HOSPITAL CHRONICLES 2013, 8(4): 151–163

EDITORIAL

Novel Oral Anticoagulants for Stroke Prophylaxis in Non-Valvular Atrial Fibrillation: Agent Selection and Patient Monitoring

Antonis S. Manolis, MD,[1] Theodora A. Manolis, MD,[2] Helen Melita, MD[3]

[1]*Evagelismos Hospital, Athens,*
[2]*Patras University Medical School, Patras, &*
[3]*Onassis Cardiac Surgery Center, Athens, Greece*

KEY WORDS: *novel anticoagulants; dabigatran; rivaroxaban; apixaban; edoxaban; atrial fibrillation; stroke; systemic thromboembolism*

ABBREVIATIONS
AF = atrial fibrillation
aPTT = activated thromboplastin time
CIED = cardiac implantable electronic devices
CrCl = creatinine clearance
eGFR = estimated glomerular filtration rate
ICD = implantable cardioverter defibrillator
INR = international normalized ratio
MI = myocardial infarction
NOAC = novel oral anticoagulant(s)
PCC = prothrombin complex concentrate
P-gp = P-glycoprotein
PPI = proton pump inhibitor(s)
TEE = transesophageal echocardiography
TIA = transient ischemic attack
TTR = time in therapeutic range
VKA = vitamin K antagonists
VTE = venous thromboembolism

Address correspondence to:
Antonis S. Manolis, MD, First Department of Cardiology, Evagelismos Hospital, Athens, Greece; E-mail: asm@otenet.gr

Manuscript received September 8, 2013; Revised manuscript accepted September 27, 2013

Conflict of Interest: none declared

ABSTRACT

Ensuing the recent approval of novel oral anticoagulant agents (NOACs) in Greece and many other countries for stoke prevention in patients with non-valvular atrial fibrillation (AF), an overview is herein attempted of some practical points concerning their use with regards to agent selection and patient monitoring. There are currently 3 NOACs, dabigatran (a direct thrombin inhibitor), rivaroxaban and apixaban (direct factor Xa inhibitors), among which physicians are called upon to choose if they decide to use these more expensive agents in lieu of the much cheaper classic vitamin K antagonists (VKA), either to initiate or switch anticoagulant therapy in patients with AF. All three NOACs were evaluated in large randomized trials and found to be effective anticoagulants in patients with non-valvular AF, with comparable to or improved efficacy over warfarin, and a significant reduction in intracranial hemorrhage compared to warfarin. There was even a significant (apixaban) or strong trend toward reduction (dabigatran and rivaroxaban) in all-cause mortality. These agents are easier to administer in fixed once or twice daily doses without the need for routine coagulation monitoring. However, in addition to their much higher pricing, it is important to appreciate the potential challenges and limitations posed by their use and to follow recommendations and guidelines, in order to achieve optimal patient outcomes.

INTRODUCTION

Apropos with the most recent approval of novel oral anticoagulant agents (NOACs) in Greece and many other countries for stoke prevention in patients with non-valvular atrial fibrillation (AF), we attempt to summarize herein some practical points concerning their use. There are currently 3 NOACs, dabigatran (Pradaxa®; Boehringer Ingelheim), rivaroxaban (Xarelto®; Bayer) and apixaban (Eliquis®; Bristol Myers Squibb), among which physicians are called upon to choose if they decide to use them in lieu of the classic vitamin K antagonists (VKA), either to commence or switch anticoagulant therapy in patients with AF.[1,2] A fourth agent, edoxaban (Lixiana®; Daiichi Sankyo), is also going to be available in the near future. The -gatrans are direct thrombin inhibitors, while the -xabans are direct factor Xa inhibitors. We will not deal herein with the controversial issue whether one should opt for a new (more expensive) or a classic (much cheaper)

agent, but rather we will discuss the issue of agent selection and patient monitoring, should one decide to use one of the novel agents. All three NOACs were evaluated in large randomized trials and found to be effective anticoagulants in patients with non-valvular AF, with comparable to or improved efficacy over warfarin.[3-5] Notably all three new agents showed a significant reduction in intracranial hemorrhage compared with warfarin. There were also either significant (apixaban) or strong trends toward reductions (dabigatran and rivaroxaban) in all-cause mortality. These agents are easier to administer, as they can be given in fixed once or twice daily doses without the need for routine coagulation monitoring.

RANDOMIZED STUDIES

Dabigatran (Pradaxa®) was evaluated in the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial comprising 18,000 patients.[3] Two doses of the drug (110 mg bid and 150 mg bid) were each compared with warfarin. Both doses were noninferior to warfarin regarding the prevention of stroke and/or embolization, while the 150 mg dose was superior to warfarin. There was less major bleeding with dabigatran 110 mg than with warfarin, whereas dabigatran 150 mg had similar major bleeding. In a subanalysis of RE-LY, with better control of the international normalized ratio (INR) of 2.0-3.0 and an increasing time in therapeutic range (TTR) of the INR in the warfarin group, fewer ischemic strokes were observed, but not fewer intracranial hemorrhages compared with dabigatran.[6]

Rivaroxaban (Xarelto®) was compared with warfarin in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial comprising 14,000 patients.[4] A dose of either 20 mg daily or 15 mg daily depending on renal function was employed. Rivaroxaban was noninferior to warfarin with regards to stroke and/or embolism. Major bleeding rates were not different.

Apixaban (Eliquis®) was compared with warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial comprising 18,000 patients.[5] Apixaban dose was 5 mg bid or for individuals at higher bleeding risk 2.5 mg bid. Overall, it was superior to warfarin in terms of stroke and/or embolism and in major bleeding.

Edoxaban (Lixiana®), administered in doses of 30 mg or 60 mg once daily, is being evaluated in the ENGAGE AF-TIMI 48 (**E**ffective a**N**ticoa**G**ulation with Factor X**A** Next **GE**neration in **A**trial **F**ibrillation) trial for the prevention of stroke and systemic embolic events in patients with non-valvular AF.[7] Edoxaban is currently approved only in Japan, since 2011, for the prevention of venous thromboembolism (VTE) after major orthopedic surgery. Results from the ENGAGE AF-TIMI 48 study will be presented at the American Heart Association Scientific Sessions in November 2013.

