The rate of moderate or severe bleeding was increased with continued DAPT (2.5% vs 1.6%, P = .001). An elevated risk of stent thrombosis and myocardial infarction was observed in both groups during the 3 months after discontinuation of thienopyridine treatment.

The clinical implications of the DAPT trial are far reaching, particularly for patients with AF and an indication for oral anticoagulant therapy. First, this patient population was not represented in the trial. Second, the findings could change current clinical practice, with a much longer duration of DAPT following stent placement—possibly indefinite DAPT in the absence of bleeding complications or a moderate-to-high risk profile. Last, clinicians who previously may have been comfortable with a strategy of warfarin plus clopidogrel in stented patients with AF (or another indication for anticoagulant therapy) may have a change of heart, thus favoring DAPT and, as a result, overlooking its well-documented inferiority to oral anticoagulant therapy in preventing ischemic stroke and systemic thromboembolism.[186]

Patients with AF and CAD who have a high risk for both thrombosis and bleeding create a particularly challenging scenario for clinicians. Defining risk before procedures, particularly PCI with stenting, is important, as is a thorough understanding of prior bleeding events, inherited or acquired hemostatic abnormalities, and comorbid conditions that may influence drug kinetics and clearance. Left atrial appendage closure or partitioning may become an option for some of these patients.

Left Atrial Appendage Closure Devices

Patients with AF and a clear indication for anticoagulant therapy, particularly those in whom the risk of ischemic stroke and systemic thromboembolism is high, and a concomitant high risk for bleeding, challenge even the most experienced clinicians and evidence-based guidelines.

There are 2 general approaches to occlude the left atrial appendage (LAA) using percutaneous strategies. The first involves implantable devices that are inserted percutaneously into the LAA with the goal of "occluding or plugging" the LAA. While a number of devices are under development, the 2 with the largest clinical experience are the WATCHMAN device (Boston Scientific, Natick, MA) and the Amplatzer cardiac plug (St. Jude Medical, Plymouth, MN). The early experience with the WATCHMAN device supported noninferiority to warfarin for the composite of stroke, systemic embolism, and cardiovascular death; however, early adverse events occur in approximately 10% of patients, including pericardial bleeding.[187] A subsequent registry demonstrated that the WATCHMAN device was effective in patients who could not receive warfarin, with a declining risk of periprocedural complications among experienced operators.[188] The WATCHMAN device was approved by the FDA for patients with AF who are eligible and suitable for warfarin but have an appropriate rationale for a nonpharmacologic alternative to long-term warfarin. Importantly, warfarin plus aspirin is required for at least 45 days after implantation, then clopidogrel and aspirin through 6 months, and aspirin indefinitely.

The Amplatzer cardiac plug consists of a small proximal disc, a central polyester patch, and a larger distal disc with hooks to anchor the device in the LAA. It does not require anticoagulation. A European-based trial reported a high success rate for implantation, but with a 7% incidence of serious complications.[189] The device is not FDA approved.

The second strategy to isolate the LAA employs an epicardial snare, referred to as the LARIAT device (SentreHEART, Redwood City, CA). This device received FDA approval in 2009 for facilitation of suture placement and knot tying in surgical applications where soft tissues are being approximated. It has been adapted for use in AF and combines a percutaneous epicardial and endocardial approach. The initial experience was promising, with 97% acute obliteration of the LAA as confirmed by TEE and a favorable safety profile; however, long-term outcomes have not been studied and the learning curve for placement of this device must be taken into consideration.[190]

The FDA has not yet approved any of the percutaneous LAA occlude devices for use among patients with AF who are at high risk for bleeding.

Surgical occlusion of the LAA, most often during other procedures such as coronary artery bypass surgery or valve replacement, should be considered among patients who have AF and a concomitantly high risk for bleeding with anticoagulant therapy. The experience to date has not been particularly favorable with this approach, in part because of incomplete closure, and thus it currently has a class IIb recommendation.

Subclinical AF and Stroke: When Is Oral Anticoagulation Justified?

Implanted pacemakers allow continuous monitoring of cardiac rhythm for years and provide perhaps the most sensitive method for detecting AF. Observational studies in pacemaker patients have shown that the majority of AF episodes do not cause clinical symptoms and are not detected by surface electrocardiographic methods. This type of AF has become known as subclinical AF.

The TRENDS[191] and ASSERT[27] studies have provided great insight into the burden and significance of subclinical AF. In ASSERT, more than 40% of pacemaker and defibrillator patients had an episode of subclinical AF of at least 6 minutes in duration within 3 years, and in 85% of these cases, AF was documented *only* by the pacemaker.[27] In ASSERT, patients with at least one 6-minute episode of subclinical AF in the first 3 months had a 2.5-fold increased risk of stroke or systemic embolism compared with those who did not; with an absolute stroke risk of 1.7% per year.[27] Among patients with a $CHADS_2$ score of 1, this absolute risk of stroke was 0.6% per year, while the risk was 3.8% per year in patients with a $CHADS_2$ score of more than 2.[27] However, the frequency and duration of subclinical AF did not clearly alter risk. ASSERT patients with subclinical AF whose duration was in the longest quartile (>17.7 hours) had an HR of 4.89 (95% CI 1.96-10.07); however, given the relatively small number of strokes in ASSERT, this confidence interval substantially overlapped with the estimate for ASSERT patients whose subclinical AF was in the shortest quartile; HR 1.23 (95% CI 0.15-4.46).

The TRENDS study examined 24-hour AF burden and found that patients whose weekly burden was less than the median value of 5.5 hours did not have an increased risk of stroke, transient ischemic attack, or systemic embolism (HR 0.98; 95% CI, 0.34-2.82). However, patients with more than 5.5 hours of AF per week had an HR of 2.20 (95% CI, 0.96-5.05; $P = .06$). The total number of strokes in ASSERT and TRENDS was small, thus, these studies individually have limited ability to detect a threshold below which subclinical AF does not increase stroke risk. As well, there are issues with false-positive detections of AF, of particular concern for shorter episodes, which further complicates matters. As a result, there is no clear consensus about the minimum duration of subclinical AF required to increase stroke risk.

