Conventional and New Oral Anticoagulants in the Treatment of Chest Disease and Its Complications

Pilar Gallego[1,2], Vanessa Roldan[1], and Gregory Y. H. Lip[2]

[1]Hematology and Medical Oncology Unit, Hospital Universitario Morales Meseguer, University of Murcia, Spain; and [2]Haemostasis, Thrombosis, and Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom

Oral anticoagulants block the coagulation cascade either by an indirect mechanism (e.g., vitamin K antagonists) or by a direct one (e.g., the novel oral anticoagulants). Vitamin K antagonists are widely used as treatment of venous thromboembolism and for stroke prevention in patients with atrial fibrillation. Although low molecular weight heparin remains the first line in venous thromboembolism prophylaxis, more recently the novel oral anticoagulants such as dabigatran (initial dose of 110 mg within 1–4 h after surgery, followed by the full dose of 220 mg once daily), rivaroxaban (dose of 10 mg once daily, with the first dose administered 6–10 h after the surgery), and apixaban (dose of 2.5 mg twice daily, starting 12–24 h after surgery, but available only in Europe) are approved for prophylaxis in patients undergoing major orthopedic surgery. The period in which thromboembolic risk abates remains uncertain, and trials of extended therapy are still ongoing. After showing at least noninferiority to warfarin in RE-LY, ROCKET-AF, and ARISTOTLE trials, dabigatran (110 or 150 mg twice daily), rivaroxaban (20 or 15 mg once daily), and apixaban (5 mg twice daily), respectively, were approved also for stroke prevention in patients with atrial fibrillation. While awaiting long-term safety data, the choice among all these available therapies should be based on patient preferences, compliance, and ease of administration, as well as on local factors affecting cost-effectiveness.

Keywords: oral anticoagulants; venous thromboembolism; atrial fibrillation

Since the application of leeches, physicians have long pursued "blood fluidity" as a treatment for various maladies. With time, deeper understanding of hemostasis combined with increasing thrombotic disease in the population provided the basis for modern approaches: insightful studies of a new hemorrhagic disease in cattle in Canada in the early 1920s suggested that spoiled sweet clover contained a hemorrhagic agent (1). Subsequently, investigators at the University of Wisconsin isolated, characterized, and synthesized the active agent, dicumarol, in 1941 (1). Further efforts to develop an effective rat poison resulted in the synthesis of warfarin (named after the Wisconsin Alumni Research Foundation), which was approved for medical use in 1954, and now, 60 years later, the novel oral anticoagulants (NOACs) have reached clinical practice (1).

(*Received in original form January 23, 2013; accepted in final form April 30, 2013*)

This article is part of the Modern Pharmacotherapy of Lung Disease series.

Correspondence and requests for reprints should be addressed to Gregory Y. H. Lip, M.D., University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham, B18 7QH, UK. E-mail: g.y.h.lip@bham.ac.uk

Am J Respir Crit Care Med Vol 188, Iss. 4, pp 413–421, Aug 15, 2013

Originally Published in Press as DOI: 10.1164/rccm.201301-0141PP on May 14, 2013
Internet address: www.atsjournals.org

MECHANISMS OF ACTION

Oral anticoagulants halt the coagulation cascade, as shown in Figure 1, either by an indirect mechanism (e.g., vitamin K antagonists [VKAs]) or by a direct mechanism (e.g., the NOACs, such as direct thrombin inhibitors or Factor Xa inhibitors).

The VKAs inhibit the vitamin K oxide reductase enzyme complex (VKORC) and thus halt multiple steps of the coagulation cascade by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide, needed for the γ-carboxylation of glutamate residues on some coagulation proteins (factors II, VII, IX, and X, thus named vitamin K-dependent), eventually leading to the hepatic production of proteins with impaired coagulation activity (2, 3).

In contrast to the VKAs or even heparins (whose anticoagulant effect is due to activation of antithrombin), NOACs act by direct inhibition of their targeted substrate. For example, dabigatran inhibits thrombin directly, by binding to its active catalytic site (both to free and fibrin-bound thrombin), thus blocking interactions with its substrates (4). Rivaroxaban and apixaban are both reversible, specific active-site and directed, inhibitors of activated factor X. The latter interacts with activated factor V for the conversion of prothrombin to thrombin. They can inhibit free factor Xa as well as clot-associated factor Xa and those included in the prothrombinase complex (localized on the surface of activated platelets) (5, 6).

Pharmacokinetics and Pharmacodynamics

Warfarin, the most widely used VKA, is highly water soluble and thus is absorbed from the gastrointestinal tract with high bioavailability. It undergoes oxidative metabolism by liver enzymes of the cytochrome P450 system after a half-life of 36 to 42 hours (7). Other VKAs differ from warfarin mainly in a shorter (or longer) half-life, but for all of the agents within this class, the response to a fixed dose is variable, as it depends on genetic (polymorphisms affecting either cytochrome p450 system, as 2CYP9 *1, *2, and *3; or vitamin K oxide reductase enzyme complex, as rs2323991) and environmental factors. Thus, calculating the initial dose of VKA assisted by pharmacogenetic information could be the path to personalized medicine (8). Indeed, dose estimation through a pharmacogenetic algorithm provides more accurate dosing as well as fewer overestimations, especially for patients requiring low doses (21 mg or less of warfarin per week) or high doses (more than 49 mg per week).