In a meta-analysis of the above 3 randomized trials (RE-LY, ROCKET-AF and ARISTOTLE)[8] that compared NOACs with warfarin in AF, among a total of 50,578 patients, NOACs significantly decreased stroke or systemic embolism (2.8% vs 3.5%, odds ratio -OR 0.82, P<0.001), death (6.0% vs 6.3%, OR 0.88, P=0.001) and stroke (2.4% vs 3.0%, OR 0.79, P<0.001). The reduction in stroke was mainly driven by fewer hemorrhagic strokes (0.3% vs 0.8%, OR 0.79, P<0.001). Major bleeding occurred in 5.0% and 5.6% of patients in the NOACs and warfarin groups (OR 0.85, P=NS). NOACs were associated with lower rates of intracranial bleeding (0.6% vs 1.3%, P<0.001) and higher rates of gastrointestinal bleeding (2.3% vs 1.3%, P=0.036). The authors concluded that in patients with non-valvular AF, NOACs decrease stroke or systemic embolism, hemorrhagic stroke and mortality, with similar risk of major bleeding compared to warfarin. A similar meta-analysis of the same 3 studies indicated that patients randomized to NOACs had a decreased risk for all-cause stroke and systemic embolism (relative risk - RR 0.78), ischemic and other stroke (RR 0.87), hemorrhagic stroke (RR 0.45), and all-cause mortality (RR 0.88).[9] NOACs were associated with a lower risk for intracranial bleeding (RR 0.49). No conclusions could be drawn regarding the risks for major and gastrointestinal bleeding. The authors concluded the NOACs are more efficacious than warfarin for the prevention of stroke and systemic embolism in patients with AF with less risk for intracranial bleeding, and thus appear as promising alternatives to warfarin.[9] In another meta-analysis, the authors concluded that NOACs may reduce overall and cardiovascular mortality, stroke and systemic embolism, together with major and intracranial bleeding compared with warfarin, but these favorable results need to be confirmed in postmarketing studies.[10]

Caution in the use of NOACs is also advised by the authors of another review of 6 randomized studies involving 61,424 patients, 3 studies evaluating NOACs for chronic AF (the same as discussed above), and 3 studies examining the treatment of venous thromboembolism (VTE), all comparing NOACs with adjusted-dose warfarin and all funded by pharmaceutical companies.[11] The authors of this review indicate that subgroup analyses suggest a higher risk for myocardial infarction (MI) with direct thrombin inhibitors (dabigatran) than with factor Xa inhibitors and an increased bleeding risk for NOACs in patients older than 75 years or those receiving warfarin who have good control.[11] The authors conclude that NOACs are a viable option for patients who need long-term anticoagulation, but treatment benefits compared with warfarin are small and vary depending on the control achieved by warfarin treatment.[11]

WHICH AGENT

Without data from direct comparisons among the three NOACs, it is not proper to recommend one over the other agent. Practice guidelines have recommended a NOAC in preference to or as an alternative to warfarin but have not differentiated among the NOACs.[12-14]

EFFICACY AND SAFETY

From indirect comparisons,[15,16] high-dose (150 mg) dabigatran and apixaban appear superior to rivaroxaban for protection against systemic embolism. With regards to major bleeding, apixaban and low-dose (110 mg) dabigatran seem superior to rivaroxaban and high-dose dabigatran. Thus, when the risk of stroke is high, one may consider dabigatran 150 mg or apixaban; on the other hand, when the risk of bleeding is high, one might opt for apixaban or low-dose dabigatran. "Real world" experience suggests higher bleeding rates with high-dose dabigatran 150 mg compared to low-dose.[17,18]

ELDERLY PATIENTS

In the RE-LY trial, there was no significant interaction between age and type of anticoagulant therapy with regards to protection from thromboembolism. However, with regards to major bleeding, high-dose dabigatran may confer a higher risk in patients older than 75 years, and based on this finding, the Canadian guidelines have proposed the lower dose of dabigatran for the elderly.[14]

For rivaroxaban and apixaban, efficacy and safety are independent of age, and thus age should not affect the choice of these agents. Nevertheless, patients ≥75 years have a higher risk of stroke and might possibly achieve the best balance between efficacy and safety with apixaban.[19]

RENAL FAILURE

Use of NOACs has been recommended at the doses used in the trials for patients with eGFR >30 mL/min (>25 mL/min for apixaban). In Canada, dabigatran has not been approved for eGFR <30, while rivaroxaban was approved at a dose of 15 mg qd for eGFR at 30-49 mL/min. In the US, a dose of dabigatran 75 mg bid and rivaroxaban 15 mg qd have been proposed for patients with eGFR between 15 and 30 mL/min and 15-50 mL/min, respectively. Both the US and Canada have approved apixaban 2.5 mg bid for patients with 2 out of 3 of the following criteria: serum creatinine ≥133 mmol/L (1.5 mg/dL), age ≥80 years, and body weight ≤60 kg. For patients with eGFR 30-50 mL/min, there may a preference for apixaban over dabigatran or rivaroxaban. Finally, NOACs should not be used and VKAs may be a more suitable alternative for AF patients on hemodialysis.[20]

CORONARY ARTERY DISEASE

In the RE-LY trial, a curious finding of higher incidence of myocardial infarction (MI) with dabigatran 150 mg vs warfarin was reported. Meta-analyses of comparative data between dabigatran and warfarin have indeed shown more MI but lower mortality with dabigatran; however, this has not panned out in the "real world" experience of dabigatran.[18] On the other hand, in ROCKET-AF and ARISTOTLE and relevant meta-analyses, there were reductions in MI and all-cause mortality with rivaroxaban or apixaban. Thus, although dabigatran, in comparison with warfarin, has not conferred a worse outcome of ischemic events and despite that mortality is less, it may be prudent to select rivaroxaban or apixaban in patients with unstable coronary artery disease, as suggested in the guidelines of the European Society of Cardiology (ESC).[12]

RISK OF BLEEDING

A very important finding of all trials of NOACs is the fact that intracranial bleeding was significantly less with all these agents. Also, major bleeding was significantly less with 5 mg of apixaban and with dabigatran 110 mg, compared with warfarin, but not with dabigatran 150 mg or rivaroxaban 20 mg. Unfortunately, major gastrointestinal bleeding was significantly greater with dabigatran 150 mg and with rivaroxaban 20 mg compared with warfarin. However, apixaban and dabigatran 110 mg were not associated with increased gastrointestinal bleeding. Thus, apixaban or low-dose dabigatran might be preferred in cases of patients being at higher risk of bleeding. An exception might be a case with very high risk of stroke, whereby dabigatran 150 mg could outweigh the risk of major bleeding. In order to decrease the risk of bleeding with NOACs, one should select patients based on the status of their renal function, which should also be monitored during follow-up by checking creatinine clearance once or twice per year, especially in circumstances of exacerbation of heart failure, hypotensive episodes or any event suspected to lead to worsening renal function (hypovolemia, dehydration, co-administration of certain drugs, etc). Data analysis from the ARISTOTLE trial indicate that in patients with AF, renal impairment is associated with increased risk of cardiovascular events and bleeding.[21] However, apixaban, compared with warfarin, reduced the rates of stroke, death, and major bleeding, regardless of renal function; rather, patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban.[21]