TRENDS and ASSERT both found a low absolute risk of stroke among patients with subclinical AF, compared with earlier studies in patients with conventional, electrocardiography-detected AF.[1,2,192] These 2 studies also demonstrated that in most cases, subclinical AF did not associate temporally with strokes.[193,194] As a result, the majority of pacemaker patients with subclinical AF do not receive oral anticoagulants.[195,196] The recent IMPACT trial[197] enrolled 2718 pacemaker and defibrillator patients, half of whom randomly received remote monitoring to aid in the detection of subclinical AF and a strategy to treat with oral anticoagulation. The trial showed no reduction in its primary outcome, mainly because there was only a modest increase in anticoagulant use in the active treatment group. The ARTESiA trial will soon start: a 4000-patient, double-blind study of apixaban vs aspirin among patients with subclinical AF of 6 minutes to 24 hours in duration. A third, European trial using a new oral anticoagulant to treat subclinical AF is in the planning phases. The completion of these 3 trials should help guide the treatment of pacemaker and defibrillator patients with subclinical AF. Given the development and implementation of multiple new, invasive, and noninvasive technologies to detect subclinical AF in patients without pacemakers, the results of these studies may have a substantial impact on a much broader population.

Cost-effectiveness

NOACs have several advantages over warfarin, including no routine monitoring requirement, predictable pharmacodynamics, and fewer food and drug interactions. Their cost, however, remains an important concern for patients and care providers. Newer anticoagulants should reduce clinician and patient time commitments associated with routine monitoring of INR required with warfarin.[198] Fewer drug−drug and drug−food interactions may result in less frequent suboptimal anticoagulation and will virtually eliminate the need for dose adjustments. All anticoagulants can cause bleeding. Yet, NOACs have different pharmacodynamic properties that may reduce bleeding risk in susceptible patients.

Anticoagulant-related bleeding complications are expensive, particularly major bleeding events that require hospitalization. ICH and major gastrointestinal (GI) bleeding increase mean 12-month health care costs by

$17,774 and $16,457, respectively.[199] Overall, clinical trials have shown that ICH occurs much less frequently with dabigatran, rivaroxaban, apixaban, and edoxaban, compared with warfarin. In contrast, dabigatran, rivaroxaban, and edoxaban have produced more GI bleeding when compared with warfarin, whereas apixaban has shown similar rates of GI bleeding events.[90-92,200] Dabigatran and rivaroxaban produced similar incidences of major bleeding episodes compared with warfarin, while apixaban and edoxaban produced a lower incidence.

Several cost-effectiveness analyses have evaluated NOAC use in stroke prophylaxis. Data from the RE-LY study showed that patients' quality-adjusted life expectancy was increased from 10.28 quality-adjusted life-years (QALYs) with warfarin to 10.84 QALYS with high-dose dabigatran.[201] The incremental cost-effectiveness ratio compared with warfarin was $45,372 per QALY for high-dose dabigatran, which is cost-effective when compared with a $50,000 willingness-to-pay threshold. The cost-effectiveness of high-dose dabigatran increased with higher risk for stroke and ICH. In a hypothetical cohort study of 70-year-old AF patients evaluating dabigatran 110 or 150 mg twice daily, warfarin, dual therapy with aspirin and clopidogrel, aspirin alone, or no antithrombotic, dabigatran 150 mg twice daily had the greatest quality-adjusted survival at 8.65 QALYs, compared with 8.40 QALYs for aspirin.[201] Cost-effectiveness depended highly on stroke, risk of hemorrhage, cost of dabigatran, and time in therapeutic range (TTR) for warfarin. For patients with a $CHADS_2$ score of ≥ 3 (high risk of stroke), dabigatran 150 mg twice daily was cost-effective unless INR control was excellent (TTR $> 72.6\%$). In the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE trials, the median TTRs were 64%, 55%, 64%, and 68.4%, respectively, demonstrating that it is difficult to manage in many patients.

Rivaroxaban cost-effectiveness was compared with adjusted-dose warfarin for stroke prevention using a model with a Medicare perspective and a lifetime time horizon.[202] Outcome measurements included costs in 2011 US dollars, QALYs, and incremental cost-effectiveness ratios. Patients with AF treated with rivaroxaban lived an average of 10.03 QALYs at a lifetime treatment cost of $94,456. Those receiving warfarin lived an average of 9.81 QALYs and incurred costs of $88,544. The incremental cost-effectiveness ratio for rivaroxaban was $27,498 per QALY. This model showed that rivaroxaban therapy may be a cost-effective alternative to adjusted-dose warfarin for stroke prevention in AF.

Researchers followed a group of nonvalvular AF patients longitudinally for thrombosis and bleeding endpoints.[203] Despite their "real world" AF population comprised primarily of low-risk patients (78.5% had $CHADS_2$ scores of ≤ 2), the stroke rate was high, 5.3 events per 100 patient years overall, and 3.2 and 5.7 events per 100 patient years in those with $CHADS_2$ scores of 1 and 2, respectively. Major bleeding was also alarmingly high at 10 events per 100 patient years. The risk reductions from the ARISTOTLE trial, apixaban compared against warfarin for stroke prophylaxis, was applied to the "real world" population to determine event rates had apixaban been used instead of warfarin. The application of the apixaban risk reduction to the "real world" population avoided 1.1 stroke events per 100 patient years and avoided 2.1 major bleeding events per 100 patient years. The authors estimated that apixaban use would generate an incremental medical cost avoidance for stroke of $493 during a patient year and $752 for major bleeding events during a patient year. The combined cost avoidance for stroke and major bleeding was $1245 during a patient year. Overall, the medical cost avoidance increased as patient stroke risk increased.

