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Evidence Update

Evidence update on the use of oral anticoagulants in clinical practice

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Introduction

The only oral anticoagulant available in clinical practice for more than five decades was warfarin, a vitamin K antagonist (VKA). In the early 1950's the drug was found to be efficacious in preventing thrombosis and thromboembolism in many clinical situations and was approved for therapeutic use in 1954 and has been used widely ever since, Despite its effectiveness and feasibility for long term use, it has several shortcomings. Warfarin has a variable dose response, a narrow therapeutic index and numerous drug and dietary interactions that require frequent monitoring using the international normalized ratio (INR) to ensure an adequate yet safe dose[1].

These shortcomings have prompted the development of new oral anticoagulants (NOACs) or direct acting oral anticoagulants (DOACs) that directly act on coagulation factors such as factors Xa and IIa (thrombin). Since 2008, regulatory agencies in the EU and the US have approved several NOACs for specific indications, based on the results of clinical trials that demonstrated efficacy and safety that was, at least, non inferior, if not superior, to warfarin and heparins in stroke prevention in atrial fibrillation (AF) and in the treatment and prophylaxis of venous thromboembolism (VTE)[2]. NOACs used in clinical practice at present include dabigatran, rivaroxaban, apixaban and the recently introduced edoxaban. These agents offer major pharmacological advantages over warfarin such as rapid onset of action, minimal drug or dietary interactions and predictable pharmacokinetics, which eliminates the requirement for regular coagulation monitoring[1,2].

As clinicians now have a broader choice, this article aims at giving the clinician a concise review of the pharmacology, mechanisms of action, approved indications and interactions of warfarin and NOACs coupled with the results of clinical trials that evaluated the efficacy and safety of these novel drugs in different clinical situations.

Warfarin

Warfarin is a synthetic derivative of dicoumarol, a 4-hydroxycoumarin-derived mycotoxin anticoagulant originally discovered in spoiled sweet clover-based animal feeds. Warfarin inhibits the vitamin K-dependent synthesis of biologically active forms of clotting factors II, VII, IX and X, as well as the regulatory factors protein C and S[3]. This is mediated through its inhibitory action on vitamin K

epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it has participated in the carboxylation of the above clotting factors. The coagulation factors that are produced in the absence of vitamin K have decreased function due to under-carboxylation and are referred to as PIVKAs (proteins induced [by] vitamin K absence).

The maximum effect of warfarin is evident in two to three days and the duration of action of a single dose of warfarin is 2 to 5 days. Common clinical indications for warfarin use are stroke prevention in atrial fibrillation (AF), the presence of artificial heart valves, deep venous thrombosis (DVT) and pulmonary embolism (PE).

Warfarin activity is partially determined by two genes, namely VKORC1 and CYP2C9[4]. However, a 2014 meta-analysis showed that using genotype-based dosing did not confer any benefit with respect to time within therapeutic range, preventing excessive anticoagulation (defined as INR greater than 4) or reduction in either major bleeding or thromboembolic events.

The major side effect of warfarin use is bleeding. The rapid reversal of warfarin in such instances, or in patients requiring emergency surgery, is done with prothrombin complex concentrate (PCC), fresh frozen plasma (FFP) and intravenous vitamin K. A rare but serious complication resulting from treatment with warfarin is warfarin necrosis, which occurs shortly after commencing treatment in patients with a deficiency of protein C. Several studies have demonstrated an association between warfarin use and osteoporosis-related fractures. A 2006 retrospective study of 14,564 Medicare recipients showed that warfarin use for more than one year was associated with a 60% increased risk of osteoporosis-related fracture in men[5].

Warfarin is teratogenic in the first trimester of pregnancy and causes central nervous system disorders in late pregnancy. Therefore, anticoagulation with warfarin poses a problem in pregnant women requiring warfarin for vital indications, such as stroke prevention in those with artificial heart valves. Warfarin may be used in lactating women who wish to breast-feed their infants as available data do not suggest that warfarin crosses into the breast milk[3].

New oral anticoagulants (NOACs)

NOACs can be divided into two broad classes:

(i) Direct thrombin inhibitors (dabigatran) which inhibit thrombin (Factor IIa)
(ii) Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) which inhibit factor Xa.

Apixaban, rivaroxaban and dabigatran will be discussed in this review.

Apixaban

Apixaban is a selective, reversible, direct inhibitor of free and clot bound Factor Xa. It also inhibits thrombin generation. The maximum plasma concentration is achieved in 30 minutes to 2 hours and the half-life is 8–15 hours. Apixaban is metabolized in the liver and the route of elimination is 30% renal and 70% faecal. Apixaban has a

minimal impact on the prothrombin time (PT) and the activated partial thromboplastin time (APTT) at therapeutic concentrations but its action can be monitored by the modified chromogenic anti Xa assay. There are no significant dietary or drug interactions with apixaban and no reversing agent is available.