OTHER ISSUES

Among patients with AF and previous stroke or transient ischemic attack (TIA), either high-dose dabigatran (150 mg) or apixaban might be the preferable agents. With regards to side-effects, other than major bleeding, a difference in non-hemorrhagic side effects was observed with dabigatran, with significantly more dyspepsia (11.3% vs 5.8%). Thus, in a patient with previous dyspepsia, rivaroxaban or apixaban might be preferable to dabigatran. Regarding patient compliance, the option of once daily dosage might sway drug selection toward

rivaroxaban over dabigatran or apixaban. Recommendations for the lower dose (110 mg bid) of dabigatran pertain to elderly patients (>80 years), patients receiving P-glycoprotein inhibitors (particularly verapamil), patients with compromised renal function (creatinine clearance 30-50 mL/min), and patients with gastrointestinal or esophageal problems that might be complicated by bleeding.

Finally, the cost of all the new agents is much higher compared with the cost of warfarin, but there seem to be no differences among the three available agents. Cost-efficacy analyses are urgently needed for physicians, patients and insurance agencies to further decide on selection of a suitable agent. Some preliminary cost-effectiveness data have been provided by analysis of the RE-LY trial.[22] For low-risk patients for stroke, only aspirin was cost-effective. For patients with a moderate stroke risk rate, warfarin was cost-effective unless the risk of hemorrhage was high or INR control was poor with time in the therapeutic range (TTR) <57%. For patients with a high stroke risk, dabigatran 150 mg bid was cost-effective unless INR control was excellent with warfarin (TTR >73%). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective.[22] These data were further corroborated by recent analyses, whereby the TTR of the INR is crucial in determining cost-efficacy; when TTR is problematic and <64%, then it leaves room for better cost-efficacy of NOACs (e.g. dabigatran 150 mg bid). Ways to increase TTR to >77% (e.g. genotype-guided anticoagulation), provided that quality of life is comparable between warfarin and NOAC, might mitigate the need for more expensive NOAC therapy.[23] However, it all depends on the real cost and pricing of the NOACs, which currently remains high, and maybe prohibitively so for populations afflicted by the economic crisis. If the cost of NOACs is curtailed, then there may be real incentive to use the NOACs and when head-to-head comparisons are made available, one would be able to choose one over the other agent. A recent US study, using published clinical trial data to build a Markov decision model, indicated that for patients ≥70 years old with nonvalvular AF with an increased risk for stroke, normal renal function, and no previous contraindications to anticoagulant therapy, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg may be cost-effective substitutes for warfarin, with apixaban 5 mg being the most cost-effective anticoagulant among the 3 NOACs.[24] The results of this and another study indicate that cost-effectiveness of NOACs is really dependent on drug pricing.[24,25]

LONG-TERM SAFETY / TREATMENT OF BLEEDING

Data are also lacking with regards to the long-term safety of these agents. Some preliminary data are currently emerging. The extension of the RELY trial (RELY-ABLE) indicated that the rates of thrombo-embolic, as well as of hemorrhagic stroke events were similar with the initial trial for dabigatran.[26] However, during 2.3 years of continued treatment with dabigatran after RE-LY, there was a higher rate of major bleeding with dabigatran 150 mg twice daily in comparison with 110 mg bid; rates of stroke and death were similar.

Important potential limitations of NOACs include the following: there is no known antidote, no validated tests exist that can monitor the coagulation effect of these agents, there may be problems with compliance for agents requiring a twice daily dosage, the cost is much higher compared with warfarin and there is a lack of cost-effectiveness studies comparing them to warfarin, and finally there are no head-to-head comparison studies of these new agents. Unfortunately, soon after market approval was granted for dabigatran, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) of the USA received reports of higher incidence compared with warfarin of serious and fatal bleeding events with dabigatran.[17,27] However, following investigation, both agencies finally concluded that the risk profile of dabigatran may remain the same as bleeding rates were not higher than those with warfarin.[17,27]

When severe bleeding occurs while on NOAC, the offending agent is immediately discontinued, and intravenous fluid replacement and/or vasopressor agent support is promptly commenced to ensure hemodynamic stability and avoidance of renal insufficiency.[28] Type and cross-match for red packed cell transfusion should be urgently performed. Ingestion of activated charcoal may help prevent further absorption of recently received (<2-4 hours) dabigatran. Invasive catheter- or surgery-base cauterization or ligation of the bleeding source should be considered. When, despite the above measures, acute renal failure supervenes, hemodialysis can be useful in removing dabigatran and restoring coagulation. Finally, use of a general hemostatic agent, such as prothrombin complex concentrate (PCC)[29] has been suggested at a dose of 50 IU/kg for rivaroxaban and apixaban or anti-inhibitor coagulant complex (aPCC) at a dose of 80 U/kg for dabigatran. Activated factor VII has also been proposed as an emergency treatment for severe bleeding with the NOACs,[30-33] but experience is limited with use of this agent. Of course, one could argue that it is also difficult to rapidly reverse the anticoagulant effects of warfarin with fresh frozen plasma and vitamin K, often with a considerable delay before complete reversal of anticoagulation is achieved. In addition, activated factor VII rapidly reverses the effects of warfarin but is associated with an increased risk of thrombotic complications.[33] Specific antidotes are under development for dabigatran and the anti-factor Xa agents rivaroxaban and apixaban but are not yet approved for clinical use.

REAL-WORLD EXPERIENCE

Real-world experience with the NOACs is slowly providing us with some additional data regarding their safety.[18,34] In a Danish study, the Nationwide Pharmacoepidemiologic Cohort Study, dabigatran safety and efficacy were evaluated in the first 4 months following its approval.[34] Among 52,366 patients with AF prescribed oral anticoagulation, ~5% received dabigatran (110 mg, n=1612; 150 mg, n=1114). Among anticoagulant-naive individuals, the risk of thromboembolic events was similar between warfarin (1.3%) and both doses of dabigatran (110 mg: 1.2%; 150 mg: 1.6%). However, in patients who had previously been prescribed warfarin, thromboembolic events were more frequent for dabigatran than warfarin (warfarin: 0.2%; dabigatran 110 mg: 0.6%; dabigatran 150 mg: 0.9%); the reason for switching from warfarin to NOAC is not clear but might be ascribed to several causes, such as poor compliance, other serious comorbidities, or difficulties in regular INR monitoring and maintenance of therapeutic target.