However, VKAs are also highly susceptible to drug interactions, which can boost or decrease the anticoagulant effect of warfarin by inhibiting or enhancing, respectively, its clearance, and therefore close monitoring is always needed (9). Situations inhibiting the synthesis of vitamin K-dependent factors (such as liver impairment) entail an increase of the anticoagulant effect, as do those that interfere with hepatic metabolism (such as drug competition or liver congestion). Furthermore, the achieved

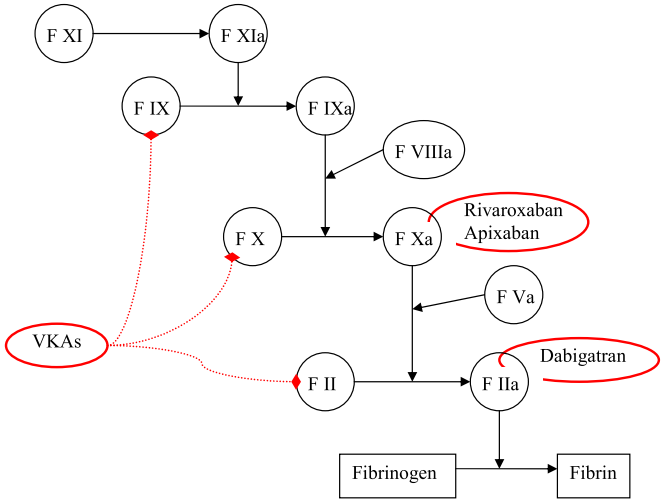

Figure 1. Coagulation cascade and action points of principal anticoagulants. VKA = vitamin K antagonists.

anticoagulation response depends also on fluctuations of the dietary intake of vitamin K as well as on endogenous production of vitamin K by gastrointestinal bacteria. Thus, doses need to be carefully adjusted, after scheduled controls, to achieve the desired international normalized ratio (INR) target of 2.5 [range, 2.0–3.0]).

Pharmacogenetics was believed to be the key to much more accurate warfarin prescription, but the technical difficulties with widespread clinical practice implementation coupled with the fact that some INR monitoring is still needed, and the availability of new oral anticoagulants that do not need monitoring, have slowed the uptake of these pharmacogenetic algorithms in everyday clinical practice.

Unlike VKAs, the dabigatran molecule is highly polar and lipophobic and thus not absorbed from the gut. To improve its poor oral bioavailability, dabigatran is administrated as an absorbable prodrug, dabigatran etexilate. Using tartaric acid, it creates an acid microenvironment favoring drug dissolution and thus enables gut absorption even when the gastric pH is high (best solubility at low pH, so factors affecting gastric pH, such as proton pump inhibitors, may influence its absorption) (10). Dabigatran etexilate is converted into the active drug by blood esterases; its metabolism is independent of the P450 cytochrome and therefore presents fewer drug interactions (11). Eighty-five percent of the dose is excreted by renal clearance, which makes the adjustment of dosage in patients with renal impairment necessary (4).

Rivaroxaban is metabolized via oxidative and hydrolytic pathways involving different classes of enzymes. With a high bioavailability (80%), it has a rapid onset of action, with a half-life of 5 to 12 hours (5, 12). Due to its mechanisms of elimination, rivaroxaban is contraindicated in patients with a creatinine clearance less than 30 mL/min and should be administrated with caution in patients with impaired renal or liver function (12).

In contrast to rivaroxaban or dabigatran, apixaban (also with a high oral bioavailability and rapid oral absorption in the stomach and small intestine) is excreted mostly in the feces after a half-life of 8 to 15 hours, making it more suitable for patients with moderate impairment of renal function (6).

Although NOACs prolong some commonly used laboratory coagulation tests (such as prothrombin time, activated partial thromboplastin time, or thrombin time [TT]), no linear dose response exists at all, and thus only qualitative measures have been done up to now. The high variability in reagent sensitivity to each drug—specific to each test system of each laboratory—leads to a lack of standard measures to quantify their effect. Thus, the anticoagulant intensity of NOACs should not be monitored with any of these laboratory tests, although a normal prothrombin time ratio usually excludes an anticoagulation effect due to rivaroxaban, and a normal activated partial thromboplastin time could exclude one due to dabigatran (Table 1) (13).

The TT measures directly the activity of thrombin and thus is the most sensitive test of dabigatran effects. When normal, TT usually excludes a remaining anticoagulant effect of dabigatran (13). Anticoagulation intensity can also be measured by noncoagulation methods (such as ecarin clotting time, or chromogenic assays), which are only available for research purposes or specialized laboratories (12, 13).

CLINICAL USE

In daily clinical practice, oral anticoagulants are more commonly used both as treatment and as secondary prophylaxis of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation (AF).

The treatment of VTE has two goals: active treatment of the thromboembolic episode (for the first 3 months) and prevention of new episodes (late phase of treatment, with no scheduled stop date). Deep vein thrombosis (DVT) and pulmonary embolism (PE) constitute the spectrum of VTE, and chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome may arise after any VTE.

Because of the potential life-threatening nature of VTE, with an estimated annual incidence of approximately 70 cases per 100,000 in the United States (14), primary prevention is recommended by all guidelines in at-risk hospitalized patients (both medical and surgery patients), unless they are bleeding. Low rates of adherence to recommended thromboprophylaxis regimens have been documented worldwide (15–18).

Classic risk factors for VTE include an elderly age ($\geq$70 yr), active cancer, recent ($\leq$1 mo) surgery or major trauma, immobilization, pregnancy and postpartum, use of oral contraceptives or hormonal treatment, and antiphospholipid antibody syndrome (19), but some other medical conditions related to inflammatory disorders (such as acute infectious disease, rheumatologic disorders, and inflammatory bowel disease) have also shown a clear association with VTE risk (20). Acute congestive heart failure (New York Heart Association Class III or IV) and acute respiratory disease (respiratory failure or an exacerbation of chronic obstructive pulmonary disease) are also well-recognized risk factors for VTE (20).