Patients have major concerns about out-of-pocket expenses associated with drug therapy. The NOACs typically fall into a higher insurance tier and have higher co-payments than warfarin. Many patients with AF are elderly, on fixed incomes, and have other medication needs, hence the importance of evaluating each patient's financial situation. While warfarin has a low acquisition cost, other less obvious expenses such as transportation to anticoagulation clinics or laboratories for INR monitoring and dose adjustments require consideration. The estimated associated annual costs range from $130 for patients attending clinics monthly to $560 for patients attending clinics weekly.[204] Warfarin therapy also consumes patient time. Anticoagulation clinic visits, phone communication with providers, and pharmacy trips require an estimated average of 91.7 hours annually for warfarin therapy. Therefore the anticoagulant choice in stroke prevention requires reflection by the patient and provider and consideration of time and financial constraints.

AF-related stroke contributes considerably to health care expenditures. Although warfarin has been the standard of preventive care for decades, the NOACs now furnish options. Early economic studies support the cost-effectiveness of NOACs, because they reduce stroke and systemic embolism as well as bleeding events, including ICH. As the cost of NOACs decreases over time, cost-effectiveness considerations may more heavily favor the NOACs over warfarin in the future.

Medication Adherence

While 48% of Americans routinely take at least one drug daily, older patients (over the age of 60 years) use prescription drugs more commonly, with about 75% of patients taking 2 or more and 40% taking 5 or more prescription drugs every day.[205,206] Yet, adherence to physician-prescribed medication regimens for chronic conditions is only about 50%.[207-209] Problems include failing to fill or refill prescriptions, omitting doses, overdosing, prematurely stopping, and taking medications prescribed for someone else. About one-third of elderly patients never comply with their medications, and more than half make errors when taking their medications.

Numerous factors contribute to failure to adhere to a prescribed medication regimen or treatment plan. Patients often do not understand the rationale for the medication, nor

the intended benefit. The regimen may be too complex to follow. Medication side effects or patient's lifestyle may also disrupt adherence. Many patients cannot afford their medications and will adjust their regimen by skipping or adjusting doses. Finally, many patients simply forget.[208,209]

This failure to follow medical direction gives rise to some 125,000 deaths annually in the US. As many as two-thirds of all medication-related hospital and nursing home admissions result from poor medication adherence. This increase in emergency department care, physician office visits, additional diagnostic tests, alternative treatments, and adverse clinical outcomes adds an estimated incremental $290 billion to annual US health care expenditures.[208,209]

AF is a chronic condition that requires long-term management with heart rate control or rhythm control medications in addition to anticoagulants. At present, oral anticoagulant options include warfarin, dabigatran, apixaban, rivaroxaban, and edoxaban. For these agents to be effective in reducing stroke risk, they must be taken every day. Furthermore, patients will not perceive any benefit (prevention of a stroke) while they take the medications, but may experience unwanted effects, most notably bleeding. The patient or a family member, or both, must be empowered to take ownership in their medication management. Strong clinician and patient relationships remain the cornerstone to success. Clinicians should provide disease and medication education at each interaction. Pharmacists can simplify medication regimen complexity by combining medication administrations and associating them to a daily event (eg, meals, sleep time, awakening).[7] Other strategies that have been successfully employed include medication diaries, calendar pillboxes, and cell phone alerts.

In summary, lack of patient adherence to prescribed medications commonly limits safe and effective disease management. There are a wide variety of reasons and no single strategy for success. Clinicians must exercise vigilance for signs of nonadherence, offering patient and family education, support, and a wide range of strategies to maximize long-term adherence.

Considerations when Choosing an Anticoagulant

With the availability of VKAs and NOACs, the inevitable question arises of which patient should be treated with which drug? While a single "right choice" seldom applies, clinicians and patients may want to consider several important considerations when deciding which anticoagulant to use.

Anticoagulation vs No Anticoagulation

The decision to prescribe *an* anticoagulant has far more importance than the choice of *which* anticoagulant. All of the available options provide substantial protection from stroke, with low rates of serious or life-threatening bleeding. The differences among anticoagulants in mechanism of action, duration of anticoagulant effect, dosing, food and drug interactions, renal clearance, metabolism, and efficacy and safety profiles offer a more modest opportunity to improve outcomes compared with the marked benefit for patients with any of these agents compared with those who do not receive anticoagulation.

VKAs vs NOACs

A meta-analysis that includes data from all 4 phase-3 trials (73,683 patients) comparing NOACs with warfarin for stroke prevention in AF showed a consistent and robust benefit of the new oral anticoagulants in reducing stroke (primarily hemorrhagic stroke), mortality, and intracranial hemorrhage.[156] The benefit of NOACs was also consistent across a wide range of subjects, including vulnerable patients such as the elderly, patients with a prior stroke, and those with renal dysfunction. The benefit of the NOACs did not depend on how well warfarin was managed with respect to the time in therapeutic range.

A question has persisted about the suitability of the NOACs for patients with AF and concomitant valvular disease as the literature, prescribing information, and guidelines recommend NOACs be used only in patients with "nonvalvular AF." The use of the term nonvalvular AF is unfortunate and misleading, as patients with a wide range of valvular pathology and severity were enrolled in all of the phase-3 NOAC trials. The only valvular heart diseases uniformly excluded from all the trials were significant mitral stenosis and mechanical heart valves (see below). Bioprosthetic valves were included in the ARISTOTLE trial with apixaban and the ENGAGE AF-TIMI 48 trial with edoxaban.

VKAs Remain the Best Option for Some AF Patients

Although NOACs have emerged as an attractive alternative to VKAs, there are certain patients in which VKAs remain the anticoagulant of choice.

- Patients with mechanical heart valves should only be prescribed VKAs, as they were excluded from all of the phase-3 NOAC trials for stroke prevention in AF. Additionally, data from the single phase II trial of a NOAC, dabigatran, in patients with mechanical heart valves (RE-ALIGN), demonstrated inferior efficacy and more bleeding.[210]
- Patients with severe (creatinine clearance <15 mL/min) or end-stage kidney disease, as there are no or very limited data about the efficacy and safety of NOACs in these patients. Although apixaban is approved for patients with end-stage renal disease with or without dialysis based on pharmacokinetic and pharmacodynamic data.
- Patients in whom medication adherence is an issue may be better served by VKA therapy for several reasons. The longer anticoagulant effects of VKAs are more forgiving of missed doses than the NOACs where missing 1-2 doses can result in patients being unprotected with regards to

stroke. INR monitoring also allows the physician to routinely monitor compliance for VKAs and establish whether a patient is therapeutically anticoagulated. There are currently no approved or widely available laboratory methods to quantify the level of anticoagulation with the NOACs, nor is there a consensus on what a therapeutic level is with any of the current assays.