Apixaban is approved for use in the prevention of stroke and systemic embolism in adult patients with nonvalvular AF by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Canada's Health Products and Food Branch (HPFB) and in the primary prevention of VTE in adult patients who have undergone elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) by the EMA and the HPFB[6]. The efficacy and safety of apixaban has been evaluated in phase 3 clinical trials which are summarized in Table 1.

The use of apixaban in postoperative VTE prophylaxis for TKA was evaluated against enoxaparin in the (ADVANCE)-1[7] and (ADVANCE)-2[8] trials. Treatment in each arm were continued for 10 to 14 days. In the ADVANCE-3 trial[9] drugs were continued for 35 days after THA. Primary efficacy (symptomatic or asymptomatic VTE, non fatal PE, death) was similar in both drugs in ADVANCE-1 and apixaban was superior to enoxaparin in the ADVANCE-2 and ADVANCE-3 trials. The combined incidence of major bleeding and clinically relevant non major bleeding was less with apixaban use compared with enoxaparin use in ADVANCE-1 but equivalent in the ADVANCE-2 and ADVANCE-3 trials.

Apixaban was evaluated for the prevention of stroke and systemic embolism in nonvalvular AF in two large randomized controlled trials, the apixaban versus aspirin to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial[10] and the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial[11]. In both trials, the primary efficacy outcome (prevention of stroke or systemic embolism) was superior with apixaban. The rate of major bleeding per year was less with apixaban compared with warfarin in ARISTOTLE.

Rivaroxaban

Rivaroxaban is a selective, reversible direct inhibitor of free and platelet -bound Factor Xa. The time to reach maximum plasma concentration is 30 minutes to 3 hours. Rivaroxaban's half-life has been reported to be 3–9 hours[5].Rivaroxaban prolongs the prothrombin time (INR) with sensitivity dependent on the reagent being used. Factor Xa inhibition may be a more appropriate marker for evaluating the plasma concentration of rivaroxaban. Rivaroxaban is approved by the FDA, the EMA and the HPFB for use in nonvalvular AF, in the primary prevention of VTE in adult patients who have undergone elective THA or TKA, in the treatment of DVT and PE and to reduce the risk of recurrent DVT and PE after initial treatment[6]. There are no specific reversing agents for this medication. The efficacy and safety of rivaroxaban has been evaluated in phase 3 clinical trials in different clinical situations which are summarized in Table 2.

The regulation of coagulation in orthopedic surgery to prevent deep venous thrombosis and pulmonary embolism (RECORD) 1,2,3,4 trials[12,13,14,15] compared rivaroxaban with enoxaparin for postoperative VTE prophylaxis in joint replacement surgery(THA and TKA). Rivaroxaban significantly reduced the total event rate compared with enoxaparin in all four trials and there was no difference in the incidence of major bleeding between the rivoroxaban and enoxaparin arms. On the basis of these results rivaroxaban was approved in Europe and Canada for the prevention of VTE in patients undergoing elective hip or knee arthroplasty.

The EINSTEIN study[16] compared oral rivaroxaban with enoxaparin followed by a VKA for 3, 6, or 12 months in patients with acute, symptomatic DVT (initial treatment study). A parallel, double blind, randomized study compared rivaroxaban with placebo for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for VTE (continued-treatment study). The EINSTEIN-PE[17] study was a similar study that evaluated the same dose of rivaroxaban vs enoxaparin/VKA in patients with acute, symptomatic PE, with or without DVT. In EINSTEIN, rivaroxaban therapy was non inferior to enoxaparin/VKA therapy with respect to recurrent VTE (2.1% vs 3.0%; P<.001). In the continued-treatment study, rivaroxaban therapy was superior to placebo use with respect to recurrent VTE (1.3% vs 7.1%; P<.001). The rates of symptomatic recurrent VTE in the EINSTEIN-PE study were similar between the rivaroxaban and enoxaparin/VKA groups.

In both studies, EINSTEIN and EINSTEIN-PE, the safety outcome of major or clinically relevant non major bleeding was similar in both treatment arms. The rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF) study[18,19] evaluated rivaroxaban for the prevention of stroke or systemic embolization in patients with nonvalvular AF (intermediate to high risk of stroke). Patients were randomly assigned to receive either rivaroxaban 20 mg/day or warfarin (target INR, 2.0-3.0) and the patients were monitored for 24 months. Rivaroxaban was non inferior to warfarin (2.1% vs 2.4% per year; P<.001 for non inferiority) in the primary efficacy outcome of stroke and systemic embolism. There was no difference between patients taking rivaroxaban and those taking warfarin in terms of all bleeding events.