Many of these risk factors are actually more frequent and enhanced in hospitalized patients. Until recently, the standard of

TABLE 1. ASSESSMENT OF ANTICOAGULATION EFFECT WITH THE NOVEL ORAL ANTICOAGULANTS

	LMWH	VKA	Dabigatran	Rivaroxaban/Apixaban
APTT	Insensitive (or slight increase)	Prolonged	Prolonged (curvilinear dose–response)	Prolonged (curvilinear dose–response)
PT/INR	No effect	Prolonged (linear relation)	Insensitive	Prolonged (linear dose–response)
TT	Prolonged	Insensitive	Prolonged (linear relation)	Insensitive

Definition of abbreviations: APTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low molecular weight heparin; PT = prothrombin time; TT = thrombin time; VKA = vitamin K antagonists.

care was heparin (mainly low molecular weight heparins [LMWH]) during hospitalization.

Prophylaxis in Orthopedic Surgery Patients

For patients undergoing major orthopedic surgery, the period of highest risk seems to be 3 to 7 days after the surgical procedure (21). Thromboprophylaxis is then recommended in moderate/high thrombotic risk patients for 10 to 14 days, except patients undergoing knee arthroscopy, in which no primary thromboprophylaxis is needed.

In the Regulation of Coagulation in Major Orthopedic surgery reducing the Risk of DVT and PE (RECORD), clinical trial program consisting of four consecutive phase III clinical trials comparing rivaroxaban with enoxaparin for the primary prevention of VTE in patients undergoing orthopedic surgery (either total hip or total knee replacement), with more than 12,700 enrolled patients, rivaroxaban was superior to standard care with enoxaparin for VTE prevention and all-cause mortality (0.4% for rivaroxaban-treated group vs. 0.8% for enoxaparin, $P < 0.001$) (22). However, rivaroxaban did not show any significant difference with regard to major bleeding (0.3 vs. 0.2%, respectively) (22).

In a similar way, the ADVANCE trial (study of an investigational drug for the prevention of thrombosis-related events following knee replacement surgery) demonstrated lower rates of VTE (1.4% in apixaban-treated group and 3.9% in enoxaparin; relative risk [RR], 0.36; 95% confidence interval [CI], 0.22–0.54; $P < 0.001$) without increased bleeding (4.8 and 5%, respectively) for apixaban against warfarin (23).

Dabigatran has shown noninferiority against enoxaparin regarding total VTE prevention and all-cause mortality in several clinical trials (RE-NOVATE and RE-MODEL), with a similar safety profile (no significant difference regarding bleeding or liver damage) (24).

Although LMWH remains the first-line treatment, some NOACs have already been approved for VTE primary prophylaxis in patients undergoing major orthopedic surgery, based on results from recent large randomized clinical trials (*see* Tables 2–5). Of these NOACs, we can use dabigatran (initial dose of 110 mg within 1–4 h after surgery, followed by the full dose of 220 mg once daily), rivaroxaban (dose of 10 mg once daily, with the first dose administered 6–10 h after the surgery), and apixaban (dose of 2.5 mg twice daily, starting 12–24 h after surgery, but approved only in Europe) (24).

Prophylaxis in Acutely Medically Ill Patients

The MAGELLAN study, a trial of VTE prophylaxis in medically ill patients, compared rivaroxaban to enoxaparin in medically ill patients (treated for 6–14 d) demonstrated lower rates of VTE for the rivaroxaban-treated group. However, an increase in treatment-related major and clinically relevant nonmajor bleeding with rivaroxaban led to a nonsignificant net clinical benefit of this drug (25).

In a similar way, the ADOPT trial (Apixaban Dosing to Optimize Protection from Thrombosis) compared apixaban at a dose of 2.5 mg twice daily (for 30 d) against enoxaparin (as standard care for 14 d), showing a small reduction in primary outcomes (a composite of both symptomatic and asymptomatic VTE, and related mortality, which occurred in 2.71% of apixaban-treated patients and in 3.06% of those treated with enoxaparin [RR with apixaban, 0.87; 95% CI, 0.62–1.23; $P = 0.44$]). However, apixaban was associated with higher rates of bleeding at day 30 (7.73% for the apixaban group and 6.81% for enoxaparin [RR, 1.13; 95% CI, 0.95–1.34; $P = 0.18$]) (26).

VTE Treatment

After a PE, mortality rates are less than 10% in patients receiving adequate anticoagulation, and thus the actual standard of care includes heparin (LMWH or unfractionated heparin) used at the beginning of oral anticoagulation and a VKA when feasible (mainly no bleeding complications after surgery), with an overlapping administration until the targeted INR (>2 for at least 24 h) is reached (27, 28). With the newer drugs, such as rivaroxaban, no overlap is needed, as it can be used as single drug for the whole VTE treatment period (and only needing a dose decrease) (27, 29).

Several trials in patients with VTE have shown the noninferiority of dabigatran to warfarin in the treatment and prevention of recurrent VTE or related death in patients with acute symptomatic VTE, with results ranging from 1.8 to 2.4% for the dabigatran-treated groups and ranging from 1.3 to 2.1% in enoxaparin-treated groups (24). However, the rates of major