- Patients with insurance coverage for VKA therapy but not NOACs, and without the resources to pay out of pocket for NOACs.

Choosing Among the NOACs

Although the clinical trials yield broadly similar results across the NOACs as compared with warfarin, the NOACs have differences in their efficacy and safety profiles as well as their mechanisms of action (inhibition of thrombin or Factor Xa), frequency of dosing (once or twice daily), criteria for dose adjustment, degree of renal clearance, and potential for drug–drug interactions that might point a physician or patient toward a specific agent or dose. It is important to qualify that any recommendation of one NOAC over another for a specific group of patients is purely speculative, as there has never been, nor is there ever likely to be, a clinical trial comparing one NOAC directly against another.

- The Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban may be preferable in patients with moderate or fluctuating renal dysfunction, as they are less dependent on renal clearance than the thrombin inhibitor dabigatran. The preference for the Factor Xa inhibitors also pertains to the elderly, who also frequently have some impairment of renal function, as dabigatran 150 mg twice daily resulted in excess bleeding (extracranial) compared with warfarin. Dabigatran 110 mg twice daily is appropriate in the elderly (not available in the US).
- Dabigatran 150 mg twice daily is an attractive agent in patients with a high risk of ischemic stroke, as it is the only agent that significantly reduced ischemic stroke, in particular, compared with warfarin.
- Apixaban and edoxaban may be preferred agents in patients with prior significant bleeding or at high risk of bleeding, as they both had significantly less major bleeding compared with warfarin. Apixaban may be particularly attractive in patients with a history of gastrointestinal bleeding in particular, as it is the only approved NOAC not associated with an increased risk of gastrointestinal bleeding compared with warfarin.
- Patients and physicians who strongly prefer once-daily medications, which have been associated with improved compliance, should be prescribed rivaroxaban or edoxaban.

PATIENT EDUCATION AND ADVOCACY TO IMPROVE PATIENT SAFETY

Patient education and advocacy form the backbone to patient safety. Continued education has particular importance for those with AF who are anticoagulated. Poor outcomes, such as hospital readmissions, link to patients' lack of knowledge about their care and treatment.[211] Various patient care models for managing anticoagulation therapy associate with improved outcomes. These models include management by specialized staff at anticoagulation clinics along with patient self-testing and self-management of INR. Health care providers including nurses, pharmacists, and physicians have the responsibility of educating patients and advocating for appropriate placement of each individual into the optimal patient care model.

Anticoagulation therapy with warfarin is a safe and effective treatment, but can be cumbersome for both clinicians and patients to manage. Initial education at the hospital or physician's office and continued education at home help patients to remain well informed about their disease state and become proactive in their care. Warfarin causes the most adverse drug events that lead to emergency department visits.[212] Studies have shown that patient education improves time spent in therapeutic range with warfarin and decreased rates of hemorrhagic and thrombotic events.[213,214] The Joint Commission's National Patient Safety Goals require a patient education component for anticoagulation.[215] Clinicians should not only initiate education, but they should also be prepared to recommend resources to patients for continued education at home.

A 2013 report showed that more than 80% of adults use the Internet, and almost 60% of them had looked online for health-related information in the previous 12 months. Some clinicians remain concerned about the quality of the information on the Web and the difficulty patients have evaluating the credibility of information. Directing patients to authoritative, commercial-free, patient-oriented medical information may help mitigate some of these concerns. An abundance of advocacy groups offer quality, up-to-date information for patients, especially those sponsored by governments, academic medical centers, and major professional organizations. Clinicians should recognize the added value in having conversations with well-informed patients. A motivated patient can discover more details on a specific health topic from the Internet than is feasible for a clinician to provide during a single office visit. When managed correctly, continued lay education using the Internet may result in a more productive patient–provider relationship and can facilitate shared decision-making.

Whenever feasible, patients taking warfarin should be referred to an Anticoagulation Management Service (clinic) for specialized care. In this setting, well-informed patients can enroll in programs for self-testing or self-management of INR. Self-testing allows patients to monitor their INR in the convenience of their own home. Self-testing increases TTR, quality of life, and patient satisfaction.[216] Patient self-management of warfarin also has proven to be a safe and effective method for well-informed and highly motivated patients. Previous studies report this model of care to be superior to management by

general practitioners or anticoagulation clinics in terms of quality of INR control and rates of thromboembolic and hemorrhagic events.[217-220] Suitable patients should have such management strategies implemented. There is considerable interest in adapting Anticoagulation Management Services to provide counseling, education, and follow-up for patients anticoagulated with the NOACs in addition to their continued services that provide important value to warfarin patients.

Initial education by a clinician and continued education by the patient is the key for successful anticoagulation. Clinicians should aid their patients to acquire the tools to be proactive in their care, and patients should be directed toward quality health care information from the Internet, books, magazines, newsletters, newspapers, or other patient-preferred media.

References

1. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123:e269-e367.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-2375.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22:983-988.
4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.
5. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272.
6. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287-2292.
7. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:546S-592S.
8. Fuster V, Ryden LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol*. 2011;57:e101-e198.
9. Boriani G, Botto GL, Padeletti L, et al. Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke*. 2011;42:1768-1770.
10. Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. *J Thromb Haemost*. 2011;9:39-48.
11. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke*. 2010;41:2731-2738.
12. Poli D, Lip GY, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a "real-world" elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol*. 2011;22:25-30.
13. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
14. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369-2429.
15. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33:2719-2747.
16. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199-e267.
17. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91-99.
18. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713-719.
19. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest*. 2006;130:1390-1396.
20. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57:173-180.
21. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58:395-401.
22. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012;380:1749-1758.
23. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093-1100.
24. Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LA, Rosenqvist M. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace*. 2013;15:135-140.
25. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost*. 2013;110:213-222.
26. Lin HJ, Wolf PA, Benjamin EJ, Belanger AJ, D'Agostino RB. Newly diagnosed atrial fibrillation and acute stroke. The Framingham Study. *Stroke*. 1995;26:1527-1530.
27. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120-129.
28. Marfella R, Sasso FC, Siniscalchi M, et al. Brief episodes of silent atrial fibrillation predict clinical vascular brain disease in type 2 diabetic patients. *J Am Coll Cardiol*. 2013;62:525-530.
29. Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. 2014;45:520-526.