Dabigatran

Dabigatran etexilate is the prodrug of dabigatran that selectively and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule. The time to maximum plasma concentration is 1.25–1.5 hours with maximum effect in 2 hours. Its half-life is about 12 hour. Over 90–95% of systemically available dabigatran is eliminated unchanged via renal excretion with the remaining 5–10% excreted in bile. Both the thrombin time (TT) and ecarin clotting time (ECT) are highly sensitive tests to monitor the anticoagulant effect of dabigatran. The prothrombin time (PT/INR) is prolonged by dabigatran, but is not sensitive enough to detect clinically relevant changes in drug concentration, and the APTT is prolonged, but not in a dose dependent manner. A specific reversing agent, idarucizumab, is available for dabigatran. Dabigatran is approved for use in nonvalvular AF by the

FDA, the EMA and the HPFB and for the primary prevention of VTE in adult patients with elective THA or TKA arthroplasty (EMA and HPFB). The efficacy and safety of dabigatran in different clinical situations has been evaluated in phase 3 clinical trials which are summarized in Table 3.

The RE-LY (randomized evaluation of long-term anticoagulant therapy)[20,21] evaluated the efficacy and safety of dabigatran at a dose of 110 or 150 mg twice daily compared with dose-adjusted warfarin targeting an INR of 2 to 3, in patients with nonvalvular AF and an intermediate risk of thromboembolism. Both doses of dabigatran were non inferior to warfarin while the higher dose proved to be superior for the primary outcome. Major bleeding occurred at a rate of 3.11, 2.71, and 3.36% per year for the patients treated with dabigatran 150 mg, dabigatran 110 mg, and warfarin respectively. The differences in both the efficacy and safety outcomes were statistically significant.

The RE-COVER study[22] evaluated patients with acute VTE for a period of 6 months. The 6 month incidence of recurrent symptomatic VTE and related deaths was 2.4% in patients treated with dabigatran vs 2.1% in those treated with warfarin (P<.001 for non inferiority).The rate of major bleeding episodes was similar in both groups.

Dabigatran for postoperative VTE prophylaxis in joint replacement surgery was evaluated in the European RE-MODEL study, the North American RE-MOBILIZE study, the European RE-NOVATE(I) and the North American RE-NOVATE(II) studies. There were conflicting results between the first 2 trials in post-op TKA. In RE-MODEL[23], the incidence of VTE or mortality was 37.7% in the enoxaparin arm compared with 36.4% in the dabigatran 220-mg arm (P=.0003 for non inferiority) and 40.5% in the dabigatran 150-mg, arm (P=.017 for non inferiority). However, in RE-MOBILIZE[24], the composite of VTE and death occurred in 25.3% of those in the enoxaparin arm compared with 31.1% of those in the dabigatran 220-mg arm (P=.02) and 33.7% of those in the dabigatran 150-mg arm (P<.001). The differences in efficacy between the 2 trials may be due to the different dosing schedules of enoxaparin. So, dabigatran may not be an equally efficacious prophylaxis option in this setting. Among the 3 arms, the incidence of major bleeding did not differ significantly in the two trials.

The RE-NOVATE I and II studies[25,26] evaluated dabigatran for preventing VTE after THA compared with enoxaparin. In RE-NOVATE I, the findings confirmed non inferiority for dabigatran (P<.0001 for non inferiority). Furthermore, RE-NOVATE II detected total VTE and death in 7.7% in the dabigatran 220-mg arm vs 8.8% in the enoxaparin arm (P=.43). In both RE-NOVATE studies there was no difference in major bleeding rates with either dose of dabigatran compared with enoxaparin.

Conclusion

Warfarin has been the most widely used oral anticoagulant for decades, despite its shortcomings. Since the introduction of NOACs in 2008, warfarin market share has declined from 87.5% to 72% (through 2008 to 2014) while NOACs have shown an upward trend with a market share of 15.5% as of 2014[2]. The question of whether

these agents will replace warfarin and heparins, which have been accepted as the gold standard during all these years, is one that needs to be answered after a thorough evaluation of several aspects including high cost of NOACs, lack of specific antidotes and lack of long-term safety data. So, it might take several years for warfarin to become redundant for clinical use in NVAF, VTE and pulmonary embolism and NOACs to dominate. Until further data are available NOACs should be avoided in pregnancy, in patients with mechanical heart valves and in those with severe renal insufficiency.