In another Danish study, a dabigatran-treated group (n=4978) and a 1:2 propensity-matched warfarin-treated group (n=8,936) were compared.[18] In this registry, stroke and systemic embolism were not significantly different between the 2 groups. Adjusted mortality was significantly lower with both dabigatran doses (110 mg bid, hazard ratio-HR: 0.79; 150 mg bid, HR: 0.57). Less intracranial bleeding was seen with both dabigatran doses (110 mg, HR: 0.24; 150 mg, HR: 0.08). As there was an initial concern regarding a possible increase in myocardial infarction (MI) with dabigatran, this was not confirmed for either dose of dabigatran, rather a lower incidence of MI was noted (110 mg, HR: 0.30; 150 mg, HR: 0.40). Gastrointestinal bleeding was lower with the lower dose of dabigatran 110 mg (HR: 0.60) but not with the higher dose. Thus, it seems that in this "everyday clinical practice", there were similar stroke/systemic embolism and major bleeding rates with both doses of dabigatran compared with warfarin. Mortality, intracranial bleeding, pulmonary embolism, and MI were lower with dabigatran, compared with warfarin.[18,35]

In a US study, among patients receiving dabigatran (n=14,297) or warfarin (n=33,548), there was no difference in systemic thromboembolic rates between groups, but intracranial hemorrhage and MI were lower for dabigatran, and gastrointestinal bleeding was higher compared to warfarin.[36] In a retrospective analysis of a US database, among AF patients naive to warfarin (n=7202) or dabigatran (n=1090) therapy, 4-month event rates were higher compared with the RE-LY trial; however, there was no difference in embolic and bleeding outcomes between warfarin and dabigatran.[37] More data were provided by the Outcomes Registry for Better informed Treatment of Atrial Fibrillation (ORBIT-AF).[38] In this registry, use of warfarin or dabigatran was analyzed among 10,098 patients with AF (mean age 73 years). Overall, 76% of patients received an oral anticoagulant (71% warfarin and 5% dabigatran) with a higher use among those with higher stroke risk scores. Among those with low bleeding risk, anticoagulant use increased significantly with increasing stroke risk. Among those with high bleeding risk, stroke risk had a smaller impact on use of oral anticoagulant.

Thus, there appears that real-world data of the use of NOACs provide reassurance of both the efficacy and safety of dabigatran, further confirming a lower rate of intracranial bleeding with dabigatran compared to warfarin and similar other bleeding events. Finally, further information is expected from the ongoing registry, the Global Anticoagulant Registry in the FIELD (GARFIELD).[39] In an initial report of a cohort of 10,614 adults diagnosed with non-valvular AF, a total of 38% of patients with a CHADS2 score ≥2 did not receive anticoagulant therapy, whereas 42.5% of those at low risk (score 0) received anticoagulant therapy.[39] The authors concluded that these observational worldwide data on non-valvular AF, collected at the end of the VKA-predominant era, indicate that these drugs are frequently not being used according to stroke risk scores and guidelines, with overuse in patients at low risk and underuse in those at high risk of stroke. There remains to see how the NOACs will fill in these gaps.

TRANSITIONING FROM WARFARIN TO NOAC

Another issue pertains to transitioning from warfarin to NOAC. In the ROCKET AF trial, 7897 (~55%) patients were warfarin-experienced (with at least 6 weeks of prior treatment) and 6367 (~45%) were warfarin-naive.[35,40] The beneficial effect of rivaroxaban vs warfarin on stroke was consistent: 2.32 rates per 100 patient-years of follow-up vs 2.87 for warfarin-naive patients (hazard ratio-HR, 0.81) and 1.98 vs 2.09 for warfarin-experienced patients (HR, 0.94; *P=NS*). During the first 7 days of switching, rivaroxaban was associated with more bleeding than warfarin (HR in warfarin-naive patients 5.83, and in warfarin-experienced patients, 6.66). After 30 days, rivaroxaban had less bleeding than warfarin in warfarin-naive patients (HR, 0.84) and similar bleeding in warfarin-experienced patients (HR, 1.06; $P = 0.003$). Patients enrolled with INRs of 2.0-3.0 had outcomes similar to those with INRs <2.0. The authors recommend that patients who are going to switch from warfarin to rivaroxaban should start 20 mg of rivaroxaban and stop warfarin only when the INR is <3.0.[35,40] A brief guide for switching between anticoagulants is provided in Table 1.

PERI-PROCEDURAL USE OF NOACS

One of the main advantages of the NOACs is their short

TABLE 1. Novel Oral Anticoagulants / Practical Points

Agent	Dabigatran	Rivaroxaban	Apixaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Biovailability	5-7%	65% with no food/ 100% with food	50%
Prodrug	Yes	No	No
Clearance: renal/other	80%/20%	65% (half unchanged)/ 35%	27% / 73%
Protein binding	35%	90-95%	Circa 87%
Liver metabolism: via CYP3A4?	No	Yes (elimination)	Yes (elimination; little via CYP3A4)
Half-life	12-17 h	5-9 h (young) / 11-13 h (elderly)	12 h
Time to peak action	0.5-3 h	1-4 h	1-4 h
Dose CrCl 15-50 mL/min CrCl<15 mL/min or on HD	**150 mg bid /** **110 mg bid** **75 mg bid** Not recommended	**20 mg qd** **15 mg qd** Not recommended	**5 mg bid** **2.5 mg bid** (pts with ↑ bleeding risk: >80y/<60 kg/Crea >1.5 mg/dl) Not recommended
Surgery & Procedures			
Low bleeding risk	• stop 24 h prior**/restart @ 6-8 h after hemostasis	• stop 24 h prior**/restart @ 6-8 h after hemostasis	• stop 24 h prior**/restart @ 6-8 h after hemostasis
High bleeding risk	• stop 48 h prior**/restart after balancing bleeding vs thromboembolic risk	• stop 48 h prior**/restart after balancing bleeding vs thromboembolic risk	• stop 48 h prior**/restart after balancing bleeding vs thromboembolic risk
Switching	**Warfarin to dabigatran:** • Stop warfarin & start dabigatran when INR <2 **Dabigatran to warfarin:** • Start warfarin (nl CrCl)/3 days later, stop dabigatran/wait 24 h, then measure INR **IV heparin to dabigatran:** • Start dabigatran 2-3 h after DC heparin **Dabigatran to IV heparin:** • Stop dabigatran & start heparin 12 h later (or 2-3 d later if CrCl 30-50 mL/min)	**Warfarin to rivaroxaban:** • DC warfarin & start rivaroxaban when INR <3 **IV heparin to rivaroxaban:** • Start rivaroxaban at time heparin is discontinued **LMWH to rivaroxaban:** • Give rivaroxaban 0-2 h before next scheduled evening dose	**Warfarin to apixaban:** • DC warfarin & start apixaban when INR <2 **Apixaban to warfarin:** • DC apixaban & start warfarin + heparin bridge at time of next dose of apixaban/DC heparin when INR >2 **Apixaban to other agent:** • DC one & begin the other at next scheduled dose