30. Flint AC, Banki NM, Ren X, Rao VA, Go AS. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke*. 2012;43:2788-2790.

31. Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology*. 2013;80:1546-1550.

32. Culebras A, Messe SR, Chaturvedi S, Kase CS, Gronseth G. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2014;82:716-724.

33. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739-745.

34. Schnabel RB, Aspelund T, Li G, et al. Validation of an atrial fibrillation risk algorithm in whites and African Americans. *Arch Intern Med*. 2010;170:1909-1917.

35. Chamberlain AM, Agarwal SK, Folsom AR, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011;107:85-91.

36. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J*. 2013;34:2243-2251.

37. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2(2):e000102.

38. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J*. 2013;34:1475-1480.

39. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation*. 2009;119:2408-2416.

40. Schnabel RB, Larson MG, Yamamoto JF, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation*. 2010;121:200-207.

41. Smith JG, Newton-Cheh C, Almgren P, et al. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. *J Am Coll Cardiol*. 2010;56:1712-1719.

42. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. *N Engl J Med*. 1997;336:905-911.

43. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA. Familial aggregation in lone atrial fibrillation. *Hum Genet*. 2005;118:179-184.

44. Fox CS, Parise H, D'Agostino RB Sr, et al. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *JAMA*. 2004;291:2851-2855.

45. Lubitz SA, Yin X, Fontes JD, et al. Association between familial atrial fibrillation and risk of new-onset atrial fibrillation. *JAMA*. 2010;304:2263-2269.

46. Arnar DO, Thorvaldsson S, Manolio TA, et al. Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J*. 2006;27:708-712.

47. Gudbjartsson DF, Arnar DO, Helgadottir A, et al. Variants conferring risk of atrial fibrillation on chromosome 4q25. *Nature*. 2007;448:353-357.

48. Benjamin EJ, Rice KM, Arking DE, et al. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. *Nat Genet*. 2009;41:879-881.

49. Gudbjartsson DF, Holm H, Gretarsdottir S, et al. A sequence variant in ZFHX3 on 16q22 associates with atrial fibrillation and ischemic stroke. *Nat Genet*. 2009;41:876-878.

50. Ellinor PT, Lunetta KL, Glazer NL, et al. Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat Genet*. 2010;42:240-244.

51. Ellinor PT, Lunetta KL, Albert CM, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet*. 2012;44:670-675.

52. Lubitz SA, Lunetta KL, Lin H, et al. Novel genetic markers associate with atrial fibrillation risk in Europeans and Japanese. *J Am Coll Cardiol*. 2014;63(12):1200-1210.

53. Smith JG, Newton-Cheh C, Almgren P, Melander O, Platonov PG. Genetic polymorphisms for estimating risk of atrial fibrillation in the general population: a prospective study. *Arch Intern Med*. 2012;172:742-744.

54. Benjamin EJ, Chen PS, Bild DE, et al. Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation*. 2009;119:606-618.

55. Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. *Circulation*. 2012;125:1605-1616.

56. Hijazi Z, Wallentin L, Siegbahn A, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). *J Am Coll Cardiol*. 2013;61:2274-2284.

57. Hijazi Z, Siegbahn A, Andersson U, et al. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Circulation*. 2014;129:625-634.

58. Hijazi Z, Wallentin L, Siegbahn A, et al. High-sensitivity troponin T and risk stratification in patients with atrial fibrillation during treatment with apixaban or warfarin. *J Am Coll Cardiol*. 2014;63:52-61.

59. Roldan V, Marin F, Diaz J, et al. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *J Thromb Haemost*. 2012;10:1500-1507.

60. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;119:1363-1369.

61. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821-2830.

62. Hijazi Z, Oldgren J, Andersson U, et al. Cystatin c is prognostic for stroke, death, and bleeding during anticoagulation of atrial fibrillation − a RELY substudy. *Circulation* 2011;(Abstract suppl 124):A12492.

63. Eikelboom J, Hijazi Z, Oldgren J, et al. D-dimer is prognostic for stroke, major bleeding, and death during anticoagulation of atrial fibrillation − a RELY substudy. *Circulation* 2010;(Abstract suppl 122):A18321.

64. Christersson C, Schollin M, Alexander J, et al. Increased levels of D-dimer in atrial fibrillation indentify patients with higher risk of thromboembolic events and death. *Eur Heart J*. 2012;33. (Abstract Supplement, 51, Abstract session 5297).

65. Siegbahn A, Christersson C, Schollin M, et al. Increased levels of D-dimer identify patients with atrial fibrillation at high risk for bleeding an ARISTOTLE substudy. *Eur Heart J*. 2012;33. (Abstract Supplement 51).

66. Lip GY, Patel JV, Hughes E, Hart RG. High-sensitivity C-reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. *Stroke*. 2007;38:1229-1237.

67. Hermida J, Lopez FL, Montes R, Matsushita K, Astor BC, Alonso A. Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol*. 2012;109:95-99.

68. Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther*. 2011;90(4):625-629.

69. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med.* 2013;369:2283-2293.

70. Mega JL, Giugliano RP. Genotype-guided dosing of warfarin. *Clin Chem.* 2014;60:920-922.

71. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med.* 2013;369: 2294-2303.

72. Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. *N Engl J Med.* 2013;369:2304-2312.

73. Mega JL, Walker JR, Ruff CT, et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet.* 2015;385(9984): 2280-2287.

74. Pare G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation.* 2013;127: 1404-1412.

75. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857-867.

76. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e44S-e88S.