TABLE 2. CLINICAL TRIALS WITH THE NOVEL ORAL ANTICOAGULANTS: VENOUS THROMBOEMBOLISM PROPHYLAXIS

Clinical Trial	RE-NOVATE	RE-MODEL	ADVANCE	RECORD	STARS
Patients	Hip replacement	Knee replacement	Orthopedic surgery	Hip and knee replacement	Orthopedic surgery
Study design	Randomized double-blind controlled trial Multicenter, international	Randomized double-blind controlled trial Multicenter, international	Randomized double-blind controlled trial Multicenter, international	Randomized, double-blind, phase III study Multicenter, international	Randomized double-blind controlled trial Multicenter, Japan
Participants	RE-NOVATE: 3,494 RE-NOVATE II: 2,055	2,076	ADVANCE1: 3,195 ADVANCE2: 3,057 ADVANCE3: 5,407	RECORD1-2: 7,050 RECORD3-4: 5,679	523
Follow-up	28-35 d	90 d	95 d	36 (30–42) d	25–35 d
Primary efficacy end point	Total VTE + all-cause mortality	Total VTE + all-cause mortality	Total VTE incidence and related mortality		Symptomatic VTE incidence and related mortality
Safety end point	Major bleeding	All bleeding	Major bleeding	All bleeding	Major and clinically significant bleeding
Drugs	Dabigatran 150 mg OD Dabigatran 220 mg OD Enoxaparin 40 mg SC OD	Dabigatran 150 mg OD Dabigatran 220 mg OD Enoxaparin 40 mg SC OD	Apixaban 2.5 mg BID Enoxaparin 40 mg SC OD	Rivaroxaban 10 mg OD Enoxaparin 40 mg SC OD	Edoxaban 30 mg OD Enoxaparin 20 mg SC OD
Results	Both dabigatran doses noninferior for efficacy ($P < 0.001$) No differences in bleeding rates for both doses compared to enoxaparin	Noninferiority of dabigatran	Lower rates of VTE with apixaban Similar bleeding rates	Superior to enoxaparin for VTE prevention ($P < 0.001$) No differences in bleeding rates	Lower rates of VTE with edoxaban Nonsignificant differences regarding bleeding

Definition of abbreviations: BID = twice daily; OD = once daily; SC = subcutaneous; VKA = vitamin K antagonists; VTE = venous thromboembolism.

TABLE 3. CLINICAL TRIALS WITH THE NOVEL ORAL ANTICOAGULANTS: VENOUS THROMBOEMBOLISM TREATMENT

Clinical Trial	RE-COVER	EINSTEIN-PE	AMPLIFY
Patients	Previous treated VTE	Previous treated VTE	Previous DVT or PE
Study design	Randomized double-blind multicenter controlled trial	Randomized open-label multicenter	Randomized double-blind
Participants	RE-COVER: 2,564 RE-COVER II:1,279	4,832	4,816
Follow-up	6 mo	9 mo	Not yet completed
Primary efficacy end point	Symptomatic recurrent VTE and related death	Symptomatic recurrent VTE	Recurrent VTE or death
Safety end points	Major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding
Drugs	Dabigatran 150 mg BID VKA	Rivaroxaban 15 mg BID 3 wk + 20 mg OD Enoxaparin + VKA	Apixaban 10 mg BID 7 d + 5 mg OD 6 mo Enoxaparin 1 mg/kg SC OD + VKA 6 mo
Results	Noninferiority of dabigatran No differences regarding bleeding	Rivaroxaban noninferior for preventing recurrent VTE Lower rate of major bleeding for rivaroxaban	Not yet completed

Definition of abbreviations: BID = twice daily; OD = once daily; SC = subcutaneous; VKA = vitamin K antagonists; VTE = venous thromboembolism.

bleeding were comparable in both groups (1.6 to 0.9% vs. 1.9 to 0.2% in dabigatran and warfarin, respectively) (24).

In the EINSTEIN trials, rivaroxaban 15 mg twice daily showed lower rates of VTE recurrence (2.1 vs. 3.0% in VKA-treated group) as well as lower bleeding rates, and therefore an extension was pursued comparing rivaroxaban 6- versus 12-month treatment, showing lower recurrence rates for 12 months (1.3 vs. 7.1% in placebo patients). In both cases, no significant differences were found in bleeding rates (24, 29).

Prolonged Therapy

The risk of venous thromboembolism rarely abates by the time a patient is ready for discharge home, and they often receive less physical therapy after discharge than during admission. In fact, risk of recurrence has been shown to be highest in the first 6 to 12 months after the initial episode, and a certain level of risk may continue for 10 years (30). Thus, the optimal duration of anticoagulation therapy remains uncertain, requiring a balance between the estimated risk of recurrence after treatment discontinuation (which may vary according to the individual risk of the patient, existing precipitating factors for VTE, and by the duration of initial therapy [14]) and the risk of subsequent bleeding complications while on treatment.

Extended treatment regimens have been recommended in light of the recent clinical trial results with the NOACs. For example, event rates of VTE at Day 30 according to clinical trial data ranged from 3% (in the ADOPT trial) to 5 to 6% (in the EXCLAIM [Extended Clinical Prophylaxis in Acutely Ill Medical Patients with prolonged immobilization] and MAGELLAN trials, respectively) (25). These highlight that the risk of VTE increases beyond the time of hospital discharge (25), and more

TABLE 4. CLINICAL TRIALS WITH THE NOVEL ORAL ANTICOAGULANTS: EXTENDED TREATMENT

Clinical Trial	RE-MEDY	ADOPT	AMPLIFY	MAGELLAN	EINSTEIN Extension
Patients	Previously treated VTE (at least 3 mo)	Medically ill	VTE previously treated (for 6–12 mo)	Medically ill	Medically ill after 3 mo treatment for VTE
Study design	International multicenter randomized double-blind controlled trial	International multicenter randomized double-blind controlled trial	Randomized, double-blind	International, randomized, blinded, controlled trial	Randomized controlled trial
Participants	2,866	6,524	2,486	8,101	1,197
Follow-up	3 cohorts: <18 mo, 18 mo, and >18 mo	90 d	13 mo	90 d	12 mo
Primary efficacy end point	Composite of recurrent symptomatic VTE and related mortality	Composite of recurrent total VTE incidence and related mortality	Composite of recurrent symptomatic VTE and related mortality	Composite of recurrent total VTE incidence and related mortality	Recurrent VTE incidence
Safety end points	Major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding	Major bleeding Composite of major and nonmajor clinically significant bleeding	Major and nonmajor clinically significant bleeding	Major bleeding
Drugs	Dabigatran 150 mg BID 36 mo	Apixaban 2.5 mg BID for 30 d	Apixaban 2.5 mg BID	Rivaroxaban 10 mg OD	Rivaroxaban 10 mg OD 6 mo
	Warfarin 36 mo	Enoxaparin 40 mg SC OD	Apixaban 5 mg BID	Enoxaparin 40 mg SC OD	Rivaroxaban 10 mg OD 12 mo
			Placebo		Placebo
Results	Lower rate of recurrent VTE with dabigatran	Lower rates of VTE and related mortality	Both apixaban doses were superior with respect to efficacy ($P < 0.001$)	Lower rates of VTE and mortality	Lower rates of VTE incidence (rivaroxaban superior to placebo, $P < 0.001$)
	Significant more acute coronary syndrome with dabigatran	Higher rates of bleeding at Day 30	Similar rates of bleeding in the 3 groups	Increased bleeding rates	No significant differences regarding bleeding
				Nonsignificant net clinical benefit	