TABLE 1. (continued) Novel Oral Anticoagulants / Practical Points

Drug-drug interactions	Atorvastatin: ↑ Verapamil: ↑↑ Quinidine: ↑↑ Amiodarone: ↑ Dronedarone: ↑↑↑* Ketokonazole/ Itraconazole: ↑↑↑* Clarithromycin/ Erythromycin: ↑ Rifampicin/ Carbamazepine/ Phenytoin: ↓↓↓* Antacids: ↓	• Do not use with drugs that are combined P-gp & strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, indinavir/ ritonavir, conivaptan) • Do not use with drugs that are combined P-gp & strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin) • Only use if the potential benefit justifies the potential risk with CrCL 15-50 mL/min and concomitant combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, dronedarone, diltiazem, verapamil, quinidine, ranolazine, felodipine, erythromycin, azithromycin)	Diltiazem: ↑ Ketokonazole/Itraconazole: ↑↑↑* HIV protease inhibitors: ↑↑↑ Rifampicin/Carbamazepine/Phenytoin: ↓↓↓*
Reversal	• **DC drug/ No specific antidote** • Due to low plasma protein binding, **dialysis** may remove dabigatran • Use of procoagulant reversal agents (PCC, aPCC, rFVIIa) may be considered, but has not been evaluated in clinical trials • Activated oral charcoal ↓ absorption of recently (<2-4h) received drug	• **DC drug/ No specific antidote** • Due to high plasma protein binding, dialysis may not remove rivaroxaban • Use of procoagulant reversal agents (PCC, aPCC, rFVIIa) may be considered, but has not been evaluated in clinical trials • Activated oral charcoal may ↓ absorption of recently (<2-4 h) received drug	• **DC drug/ No specific antidote** • Due to high plasma protein binding, dialysis may not remove apixaban • Use of procoagulant reversal agents (PCC, aPCC, rFVIIa) may be considered, but has not been evaluated in clinical trials • Activated oral charcoal may ↓ absorption of recently (<2-4 h) received drug
Coagulation tests			
INR	NA	NA	NA
PT	Sensitive to presence	Detects presence but not effect	NA
aPTT	@ trough if >2x ULN→ excess bleeding risk	NA	NA
TT	↑ (if too ↑: ↑bleeding risk)	NA	NA
Anti-factor Xa assay	NA	Quantitative/no full data	Quantitative/no full data
ECT	@ trough if >3x ULN→ excess bleeding risk	NA	NA

*** do not use**

**** in patients with normal renal function (>80 mL/min)**

• CrCl 50-80 mL/min: for low-risk → stop xabans 24 h prior & gatrans 36 h prior; for high-risk → stop xabans 48 h prior & gatrans 72 h prior

• CrCl 30-50 mL/min: for low-risk → stop xabans 24 h prior & gatrans 48 h prior; for high-risk → stop xabans 48 h prior & gatrans 96 h prior

• CrCl 15-30 mL/min: do not use gatrans; for low-risk → stop xabans 36 h prior; for high-risk → stop xabans 48 h prior

• CrCl <15 mL/min: do not use

aPCC = activated prothrombin complex concentrate; aPTT = activated partial thromboplastin time; CrCl = creatinine clearance; DC = discontinue; ECT = ecarin clotting time; HD = hemodialysis; HIV = human immunodeficiency virus; INR = international normalized ratio; LMWH = low-molecular weight heparin; NA = not applicable; nl = normal; PCC = prothrombin complex concentrate; P-gp = P-glycoprotein; PT = prothrombin time; pts = patients; rFVIIa = recombinant factor VIIa; TT = thrombin time; ULN = upper limits of normal

half-life (Table 1), which facilitates short interruption and rapid reintroduction around the time of surgery without the need for coagulation testing and monitoring, as confirmed by the RE-LY trial, in which 46% of patients treated with dabigatran were able to have their procedure within 48 hours of stopping dabigatran, compared with only 11% of patients treated with warfarin.[41] Nevertheless, a strategy of uninterrupted coagulation therapy is emerging for the management of patients with moderate or high thromboembolic risk undergoing low bleeding risk procedures. This strategy has gained acceptance for patients having cataract, dental, and pacemaker or ICD surgery, all these procedures accounting for ~30% of the procedures among patients with AF.[42] Finally, the timing of the procedure is important; if the procedure is needed on an urgent or emergent basis, increased bleeding rates should be anticipated and relevant measures should be taken, including immediate discontinuation of the anticoagulant, proper means for local or surgical hemostasis, volume replacement, transfusion of blood products and other hemodynamic support (e.g. inotropes and/or vasopressors) as needed.

IMPLANTATION OF CARDIAC IMPLANTABLE ELECTRONIC DEVICES (CIEDS) / CATHETER ABLATION

A strategy of uninterrupted warfarin therapy at the time of pacemaker or ICD implantation has been recently suggested and followed by many centers, as studies, like BRUISE CONTROL and others, have shown that, compared with bridging therapy with heparin, a strategy of uninterrupted warfarin treatment at the time of pacemaker or ICD implantation significantly reduces the rate of bleeding (mostly device-pocket hematomas), without a difference in the risk of thromboembolic events.[43,44] Preliminary data indicate that a similar strategy could be followed with continuous anticoagulation with dabigatran during implantation of CIEDs.[45] Further information will be provided by BRUISE CONTROL 2 study, a randomized trial of continued vs interrupted dabigatran in pacemaker patients.