77. Garcia D, Regan S, Crowther M, Hughes RA, Hylek EM. Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest.* 2005;127:2049-2056.

78. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One.* 2013;8:e63479.

79. Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. *Circulation.* 2014;129:1407-1414.

80. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clin Pharmacokinet.* 2009;48:1-22.

81. Van der Donckt C, Van Herck JL, Schrijvers DM, et al. Elastin fragmentation in atherosclerotic mice leads to intraplaque neovascularization, plaque rupture, myocardial infarction, stroke, and sudden death. *Eur Heart J.* 2015;36:1049-1058.

82. Chatterjee S, Giri J. Benefits and risks associated with thrombolysis for pulmonary embolism—reply. *JAMA.* 2014;312:1589-1590.

83. Sardar P, Nairooz R, Chatterjee S. Intensive glucose control for acute myocardial infarction: an unresolved clinical conundrum. *JAMA Intern Med.* 2014;174:825-826.

84. Ansell J. Will the new target-specific oral anticoagulants improve the treatment of venous thromboembolism? *Thromb Haemost.* 2012;107: 1009-1011.

85. Gonzalez-Quesada CJ, Giugliano RP. Comparison of the phase III clinical trial designs of novel oral anticoagulants versus warfarin for the treatment of nonvalvular atrial fibrillation: implications for clinical practice. *Am J Cardiovasc Drugs.* 2014;14:111-127.

86. Matsushima N, Lee F, Sato T, Weiss D, Mendell J. Bioavailability and safety of the factor Xa inhibitor edoxaban and the effects of quinidine in healthy subjects. *Clin Pharm Drug Dev.* 2013;2:358-366.

87. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol.* 2010;50:743-753.

88. Ruff CT, Giugliano RP. New oral antithrombotic strategies. *Hot Topics Cardiol.* 2011;22:7-14.

89. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361: 1139-1151.

90. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883-891.

91. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365: 981-992.

92. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093-2104.

93. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. Establishing comparable requirements and treatment groups before applying statistical comparison-reply. *JAMA Neurol.* 2014;71:371-372.

94. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. *N Engl J Med.* 2010;363: 1875-1876.

95. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet.* 2010;376:975-983.

96. Boehringer Ingelheim. Dabigatran briefing document. Available at: http:// www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/ drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm226009. pdf. Accessed January 1, 2016.

97. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. *Circulation.* 2014;131:157-164.

98. Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation.* 2011;123:131-136.

99. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation − the J-ROCKET AF study. *Circ J.* 2012;76:2104-2111.

100. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364:806-817.

101. Salazar DE, Mendell J, Kastrissios H, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost.* 2012;107:925-936.

102. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e531S-e575S.

103. Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring oral direct inhibitors (ODIs) of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. *J Thromb Haemost.* 2013;11:756-760.

104. Ansell J. New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. *Circulation.* 2012;125:165-170, discussion 170.

105. Garcia D, Barrett YC, Ramacciotti E, Weitz JI. Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. *J Thromb Haemost.* 2013;11:245-252.

106. Harenberg J, Erdle S, Marx S, Kramer R. Determination of rivaroxaban in human plasma samples. *Semin Thromb Hemost.* 2012;38: 178-184.

107. Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. *Blood.* 2012;119:3016-3023.

108. Tripodi A. The laboratory and the direct oral anticoagulants. *Blood.* 2013;121:4032-4035.

109. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103:1116-1127.

110. Samama MM, Contant G, Spiro TE, et al. Evaluation of the prothrombin time for measuring rivaroxaban plasma concentrations using calibrators and controls: results of a multicenter field trial. *Clin Appl Thromb Hemost.* 2012;18:150-158.

111. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogne JM. Impact of dabigatran on a large panel of routine or

specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thromb Haemost*. 2012;107: 985-997.

112. Hapgood G, Butler J, Malan E, Chunilal S, Tran H. The effect of dabigatran on the activated partial thromboplastin time and thrombin time as determined by the Hemoclot thrombin inhibitor assay in patient plasma samples. *Thromb Haemost*. 2013;110:308-315.

113. Hillarp A, Baghaei F, Fagerberg Blixter I, et al. Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used coagulation assays. *J Thromb Haemost*. 2011;9:133-139.

114. Lindahl TL, Baghaei F, Blixter IF, et al. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost*. 2011;105:371-378.

115. Baruch L, Sherman O. Potential inaccuracy of point-of-care INR in dabigatran-treated patients. *Ann Pharmacother*. 2011;45:e40.

116. Hawes EM, Deal AM, Funk-Adcock D, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. *J Thromb Haemost*. 2013;11:1493-1502.

117. Samama MM, Contant G, Spiro TE, et al. Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. *Thromb Haemost*. 2012;107:379-387.

118. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol*. 2014;64:1128-1139.

119. Kitchen S, Gray E, Mackie I, Baglin T, Makris M. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. *Br J Haematol*. 2014;166:830-841.

120. Eby CS. Warfarin replacements: good for patients, challenging for laboratories. *Clin Chem*. 2013;59:732-734.

121. Garcia D, Crowther MA, Ageno W. Practical management of coagulopathy associated with warfarin. *BMJ*. 2010;340:c1813.

122. Kaatz S, Crowther M. Reversal of target-specific oral anticoagulants. *J Thromb Thrombolysis*. 2013;36:195-202.

123. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. *Circulation*. 2012;126:2428-2432.

124. Lazo-Langner A, Lang ES, Douketis J. Clinical review: clinical management of new oral anticoagulants: a structured review with emphasis on the reversal of bleeding complications. *Crit Care*. 2013;17:230.

125. Weitz JI, Pollack CV Jr. Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thromb Haemost*. 2015;114:1113-1126.

126. Pollack CV Jr, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373:511-520.

127. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373: 2413-2424.

128. Wann LS, Curtis AB, Ellenbogen KA, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;127:1916-1926.

129. Flaker G, Lopes RD, Al-Khatib SM, et al. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol*. 2014;63:1082-1087.