Definition of abbreviations: BID = twice daily; OD = once daily; SC = subcutaneous; VKA = vitamin K antagonists; VTE = venous thromboembolism.

TABLE 5. CLINICAL TRIALS WITH THE NOVEL ORAL ANTICOAGULANTS: PATIENTS WITH ATRIAL FIBRILLATION

Clinical Trial	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI
Participants	18,113	14,264	18,201	21,107
Study design	Open-labeled, noninferiority	Randomized, double-blind, noninferiority	Double-blind, noninferiority	Randomized, double-blind, international, noninferiority
Patients	Non-valvular AF + 1 more risk factor	$CHADS_2$: 3.5	Nonvalvular AF + 1 more risk factor	
	$CHADS_2$: 2.1		$CHADS_2$: 2.1	
Follow-up	24 mo	707 d (1.9 yr)	1.8 yr	24 mo
Primary efficacy end point	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Safety end points	Major bleeding	Major and nonmajor clinically significant bleeding	Major bleeding	Major and nonmajor clinically significant bleeding
Drugs	Dabigatran 110 mg BID	Rivaroxaban 20 mg OD	Apixaban 5mg BID	Edoxaban 30 mg OD
	Dabigatran 150 mg BID	Warfarin	Warfarin	Edoxaban 60 mg OD
	Warfarin			Aspirin
Results	Noninferior in the efficacy outcome	Noninferior regarding efficacy and safety	Lower rates of stroke	Numerical increase in all bleeding across the dose range, but not significant
	Lower rates of bleeding for dabigatran 110 mg BID	Lower rates of intracranial bleeding for rivaroxaban	Lower major bleeding	No significant differences in stroke or systemic embolism
	No differences in bleeding for dabigatran 150 mg BID and warfarin		Lower mortality rates	

Definition of abbreviations: BID = twice daily; OD = once daily; SC = subcutaneous; VKA = vitamin K antagonists; VTE = venous thromboembolism.

precise risk-stratification methods are perhaps needed to identify a more defined spectrum of medically ill patients who may benefit from extended prophylaxis, even if bleeding may occur.

A recent trial on apixaban (AMPLIFY) provides evidence for continuing anticoagulation therapy for an additional 12 months beyond the initial 6-month treatment (31). Also, extended secondary prophylaxis with dabigatran in RE-COVER trial was associated with risk reduction for recurrent VTE compared with placebo (in patients who had already received 6–18 mo of anticoagulant therapy for a VTE). Unfortunately, higher rates of clinically relevant bleeding led to no net benefit of extended therapy (32).

Moreover, a recent metaanalysis implies that dabigatran was associated with a higher risk of myocardial infarction or acute coronary events compared with warfarin, although no significant differences were found between dabigatran and placebo, suggesting a protective role of warfarin rather than an adverse effect of dabigatran (24, 33, 34).

Atrial Fibrillation

The need for long-term anticoagulation in patients with AF is already well known, and until recently, VKAs were the only option to reduce stroke risk.

The RE-LY trial led to the approval of dabigatran after showing its noninferiority to warfarin for preventing stroke or systemic embolism (rate of 1.53% for dabigatran 110 mg vs. 1.11% in dabigatran 150 mg group vs. 1.69% for the warfarin-treated patients; $P < 0.001$ in both cases). Regarding major bleeding rates, the higher dose of dabigatran showed no difference compared with warfarin (3.11 vs. 3.36%, respectively), although the group treated with lower dose of dabigatran had 20% lower bleeding rates (2.71 vs. 3.36% in warfarin-treated group, $P = 0.003$) (35).

The ROCKET-AF trial showed the noninferiority of rivaroxaban to warfarin, with rates of stroke and systemic embolism of 1.7% for rivaroxaban-treated patients (vs. 2.2% in warfarin-treated patients). Although no significant differences were found regarding major bleeding, rivaroxaban-treated patients had lower rates of intracranial bleeding (0.5 vs. 0.7% in warfarin-treated patients, $P = 0.02$) (36).

Apixaban was found to be superior to warfarin in the ARISTOTLE trial, for stroke prevention (1.6 vs. 1.27%, $P = 0.01$) as well as for major bleeding (2.13 vs. 3.09%, $P < 0.001$) and lower all-cause mortality (3.52 vs. 3.94 in warfarin-treated patients) (37).

Thus, NOACs have been shown to be at least noninferior to warfarin in stroke prevention and therefore may be used safely in patients with new AF, as all the NOACs had lower hemorrhagic stroke and intracranial bleeding. Patients already taking VKA treatment, with very well-controlled anticoagulation (with high time in therapeutic range), probably have little to gain by switching to a NOAC, especially because long-term data are needed to provide additional reassurance with, for example, the protective effect of warfarin against coronary events compared with NOACs (33, 38).