Uninterrupted oral anticoagulant therapy with warfarin has also been suggested and implemented at many centers performing catheter ablation of AF. Recent data indicate that the administration of dabigatran is also as safe and effective as warfarin for uninterrupted oral anticoagulant therapy during catheter ablation of AF.[46] In a recent study, in the warfarin group (n=251) the warfarin dose was adjusted to maintain an INR of 2–3 and warfarin was continued throughout the periprocedural period. The dabigatran group (n=212) received 150 mg of dabigatran twice daily, and patients did receive the morning dose on the day of the ablation procedure. Postprocedural warfarin or dabigatran were administered on the evening of the procedure in all patients. There were 3 complications in the dabigatran group and 6 in the warfarin group (P = NS). There were 2 bleeding complications in the dabigatran group and 6 in the warfarin group (P = NS). There was one thromboembolic complication (a possible TIA) in the dabigatran group and none in the warfarin group (P = NS). However, in another study,[47] employing a different protocol, where dabigatran was stopped for 12 hours pre-procedurally and was resumed at 24 hours after the last dose, an increased risk of major bleeding and a composite of bleeding and embolic complications was found with dabigatran compared with uninterrupted warfarin. A plausible explanation may be offered by the different protocol applied, relating to the short half-life (11–14 hours) of dabigatran with its anticoagulant effects expected to significantly decline when used in this manner.

OTHER ELECTIVE PROCEDURES

All NOACs have very short times to peak concentration (2-4 hours) and the half-life is similar, around 12 hours, and thus they are more predictable for the duration of their effect, which makes NOAC handling for elective cases of surgery much easier than managing anticoagulation with VKA therapy. One should keep in mind some important patient characteristics, such as renal function and features of the procedure, e.g. procedure of low vs high bleeding risk, when being consulted for peri-operative management of these patients. In addition to the kind of surgery, the bleeding risk specific to the type anesthesia (e.g., neuraxial blockade) must also be considered.[48] Mechanical means for hemostasis should be available. There are no specific antidotes for NOACs. Prothrombin complex concentrate (PCC) may reverse the xabans (Table 1). For excessive bleeding, the use of non-specific hemostatic agents such as PCC, factor VIII inhibitor bypass activity or recombinant factor VIIa must be weighed against the risk of thrombotic complications. The creatinine clearance should be measured. In patients with creatinine clearance ≥50 mL/min, discontinuing anticoagulation for 4-5 half-lives before surgery may be adequate, but for patients with creatinine clearance <50 mL/min, the time should be extended to 2 days. For procedures with high bleeding risk, a normal preoperative aPTT or thrombin time indicates sufficient dabigatran elimination. Currently, there is no available assay for ensuring complete rivaroxaban or apixaban elimination. Bridging therapy with heparin is generally not indicated. Postoperatively, restarting these agents should be delayed ≥48 hours and once complete hemostasis is assured. Upon re-initiation, the patient will be fully anticoagulated within 1-2 hours.

For procedures with low peri-operative risk (electrophysiology studies or simple arrhythmia ablation), one can stop NOAC 24 hours earlier and restart it 6-8 hours after secure hemostasis is achieved. For procedures of high bleeding risk (e.g. orthopedic or abdominal surgery), and a patient with normal renal function (creatinine clearance >80 ml/min), NOAC should be withheld 48 hours earlier and re-started at 6-8 hours afterwards or at a time when adequate hemostasis has been achieved or the risk of bleeding is considered low, but, as aforementioned, one should balance it out with the

risk of thromboembolism.[42,48] The time to stop a NOAC for an elective procedure in patients with renal insufficiency should be graded according with the kidney function (Table 1).

OTHER PRACTICAL POINTS

COAGULATION MONITORING

The new agents do not require routine coagulation monitoring.[49] However, in certain circumstances, one needs to know the coagulation status of the patients. This relates to emergency situations, including need for urgent surgery, when serious bleeding or thrombotic events occur, when there is need to administer thrombolysis, when there is renal or hepatic insufficiency, or when suspecting drug-drug interactions or drug overdosing. It should be pointed out that the NOAC anticoagulation assays test for an anticoagulant effect, not for intensity of anticoagulation; and the assays should not be used for dose adjusting of these agents (Table 1). Starting with the *INR*, one should know that the INR is affected by NOACs but not in the same or a consistent way that the INR is affected by VKAs, and thus it should not be used in patients taking NOACs, otherwise one may be greatly confused by the results. The activated partial thromboplastin time (*aPTT*), when measured at trough (i.e. at 12-24 hours after ingestion) and found to be prolonged, it suggests that dabigatran is present in sufficient quantity to produce an anticoagulant effect, but it cannot provide a quantitative measure of this effect, while it is insensitive to low dabigatran concentrations. When the aPTT is greater than twice the upper limit of normal, it may indicate excess bleeding risk for dabigatran, but it cannot be used for guidance with the other agents. Similarly, a trough *ecarin clotting time* level greater than 3 times the upper normal limit may suggest excess bleeding risk with dabigatran but not with other agents. For surgical procedures with a high bleeding risk, the HEMOCLOT test (direct thrombin inhibitor assay), wherever available, may be used to detect low levels of dabigatran. Prothrombin time (PT) testing is useful for detecting the presence of rivaroxaban; however, it is insensitive for measuring the effects of low levels of the drug and cannot provide a quantitative measure of anticoagulant activity. In most patients who discontinue rivaroxaban after steady-state dosing, the PT will fall rapidly within 4-6 hours and reach to near-normal levels within 24 hours.[28] A properly calibrated anti-factor Xa activity assay constitutes a quantitative test and can provide a reasonable estimate of rivaroxaban plasma level. Also for apixaban, prothrombin time may not be as reliable as with rivaroxaban, but an anti-factor Xa activity assay may be useful.

DRUG-DRUG INTERACTIONS

VKAs are associated with many drug-drug interactions. Fortunately, drug-drug interactions associated with NOACs are limited, but nevertheless, there are certain interactions (Table 1).[20] There are a least 2 important mechanisms implicated for NOAC drug-drug interactions. The first is resecretion of P-glycoprotein (P-gp) transporter after absorption in the gastrointestinal tract. The second is cytochrome P-450 3A4 inhibition. Liver metabolism concerns apixaban and rivaroxaban. There are also some patient characteristics, such as age, body weight and renal function, and also some pharmacodynamic interactions that may have an effect on the plasma level and, thus, the anticoagulant effect of NOACs potentially leading to an excessive bleeding risk (Table 1). It should be noted that dabigatran is a prodrug, whereas the other factor Xa inhibitors are not prodrugs. Dabigatran is highly renally excreted by ~80%, whereas apixaban and rivaroxaban are ´30% and edoxaban ~50% renally excreted.

There are a few important interactions with cardiac medicines, best studied for dabigatran. An interaction (P-glycoprotein mechanism) exists between dabigatran and *verapamil* and the patient should receive only the lower dose of dabigatran. Dabigatran has also a strong interaction with *dronedarone* (again P-gp mechanism) and thus this combination is contraindicated. Interestingly, however, the interaction with *amiodarone* does not appear to require a dose adjustment for dabigatran.