130. Cappato R, Ezekowitz MD, Klein AL, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35:3346-3355.

131. Santangeli P, Di Biase L, Horton R, et al. Ablation of atrial fibrillation under therapeutic warfarin reduces periprocedural complications: evidence from a meta-analysis. *Circ Arrhythm Electrophysiol*. 2012;5: 302-311.

132. Kuwahara T, Takahashi A, Takahashi Y, et al. Prevention of periprocedural ischemic stroke and management of hemorrhagic complications in atrial fibrillation ablation under continuous warfarin administration. *J Cardiovasc Electrophysiol*. 2013;24:510-515.

133. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. *Circulation*. 2014;129:2638-2644.

134. Weitz JI, Healey JS, Skanes AC, Verma A. Periprocedural management of new oral anticoagulants in patients undergoing atrial fibrillation ablation. *Circulation*. 2014;129:1688-1694.

135. Bassiouny M, Saliba W, Rickard J, et al. Use of dabigatran for periprocedural anticoagulation in patients undergoing catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2013;6: 460-466.

136. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol*. 2012;59: 1168-1174.

137. Providencia R, Albenque JP, Combes S, et al. Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2014;100:324-335.

138. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of uninterrupted rivaroxaban for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol*. 2014;63: 982-988.

139. Rillig A, Lin T, Plesman J, et al. Apixaban, rivaroxaban and dabigatran in patients undergoing atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2016;27(2):147-153.

140. Nagao T, Inden Y, Yanagisawa S, et al. Differences in activated clotting time among uninterrupted anticoagulants during the periprocedural period of atrial fibrillation ablation. *Heart Rhythm*. 2015;12:1972-1978.

141. Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e326S-e350S.

142. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation*. 2012;126:1630-1639.

143. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013;368:2084-2093.

144. Mathew JG, Spyropoulos AC, Yusuf A, et al. Efficacy and safety of early parenteral anticoagulation as a bridge to warfarin after mechanical valve replacement. *Thromb Haemost*. 2014;112:1120-1128.

145. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med*. 2015;373:823-833.

146. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206-1214.

147. Spyropoulos AC, Douketis JD. How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood*. 2012;120: 2954-2962.

148. Sherwood MW, Douketis JD, Patel MR, et al. Outcomes of temporary interruption of rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: results from 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). *Circulation*. 2014;129:1850-1859.

149. Garcia D, Alexander JH, Wallentin L, et al. Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures. *Blood*. 2014;124:3692-3698.

150. Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anti-coagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126:343-348.

151. Douketis JD, Healey JS, Brueckmann M, et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients with an elective surgery or procedure. Substudy of the RE-LY trial. *Thromb Haemost*. 2015;113:625-632.

152. Kovacs M. PERIOP2 − A safety and effectiveness study of LMWH bridging therapy versus placebo bridging therapy for patients on long term warfarin and require temporary interruption of their warfarin. ClinicalTrials.gov Identifier: NCT00432796. Available at: https://www.clinicaltrials.gov/ct2/show/NCT00432796. Accessed July 28, 2015.

153. Ortel T, Hasselblad V. Effectiveness of bridging anticoagulation for surgery (the BRIDGE study). ClinicalTrials.gov Identifier: NCT00786474. Available at: https://clinicaltrials.gov/ct2/results?term=Ortel+T%2C+Hasselblad+V.+Effectiveness+of+bridging+anticoagulation+for+surgery+%28the+BRIDGE+study%29.+ClinicalTrials.gov+Identifier%3A+Q21+NCT00786474.+Available+at%3A+—.+Accessed+April+29%2C+2015.&Search=Search. Accessed April 29, 2015.

154. Douketis J, Duncan J. Perioperative anticoagulant use for surgery evaluation study (PAUSE). ClinicalTrials.gov Identifier: NCT02228798. Available at: https://clinicaltrials.gov/ct2/show/NCT00786474. Accessed April 29, 2015.

155. Hylek EM, Frison L, Henault LE, Cupples A. Disparate stroke rates on warfarin among contemporaneous cohorts with atrial fibrillation: potential insights into risk from a comparative analysis of SPORTIF III versus SPORTIF V. *Stroke*. 2008;39:3009-3014.

156. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955-962.

157. Ezekowitz MD, Wallentin L, Connolly SJ, et al. Dabigatran and warfarin in vitamin K antagonist-naive and -experienced cohorts with atrial fibrillation. *Circulation*. 2010;122:2246-2253.

158. Garcia DA, Wallentin L, Lopes RD, et al. Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial. *Am Heart J*. 2013;166:549-558.

159. Mahaffey KW, Stevens SR, White HD, et al. Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial. *Eur Heart J*. 2014;35:233-241.

160. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke*. 2009;40:1410-1416.

161. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med*. 1993;153:1557-1562.

162. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123:2363-2372.

163. Coppens M, Eikelboom J, Ezekowitz M, et al. Abstract 15537: dabigatran versus warfarin in very elderly patients with atrial fibrillation: results from the RE-LY trial. *Circulation*. 2012;126:A15537.

164. Halperin JL, Wojdyla D, Piccini JP, et al. Abstract 148: efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the ROCKET-AF trial. *Stroke*. 2012;43:A148.

165. Dobson LE, Lewin RJ, Doherty P, Batin PD, Megarry S, Gale CP. Is cardiac rehabilitation still relevant in the new millennium? *J Cardiovasc Med (Hagerstown)*. 2012;13:32-37.

166. Kato ET, Giugliano RP, Ruff CT, et al. Abstract 16612: efficacy and safety of edoxaban for the management of elderly patients with atrial fibrillation: engage AF-TIMI 48. *Circulation*. 2014;130:A16612.

167. Pokorney SD, Sherwood MW, Becker RC. Clinical strategies for selecting oral anticoagulants in patients with atrial fibrillation. *J Thromb Thrombolysis*. 2013;36:163-174.

168. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation*. 2014;129:961-970.

169. Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. *Circulation*. 2012;125:669-676.

170. Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387-2394.

171. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet*. 2015;385:2288-2295.

172. Vivas D, Olmos C, Vilacosta I. Atrial fibrillation and anticoagulation therapy: different race, different risk, and different management? *Circ J*. 2011;75:1314-1315.