Other Clinical Indications

For VTE treatment and prophylaxis, the role of oral anticoagulation is clear, as well as for patients with AF. Still, a debate remains over the actual potential benefit of using antithrombotic therapy in heart failure in sinus rhythm. Of note, heart failure is a common event among patients with chest disease and is also associated with AF and a twofold increased risk of developing a VTE (39). There are a limited number of randomized clinical trials that have tested the efficacy of antithrombotic therapy in patients with heart failure in sinus rhythm (39), and VKA use in heart failure requires some caution. Liver congestion due to right heart failure may lead to an erratic INR control, which may help bleeding risk.

Prognosis in VTE

The main problem for VTE outcomes assessment is that asymptomatic patients are not routinely investigated for small VTE events. The fibrin degradation product D-dimer is highly sensitive (>95%) in excluding acute DVT or pulmonary embolism and thus should be used as first screening in symptomatic patients. In many diagnostic pathways, D-dimer testing is used as one of the tests to determine the probability of VTE, in conjunction with clinical assessment (based on patient history and clinical findings), before confirmation with imaging studies.

Although D-dimer is typically elevated in patients with acute DVT, levels may also be increased in a variety of nonthrombotic disorders (e.g., malignancy, disseminated intravascular coagulation, increasing age, infection, pregnancy, after surgery or trauma, inflammatory conditions, atrial fibrillation, renal failure, and stroke), which are frequent in hospitalized patients, Thus, D-dimer is a sensitive but nonspecific marker for VTE.

Treatment effectiveness can be further assessed by the limitation of thrombus extension, detected by computed tomography angiography, which is the main imaging modality in pulmonary embolism. Multidetector computed tomography angiography allows exclusion of pulmonary embolism without additional compression ultrasonography of the leg (40).

Limitations of the NOACs

Advanced age should be considered when defining the appropriate patients for NOACs, as patients included in the randomized clinical trials tend to be younger than those in daily practice (e.g., a mean age ranging from 55 yr in RE-COVER or RE-MEDY up to 73 yr in ROCKET-AF). This is a special concern, because drug clearance is usually inversely correlated with age, becoming particularly important in patients taking, for example, dabigatran.

Special attention should also be directed to those populations excluded from the clinical trials, such as underweight or obese patients; for example, the average weight in major phase III trials has been 80 kg, and weight is one of the criteria to be considered for dose adjustment of apixaban. Furthermore, limited data are available in pediatric patients or during pregnancy, and the NOACs are contraindicated.

What Do the Guidelines Say?

Updated European and American Guidelines recommend unfractionated heparin, LMWH, or fondaparinux for at least 5 days for the acute treatment of PE, followed by VKAs for at least 3 months; LMWH followed by VKAs still remains the standard of care for stroke prevention in patients with AF (Table 6) (27, 28).

After the results of EINSTEIN PE trial (a randomized, open-label, event-driven, noninferiority study designed to evaluate whether rivaroxaban was at least as effective as enoxaparin/VKA for the prevention of recurrent venous thromboembolic events in patients with acute symptomatic PE [with or without symptomatic DVT]) (29), the 9th American College of Chest Physicians guidelines also include rivaroxaban as single treatment of VTE, owing to the reduced burden and improved clinical outcomes associated with its use (27). Other new anticoagulants are not recommended as first choice by either guideline until more studies assess long-term safety. However, some clinical trials were published simultaneously or subsequent to the 9th American College of Chest Physicians guidelines, such as MAGELLAN, AMPLIFY-EXT or RE-MEDY/RE-SONATE.

ADVERSE EFFECTS

The primary adverse effect of anticoagulation—and thus the main limiting factor for extended secondary prophylaxis—is the increased risk of bleeding. Although bleeding definitions can sometimes be controversial, the International Society of Thrombosis and Haemostasis defines major bleeding as fatal bleeding, symptomatic bleeding in a critical area or organ, or bleeding causing a decrease in hemoglobin concentration of more than 20 g/L or requiring transfusion of two or more units of blood. All anticoagulant drugs can produce bleeding, especially at the start of treatment because of unmasking previous lesions. The safety of treatment can be improved by encouragement of patient compliance, avoidance of concurrent drugs with potential interactions, and restriction of alcohol ingestion.

The shorter half-life of the NOACs might facilitate the management of bleeding events as well as the control of anticoagulation during interventions or emergency situations. However, the fear of bleeding remains because of the lack of specific antidotes, limiting the therapeutic options to potential nonspecific reversal agents for the management of bleeding or over-anticoagulation, such as prothrombin complex concentrates and activate prothrombin complex concentrates, although data are still sparse (41).

Also, hemodialysis and hemofiltration could be other options for life-threatening bleeding; they are only suitable for patients taking dabigatran, which is dialyzable due to its relatively low (35%) plasma protein binding. The ability of dialysis for dabigatran is unlike rivaroxaban and apixaban, given their high protein binding (both >95%) (41).

If a patient presents with bleeding risk factors (such as active bleeding in the preceding 3 mo, lumbar puncture/epidural/spinal

TABLE 6. EUROPEAN AND AMERICAN GUIDELINE RECOMMENDATIONS

	European Guidelines	ACCP Guidelines
VTE primary prophylaxis		
Nonsurgical		None
Low thrombotic risk		None
High bleeding risk		LMWH
High thrombotic risk		If active bleeding/high bleeding risk→mechanical thromboprophylaxis
Orthopedic		10–14 d LMWH
Total hip/knee arthroplasty		Alternatives: fondaparinux/apixaban/dabigatran/rivaroxaban/VKA
High bleeding risk		No thromboprophylaxis
Arthroscopy		No thromboprophylaxis
Nonorthopedic		
Low thrombotic risk		None
Moderate/high thrombotic risk		LMWH
		If active bleeding/high bleeding risk→mechanical thromboprophylaxis
VTE treatment		
First-line	LMWH or fondaparinux at least 5 d + early initiation VKA	LMWH + early initiation VKA
Thrombolytic therapy	High-risk PE associated with cardiogenic shock and/or hypotension	Only if acute PE associated with hypotension and no bleeding risk
Length		
Low or moderate bleeding risk	3 mo + reevaluation	Extended therapy
High bleeding risk	3 mo	3 mo
Second episode	Long-term anticoagulation	