With regards to food interactions, it is well known that VKAs are associated with food interactions, particularly intake of green vegetables, which are a source of vitamin K. It is important to know that there are no food interactions with NOACs, except in the case of rivaroxaban. Rivaroxaban should be taken with meals. When rivaroxaban is taken with food, absorption increases by about 40%, which is significant. The absorption of the other NOACs is not affected by food, and they can be taken irrespective of meals. It is also important to know that there no interactions of NOACs with antacids or proton-pump inhibitors. Patients receiving dabigatran may develop dyspepsia, in which case they are advised to take the drug with food or water; proton pump inhibitors (PPIs) may also be very helpful in this situation. A cautionary advice relates to dabigatran packaging; when the drug is exposed to air, it degenerates after 30 days, and the unused pills should be discarded.

CARDIOVERSION

Cardioversion of patients presenting with new-onset AF within 48 hours can be performed regardless of anticoagulation status, albeit some latest data strongly advise for prompt initiation of heparin therapy.[50] However, for patients with AF of >48 h duration, or AF of unknown onset and duration, cardioversion should only be performed after effective oral anticoagulation has been given for at least 3 weeks prior to cardioversion. Otherwise, transesophageal echocardiography (TEE) can guide management and cardioversion can be performed when the presence of left atrial thrombi is excluded. After cardioversion, oral anticoagulation is continued for at

least another 4 weeks. Although, no prospective data exist concerning the safety of cardioversion under NOAC treatment, a similar algorithm has been followed with the exception of not being able to document effective anticoagulation by laboratory monitoring, as done in patients receiving VKAs. However, patient compliance is most important in this case and should be explicitly discussed with the patient. When there is doubt, a TEE preceding cardioversion could be a safer approach.[20]

USE OR NON-USE OF NOACS IN OTHER GROUPS

The new oral anticoagulant agents have already received an indication for use in patients afflicted by *venous thromboembolism (VTE)* or for prophylaxis against VTE. However, concern has recently been voiced and documented to alert physicians against the use of NOACs in patients with artificial *mechanical valves* and in patients with *acute coronary syndromes*. In the former group, the results of the phase II **RE-ALIGN** study were recently presented in the 2013 ESC Annual Congress, indicating that the oral anticoagulant dabigatran failed to protect patients with mechanical valves from thromboembolic events.[50] Rather, a higher number of thromboembolic and bleeding complications occurred in these patients compared to standard treatment with warfarin. This adverse outcome prompted the early termination of this study after enrolment of 252 patients. The composite of stroke, TIA, systemic embolism, MI or death occurred in 15 patients (9%) in the dabigatran group and in 4 patients (5%) in the warfarin group. Major bleeding occurred in 7 patients (4%) on dabigatran and 2 (2%) on warfarin.[50] For the latter group, a meta-analysis of 7 studies indicated that in patients with acute coronary syndrome, the addition of a NOAC to antiplatelet therapy may result in modest reduction of cardiovascular events, but a substantial increase in bleeding events, accentuated in patients who are already on dual antiplatelet therapy.[51]

PATIENTS WITH CANCER

Malignancies, interacting directly or indirectly with the coagulation system, are associated with increased risk for thromboembolic events. Other factors implicated in increased risk of bleeding in this population group may comprise surgical wounds, tissue effects of irradiation, and bone marrow effects from chemotherapy or irradiation leading to thrombocytopenia. There no data regarding the use of NOACs in patients with cancer, as this patient group was excluded from NOAC trials. Thus, until such data become available, therapy with VKAs or heparins should be considered over NOACs, as conventional anticoagulants offer the possibility of close monitoring and reversal of their action should this become necessary. In AF patients already receiving a NOAC, who develop cancer during follow-up, this therapy could be continued together with gastric protection (e.g. with use of PPIs) until cancer therapies are planned, when dose reduction or discontinuation of NOAC therapy may be considered versus close monitoring of platelet counts, liver and renal function, and for signs of bleeding.[20]

RECENT GUIDELINES

According with the recent 2012 European guidelines, the recommendations for prevention of thromboembolism in non-valvular AF using NOACs are as follows[12]:

1) In patients with a CHA_2DS_2-VASc score ≥2, oral anticoagulant therapy with:
   • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) (apixaban: pending approval)... is recommended, unless contraindicated (**Class I / Level A**)
2) In patients with a CHA_2DS_2-VASc score of 1, oral anticoagulant therapy with:
   • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) (apixaban: pending approval).... should be considered, based upon an assessment of the risk of bleeding complications and patient preferences (**Class IIa / Level A**)
3) When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an oral anticoagulant is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:
   • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban) ... is recommended (**Class I / Level A**)
4) Where oral anticoagulant is recommended, one of the NOACs, either:
   • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)... should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit (**Class IIa / Level A**).
5) Where dabigatran is prescribed, a dose of 150 mg bid should be considered for most patients in preference to 110 mg bid, with the latter dose recommended in:
   • elderly patients, age ≥80; • concomitant use of interacting drugs (e.g. verapamil); • high bleeding risk (HAS-BLED score ≥3); • moderate renal impairment (CrCl 30–49 mL/min) (**Class IIa / Level B**)
6) Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg od, with the latter dose recommended in:
   • high bleeding risk (HAS-BLED score ≥3); • moderate renal impairment (CrCl 30–49 mL/min) (**Class IIa / Level C**)

7) Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year (**Class IIa / Level B**)
8) NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min) (**Class III / Level A**)
According with the most recent 2013 combined American and European guidelines, the indications for dabigatran are as follows[52]:
● "CLASS I / *2011 New Recommendation:* Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15 mL/min) or advanced liver disease (impaired baseline clotting function). *(Level of Evidence: B)".*

CONCLUSION

Although the new anticoagulants may finally replace VKAs, certain changes in hospital and outpatient routine and patient management strategies are required when introducing these new, more expensive, agents to clinical practice. It is anticipated that the new agents may simplify the routine of patient management and, finally, improve their clinical course. However, it is important to appreciate the potential challenges and limitations posed by their use and to follow recommendations and guidelines, to achieve optimal patient outcomes.