173. Hernandez W, Aquino-Michaels K, Drozda K, et al. Novel single nucleotide polymorphism in CYP2C9 is associated with changes in warfarin clearance and CYP2C9 expression levels in African Americans. *Transl Res*. 2015;165(6):651-657.

174. Hylek EM, Ko D, Cove CL. Gaps in translation from trials to practice: non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation. *Thromb Haemost*. 2014;111:783-788.

175. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835-842.

176. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.

177. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:645-681.

178. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:e78-e140.

179. Wisler JW, Becker RC. A guidance pathway for the selection of novel anticoagulants in the treatment of atrial fibrillation. *Crit Pathw Cardiol*. 2012;11:55-61.

180. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. *Europace*. 2014;16:631-638.

181. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation*. 2012;126:2381-2391.

182. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized

Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127:634-640.

183. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107-1115.

184. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365:699-708.

185. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9-19.

186. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155-2166.

187. Reddy VY, Doshi SK, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. *Circulation*. 2013;127(6):720-729.

188. Reddy VY, Mobius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol*. 2013;61:2551-2556.

189. Park JW, Bethencourt A, Sievert H, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. *Catheter Cardiovasc Interv*. 2011;77(5):700-706.

190. Bartus K, Han FT, Bednarek J, et al. Percutaneous left atrial appendage suture ligation using the LARIAT device in patients with atrial fibrillation: initial clinical experience. *J Am Coll Cardiol*. 2013;62:108-118.

191. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474-480.

192. Lip GY, Camm AJ, Hylek EM, Halperin JL, Weitz JI. Non-vitamin K antagonist oral anticoagulants: an appeal for consensus on terminology. *Chest*. 2014;145:1177-1178.

193. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm*. 2011;8:1416-1423.

194. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129:2094-2099.

195. Anderson K, Benzauqen B. Do patients with pacemaker-detected atrial fibrillation receive appropriate anticoagulation? *Europace*. 2011;13:P519.

196. Healey JS, Martin JL, Duncan A, et al. Pacemaker-detected atrial fibrillation in patients with pacemakers: prevalence, predictors, and current use of oral anticoagulation. *Can J Cardiol*. 2013;29:224-228.

197. Ip J, Waldo AL, Lip GY, et al. Multicenter randomized study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices: rationale, design, and clinical characteristics of the initially enrolled cohort The IMPACT study. *Am Heart J*. 2009;158:364-370.

198. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133:160S-198S.

199. Ghate SR, Biskupiak J, Ye X, Kwong WJ, Brixner DI. All-cause and bleeding-related health care costs in warfarin-treated patients with atrial fibrillation. *J Manag Care Pharm*. 2011;17:672-684.

200. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:1-11.

201. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123:2562-2570.

202. Amin A, Stokes M, Wu N, et al. Estimated medical cost reductions associated with apixaban in real-world patients with non-valvular atrial fibrillation. *J Med Econ*. 2013;16:1193-1202.

203. Hwang JM, Clemente J, Sharma KP, Taylor TN, Garwood CL. Transportation cost of anticoagulation clinic visits in an urban setting. *J Manag Care Pharm*. 2011;17:635-640.

204. Jonas DE, Bryant Shilliday B, Laundon WR, Pignone M. Patient time requirements for anticoagulation therapy with warfarin. *Med Decis Making*. 2010;30:206-216.

205. Centers for Disease Control and Prevention (CDC). *US Prescription Drug Data*. 2014. Available at: http://www.cdc.gov/nchs/data/databriefs/db42.htm. Accessed May 12, 2014.

206. Centers for Disease Control and Prevention (CDC). Health, United States, 2010: with special feature on death and dying. Available at: http://www.cdc.gov/nchs/data/hus/hus10.pdf. Accessed May 12, 2014.

207. Office of Inspector General; US Department of Health and Human Services. *Medication Regimens: Cause of Non Compliance*. 2014. Available at: http://oig.hhs.gov/oei/reports/oei-04-89-89121.pdf. Accessed May 12, 2014.

208. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487-497.

209. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43:521-530.

210. Van de Werf F, Brueckmann M, Connolly SJ, et al. A comparison of dabigatran etexilate with warfarin in patients with mechanical heart valves: THE Randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). *Am Heart J*. 2012;163:931-937.

211. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med*. 2003;138:161-167.

212. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med*. 2007;147:755-765.

213. Pernod G, Labarere J, Yver J, et al. EDUC'AVK: reduction of oral anticoagulant-related adverse events after patient education: a prospective multicenter open randomized study. *J Gen Intern Med*. 2008;23(9):1441-1446.

214. Wilhelm SM, Petrovitch EA. Implementation of an inpatient anticoagulation teaching service: expanding the role of pharmacy students and residents in patient education. *Am J Health Syst Pharm*. 2011;68:2086-2093.

215. Joint Commission. Anticoagulation therapy, NPSG 03.05.01. Available at: www.jointcommission.org/assets/1/6/2011_NPSGs_HAP.pdf. Accessed June 27, 2011.

216. Matchar DB, Jacobson A, Dolor R, et al. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363:1608-1620.

217. Kortke H, Korfer R. International normalized ratio self-management after mechanical heart valve replacement: is an early start advantageous? *Ann Thorac Surg*. 2001;72:44-48.

218. Voller H, Glatz J, Taborski U, Bernardo A, Dovifat C, Heidinger K. Self-management of oral anticoagulation in nonvalvular atrial fibrillation (SMAAF study). *Z Kardiol*. 2005;94:182-186.

219. Watzke HH, Forberg E, Svolba G, Jimenez-Boj E, Krinninger B. A prospective controlled trial comparing weekly self-testing and self-dosing with the standard management of patients on stable oral anticoagulation. *Thromb Haemost*. 2000;83:661-665.

220. Khan TI, Kamali F, Kesteven P, Avery P, Wynne H. The value of education and self-monitoring in the management of warfarin therapy in older patients with unstable control of anticoagulation. *Br J Haematol*. 2004;126:557-564.