Definition of abbreviations: ACCP = American College of Chest Physicians; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonists; VTE = venous thromboembolism.

anesthesia within the previous 4 h or expected within the next 12 h, acquired bleeding disorders [e.g., acute liver failure], mucosal lesions [e.g., active peptic ulceration, bronchiectasis], acute stroke [within 24 h], thrombocytopenia [platelets $< 75 \times 10^9$/L], uncontrolled systolic hypertension [>230/120 mm Hg] or untreated inherited bleeding disorders [e.g., hemophilia or von Willebrand disease]) or has cancer, the use of oral anticoagulation should be with caution or avoided (20).

Dabigatran should also be avoid in patients with peptic ulcer disease, as it requires an acidic environment for absorption, and its commercial formula leads to increased rates of dyspepsia. Other adverse effects regarding new oral anticoagulants are less well known, and (as mentioned earlier) one recent metaanalysis implies that dabigatran was associated with a higher risk of myocardial infarction or acute coronary events compared with control treatment, although a protective role of warfarin may also be possible (33).

Further studies regarding long-term safety are awaited. Nonetheless, recent "real-world" data for dabigatran are reassuring, at least from a nationwide cohort study from Denmark (42). In a large post-approval nationwide clinical cohort, there were similar stroke/systemic embolism and major bleeding rates with dabigatran (both doses) when compared with warfarin (42). Reassuringly, mortality, intracranial bleeding, pulmonary embolism, and myocardial infarction were significantly lower with dabigatran in a propensity-matched comparison against warfarin, even in the subgroup with one or more years of follow-up. Similar reassuring data on bleeding were obtained from a FDA surveillance report (43).

Combination Therapy

Concomitant drugs that may enhance the antithrombotic response, such as antiplatelet drugs, are not recommended for VTE treatment and/or prophylaxis because no evidence of efficacy has been shown, and they increase the risk of bleeding (14, 28, 30).

Regarding the combination of antiplatelet drugs and NOACs, it seems logical to avoid them if possible. However, if antiplatelet therapy is needed, the practitioner must be aware of higher bleeding rates by combination therapy.

If anticoagulation is used, the combination of an oral anticoagulant with an antiplatelet agent is not recommended in patients with chronic (12 mo after an acute event) coronary or other arterial disease, because of a high risk of bleeding and the lack of clear benefit of combination therapy on thrombotic outcomes (39).

COST-EFFECTIVENESS

There is no clear evidence in the current literature to support choosing one form of pharmacoprophylaxis over another in the medical population based on outcomes or from a cost-effectiveness standpoint. The initial higher cost of NOACs should perhaps be overcome somewhat by fewer adverse events and the absence of coagulation monitoring.

Some cost-effectiveness studies among orthopedic patients have shown that rivaroxaban is the most cost-effective option to prevent VTE (44). However, the studies performed among patients with AF have shown conflicting results depending on the country: dabigatran etexilate as a first-line treatment for the prevention of stroke and systemic embolism seems to be cost-effective in the UK (£4,831 vs. £7,090/quality-adjusted life years for warfarin) (45) and is a highly cost-effective alternative in Canada (where dabigatran costs $10,440/quality-adjusted life years) (46).

CONCLUSIONS

Anticoagulant therapy should be started as soon as the clinical suspicion of VTE is confirmed, after individual assessment of bleeding risk. NOACs have shown efficacy and safety, promising advantages in quality of life, and a more convenient use. Thus, the NOACs are increasingly preferred to warfarin therapy in patients unless they have well-controlled time in therapeutic range (TTR) or severe renal impairment (e.g., creatinine clearance < 30 ml/min).

TABLE 7. THE SAMe-TT_2R_2 SCORE FOR PREDICTING PATIENTS THAT WOULD DO WELL ON VKAs, WITH HIGH TIME IN THERAPEUTIC RANGE

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (<60 yr)	1
Me	Medical history*	1
T	Treatment (interacting Rx, eg., amiodarone for rhythm control)	1
T	Tobacco use (within 2 yr)	2
R	Race (nonwhite)	2
Maximum points		8

Definition of abbreviations: Rx = prescriptions; VKAs = vitamin K antagonists. *Two of the following: hypertension, diabetes, myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, hepatic disease, or renal disease.

One challenge is to perhaps identify those patients who could potentially do well on a NOAC or a VKA, with a high TTR. Use of the recently described SAMe-TT2R2 score (Table 7) could potentially help here, given that this score could help predict those who could do well on warfarin (SAMe-TT2R2 score 0–1) or those patients who may have poor anticoagulation control if warfarin is used (SAMe-TT2R2 score ≥ 2) where use of a NOAC could be a better option (47).

Other limitations include the lack of a specific antidote for the NOACs that can be available for drug reversal during excessive bleeding or urgent surgery. Specific antidotes are under early development for dabigatran and the oral Factor Xa inhibitors but are not yet approved clinically. For example, aDabi-Fab is a humanized antibody fragment that can specifically bind dabigatran and reverse its anticoagulant effects, at least experimentally (48). Another possible antidote for the Factor Xa inhibitors is the r-Antidote (PRT064445), which is a catalytically inactive recombinant protein that lacks the membrane-binding γ-carboxyglutamic acid domain of native Factor Xa; this agent retains the ability to bind apixaban and rivaroxaban as well as LMWH-activated antithrombin III (ATIII) (48, 49). The effect is mediated by reducing plasma anti-Factor Xa activity and the non–protein bound fraction of the Factor Xa inhibitor in plasma.