N.B.: *$CHADS_2$* & *CHA_2DS_2-VASc* are risk scores proposed to determine the risk of thromboembolism in patients with AF and the acronyms represent the following parameters: C = congestive heart failure; H = hypertension; A = age >75 years; D = diabetes mellitus; S = stroke; V = vascular disease; A = age 65-74; S = female gender (each parameter receives 1 point except for stroke receiving 2 points in CHADS2; age >75 also receives 2 points in CHA_2DS_2-VASc; maximum score for $CHADS_2$ is 6 and for CHA_2DS_2-VASc is 9).
HAS-BLED is a risk score for bleeding (H = hypertension; A = abnormal liver and/or renal function; S = stroke; B = bleeding; L = labile INRs; E = elderly >65; D = drugs or alcohol)

REFERENCES

1. Steffel J, Braunwald E. Novel oral anticoagulants: focus on stroke prevention and treatment of venous thrombo-embolism. *Eur Heart J* 2011;32:1968-1976.
2. Caterina RD, Husted S, Wallentin L, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes. ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper. *J Am Coll Cardiol* 2012;59:1413–1425.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151.
4. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-891.
5. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992.
6. Wallentin L, Yusuf S, Ezekowitz MD, et al. RE-LY investigators. 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(9745):975-983.
7. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel Factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010; 160:635-641.
8. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients. *Int J Cardiol* 2013; 167:1237–1241.
9. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *Am J Cardiol* 2012;110:453-460.
10. Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, 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.
11. Adam SS, McDuffie JR, Ortel TL, Williams JW Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial Fibrillation and venous thromboembolism. A systematic review. *Ann Intern Med* 2012;157:796-807.
12. 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.
13. 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(2 suppl):e531S-575S.

14. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012; 28:125-136.
15. Lip GY, Larsen TB, Skjoth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol* 2012; 60:738-746.
16. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. *Thromb Haemost* 2012; 108:476-484.
17. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 2013; 368:1272-1274.
18. Larsen TB, Rasmussen LH, Skjoth F, et al. 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.
19. Cairns JA. Which oral anticoagulant for which atrial fibrillation patient: recent clinical trials and evidence-based choices. *Can J Cardiol* 2013 Aug 7. doi:pii: S0828-282X(13)00328-0. 10.1016/j.cjca.2013.05.010. [Epub ahead of print]
20. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013; 15:625-651.
21. 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.
22. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 2011; 123:2562-2570.
23. You JHS, Tsui KKN, Wong RSM, Cheng G. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. *PLoS One* 2012; 7(6):e39640.
24. Harrington AR, Armstrong EP, Nolan PE Jr, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke* 2013; 44:1676-1681.
25. 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.
26. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) Study. *Circulation* 2013; 128:237-243.
27. European Medicines agency. Questions and answers on the review of bleeding risk with Pradaxa (dabigatran etexilate). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/05/WC500127768.pdf. 24 May 2012. (accessed August 20, 2013).
28. Peacock WF, Gearhart MM, Mills RM. Emergency management of bleeding associated with old and new oral anticoagulants. *Clin Cardiol* 2012; 35:730-737.
29. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124:1573-1579.
30. Sartori MT, Imbergamo S, Zanon E, et al. Effect of recombinant activated factor VII in critical bleeding: Clinical experience of a single center. *Clin Appl Thromb Hemost* 2009; 119:121-127.
31. van Ryn J, Ruehl D, Priepke H, Hauel N, Wienen W. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate (Abstract 0370). Haematologica 2008;93(Suppl. 1):148.
32. Mayer SA, Brun NC, Begtrup K, et al; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358:2127-2137.
33. Brody DL, Aiyagari V, Shackelford AM, Diringer MN. Use of recombinant factor VIIa in patients with warfarin-associated intracranial hemorrhage. *Neurocrit Care* 2005; 2:263-267.
34. Sorensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. *BMJ Open* 2013; 3(5).
35. Manolis AS, Rouska E, Anninos H. Cardiology news/recent literature review/second quarter 2013. *Rhythmos* 2013; 8:38-43
36. Thelus R, Villines TC, Coster TS. Dabigatran versus warfarin among patients with atrial fibrillation: real-world postmarket results. American Heart Association, Los Angeles, November 3-7, 2012; abstract 14877. Available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=4911efc8-20d6-42ba-a562-4087d52e57e4&cKey=3972b1a9-f575-449b-a713-2a45b15fca04&mKey={14145D5B-F96B-4354-8237-8F0937744BA4}
37. Charland SL, Malone DC, Agatep BC, et al. Real-world risk of thromboembolism or bleeding with warfarin or dabigatran therapy in patients with atrial Fibrillation. American Heart Association, Los Angeles, November 3-7, 2012; abstract 16370. Available at: http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=a0bb3efd-f070-4c37-81c3-0ee0ede4c5a4&cKey=b91dba5f-391f-4f6c-a86d-bc17b62b3299&mKey={14145D5B-F96B-4354-8237-8F0937744BA4}
38. Cullen MW, Kim S, Piccini JP Sr, et al. ORBIT-AF Investigators. Risks and benefits of anticoagulation in atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Circ Cardiovasc Qual Outcomes* 2013; 6:461-469.
39. Kakkar AK, Mueller I, Bassand JP, et al; GARFIELD Registry Investigators. 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(5):e63479.
40. Mahaffey KW, Wojdyla D, Hankey GJ, et al. Clinical outcomes with rivaroxaban in patients transitioned from vitamin

K antagonist therapy: a subgroup analysis of a randomized trial. *Ann Intern Med* 2013; 158:861-868.
41. Healey JS, Eikelboom J, Douketis JD, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation* 2012; 126:343-348.
42. Healey JS, Brambatti M. Periprocedural Management of oral anticoagulation in patients with atrial fibrillation: approach in the era of new oral anticoagulants. *Can J Cardiol* 2013; 29: S54-S59.
43. Birnie DH, Healey JS, Wells GA, et al; BRUISE CONTROL Investigators. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med* 2013; 368:2084-2093.
44. 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.
45. Rowley CP, Bernard ML, Brabham WW, et al. Safety of continuous anticoagulation with dabigatran during implantation of cardiac rhythm devices. *Am J Cardiol* 2013; 111:1165-1168.
46. Maddox W, Kay GN, Yamada T, et al. Dabigatran versus warfarin therapy for uninterrupted oral anticoagulation during atrial fibrillation ablation. *J Cardiovasc Electrophysiol* 2013; 24:861-865.
47. Lakkireddy D, Reddy YM, DiBiase 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.
48. Wysokinski WE, McBane II RD. Periprocedural bridging management of anticoagulation. *Circulation* 2012; 126:486-490.
49. Liew A, Eikelboom JW, O'Donnell M, Hart RG. Assessment of anticoagulation intensity and management of bleeding with old and new oral anticoagulants. *Can J Cardiol* 2013; 29:eS34-S44.
50. Manolis AS, Rouska E, Anninos H. Cardiology news/recent literature review/third quarter 2013. *Rhythmos* 2013; 8:54-61.
51. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J* 2013; 34:1670–1680.
52. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61:1935–1944.