There are also long-term possible concerns of a numerical increase in cardiac events with one NOAC (dabigatran) in some clinical trials. As mentioned above, recent postmarketing data are reassuring (42, 43). As these drugs are increasingly used, long-term clinical experience and postmarketing surveillance will certainly provide additional reassurance.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Francis CW. Warfarin: an historical perspective. *Hematology Am Soc Hematol Educ Program* 2008;251.
2. Whitlon DS, Sadowski JA, Suttie JW. Mechanism of coumarin action: significance of vitamin K epoxide reductase inhibition. *Biochemistry* 1978;17:1371–1377.
3. Stafford DW. The vitamin K cycle. *J Thromb Haemost* 2005;3:1873–1878.
4. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos* 2008;36:386–399.

5. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther* 2005;78:412–421.
6. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, Pinto D, Chen S, Bonacorsi S, Wong PC, *et al*. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos* 2009;37:74–81.
7. Breckenridge A. Oral anticoagulant drugs: pharmacokinetic aspects. *Semin Hematol* 1978;15:19–26.
8. Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, *et al*.; International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;360: 753–764. [Published erratum appears in *N Engl J Med* 361:1613.]
9. Orme M, Breckenridge A. Enantiomers of warfarin and phenobarbital. *N Engl J Med* 1976;295:1482–1483.
10. Stangier J, Stähle H, Rathgen K, Fuhr R. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. *Clin Pharmacokinet* 2008;47:47–59.
11. Hauel NH, Nar H, Priepke H, Ries U, Stassen JM, Wienen W. Structure-based design of novel potent nonpeptide thrombin inhibitors. *J Med Chem* 2002;45:1757–1766.
12. Montoya RC, Gajra A. Current status of new anticoagulants in the management of venous thromboembolism. *Adv Hematol* 2012;2012:856341.
13. Baglin T, Keeling D, Kitchen S; British Committee for Standards in Haematology. Effects on routine coagulation screens and assessment of anticoagulant intensity in patients taking oral dabigatran or rivaroxaban: guidance from the British Committee for Standards in Haematology. *Br J Haematol* 2012;159:427–429.
14. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–593.
15. Tapson VF, Decousus H, Pini M, Chong BH, Froehlich JB, Monreal M, Spyropoulos AC, Merli GJ, Zotz RB, Bergmann JF, *et al*.; IMPROVE Investigators. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;132: 936–945.
16. Cohen AT, Tapson VF, Bergmann JF, Goldhaber SZ, Kakkar AK, Deslandes B, Huang W, Zayaruzny M, Emery L, Anderson FA Jr; ENDORSE Investigators. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008;371:387–394.
17. Tooher R, Middleton P, Pham C, Fitridge R, Rowe S, Babidge W, Maddern G. A systematic review of strategies to improve prophylaxis for venous thromboembolism in hospitals. *Ann Surg* 2005;241:397–415.
18. Amin A, Stemkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? *J Thromb Haemost* 2007;5:1610–1616.
19. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, Le H, *et al*.; American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e195S–e226S.
20. Dobromirski M, Cohen AT. How I manage venous thromboembolism risk in hospitalized medical patients. *Blood* 2012;120:1562–1569.
21. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107:I22–I30.
22. Ageno W. Rivaroxaban for the prevention of venous thromboembolism following major orthopedic surgery: the RECORD trials. *Expert Rev Cardiovasc Ther* 2009;7:569–576.
23. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487–2498.
24. Ahrens I, Peter K, Lip GY, Bode C. Development and clinical applications of novel oral anticoagulants. Part I. Clinically approved drugs. *Discov Med* 2012;13:433–443. (Review).
25. Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G, Schellong S, Spyropoulos AC, *et al*.; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368:513–523.
26. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, Weitz JI; ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365: 2167–2177.
27. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, *et al*. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141:e419S–e494S.
28. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, *et al*.; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008;29:2276–2315.
29. Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, *et al*.; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–1297.
30. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000;160:761–768.
31. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; PLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699–708.
32. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–2352.
33. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012;172:397–402.
34. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709–718.
35. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, *et al*.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
36. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, *et al*.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
37. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, *et al*.; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365: 981–992.
38. Potpara TS, Lip GYH, Apostolakis S. New anticoagulant treatments to protect against stroke in atrial fibrillation. *Heart* 2012;98:1341–1347.
39. Lip GY, Ponikowski P, Andreotti F, Anker SD, Filippatos G, Homma S, Morais J, Pullicino P, Rasmussen LH, Marin F, *et al*.; ESC Task Force. Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A joint consensus document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis. *Eur J Heart Fail* 2012;14:681–695.
40. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012;379:1835–1846.
41. Miesbach W, Seifried E. New direct oral anticoagulants—current therapeutic options and treatment recommendations for bleeding complications. *Thromb Haemost* 2012;108:625–632.
42. Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M, Lip GY. Efficacy and safety of dabigatran etexilate and warfarin in

'real world' patients with atrial fibrillation: a prospective nationwide cohort study. *J Am Coll Cardiol* 2013;61:2264–2273.
43. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 2013;368:1272–1274.
44. McCullagh L, Tilson L, Walsh C, Barry M. A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the Irish healthcare setting. *Pharmacoeconomics* 2009;27:829–846.
45. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, Cowie MR. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. *Heart* 2012;98:573–578.
46. Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb JM. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost* 2011;105:908–919.
47. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin: the SAMe-TT2R2 (sex female, age less than 60, medical history, treatment [interacting drugs, eg amiodarone for rhythm control], tobacco use [doubled], race [doubled] score. *Chest* (In press)
48. Schiele F, van Ryn J, Canada K, Newsome C, Sepulveda E, Park J, Nar H, Litzenburger T. A specific antidote for dabigatran: functional and structural characterization. *Blood* 2013;121:3554–3562.
49. Lu G, Deguzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, *et al*. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013;19:446–451.