Table 1: Apixaban Phase 3 clinical trials

Trial	Study design	Primary efficacy	Primary safety
ADVANCE-1 **2009** **Postop TKA** **N=3195**	Apixaban 2.5 mg bd Vs Enoxaparin 30 mg bd Started 12-24 hrs postop	**Composite VTE and mortality:** Enoxaparin 100/1130(8.8%) Apixaban 104/1157(9.0%) **P=0.06 for non inferiority**	**Clinically relevant bleeding**: Enoxaparin 69/1588(4.3%) Apixaban 46/1596(2.9%) P=0.03
ADVANCE-2 **2010** **Postop TKA** **N=3057** **(1973 evaluable for primary efficacy)**	Apixaban 2.5 mg bd Started 12-24 hrs post op Vs Enoxaparin, 40 mg Started 12 hrs pre op	**Composite VTE and mortality**: Enoxaparin 243/997(24.4%) Apixaban 147/976(15.1%) **P<0.0001 for superiority**	**Clinically relevant bleeding:** Enoxaparin 72/1508)(4.8%) Apixaban 53/1501(3.5%) P=0.09
ADVANCE-3 **2010** **Postop THA** **N=5407** **(3866 evaluable for primary efficacy)**	Apixaban 2.5 mg bd Started 12-24 hrs post op vs Enoxaparin, 40 mg Started 12 hrs pre op	**Composite VTE and mortality:** Enoxaparin 74/1917(3.9%) Apixaban 27/1949(1.4%) **P<.001 for superiority**	**Clinically relevant bleeding:** Enoxaparin 134/2659(5.0%) Apixaban 129/2673(4.8%) P=0.72
AVERROES **2011** **Atrial fibrillation** **N=5599**	Apixaban 5 mg bd Vs Aspirin (81-324 mg)	**Composite VTE per year:** Aspirin 113/2791(3.7%) Apixaban 51/2808(1.6%), **P<.001 for superiority**	**Major bleeding per year**: Aspirin, 39/2791(1.2%) Apixaban 144/280(8.4%) P=0.57
ARISTOTLE **2011** **Atrial fibrillation** **N=18,201**	Apixaban5 mg bd vs Warfarin	**Composite VTE per year:** Warfarin 265/9081(1.6%), Apixaban 212/9120(1.27%), **P=0.01 for superiority**	**Major bleeding per year:** Warfarin 462/9052(3.09%), Apixaban 327/9088(2.13%) P<0.001

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Table 2: Rivaroxaban Phase 3 clinical trials

Trial	Study design	Primary efficacy	Safety
RECORD 1, 2008 THA N=4541	Rivaroxaban 10 mg/d started 6-8 hrs postop vs Enoxaparin 40 mg/d started 12 hrs preop duration 34 days	**Composite VTE and mortality:** Rivaroxaban 18/1595(1.1%) Enoxaparin 58/155(3.7%) **P<0.001 for superiority**	**Major bleeding**: Rivaroxaban 6/2209(03%) Enoxaparin 2/2224(0.1%) P=0.18
RECORD 2,2008 THA N=2509	Rivaroxaban 10 mg/d Started 6-8 hrs postop, 34days vs Enoxaparin 40 mg/d started 12 hrs preop,10-14d	**Composite VTE and mortality**: Rivaroxaban: 17/864(2.0%) Enoxaparin: 81/869(9.3%) **P<0.0001 for superiority**	**Major bleeding:** Rivaroxaban: 1/1228(<0.1%) Enoxaparin : 1/1229(<0.1%) P not significant.
RECORD 3,2008 TKA N=2531	Rivaroxaban 10 mg/d Started 6-8 hrs postop, Vs Enoxaparin 40 mg/d started 12 hrs preop, duration 12 days	**Composite VTE and mortality**: Rivaroxaban: 79/824(9.6%) Enoxaparin: 66/878(18.9%) **P<0.001 for superiority**	**Major bleeding:** Rivaroxaban: 7/1220(0.6%) Enoxaparin: 6/1239(0.5%) P=0.77
RECORD 4,2009 TKA N=3148	Rivaroxaban 10 mg/d Started 6-8 hrs postop vs Enoxaparin,30 mg bd Started 12-24 hrs postop duration 11days	**Composite VTE and mortality**: Rivaroxaban: 67/965(6.9%) Enoxaparin: 97/959(10.1%) **P=0.0118 for superiority**	**Major bleeding:** Rivaroxaban: 10/1526(0.7%) Enoxaparin: 4/1508(0.3%) P=0.1096
EINSTEIN,2010 Acute DVT N=3449	Rivaroxaban 15 mg bd 3 wk followed by 20 mg /d for3, 6, or 12 mo vs Enoxaparin bridging to warfarin for 3, 6, or 12 mo	**Recurrent, symptomatic VTE**: Rivaroxaban: 6/1731(2.1%) Warfarin: 51/1718(3.0% **P<.001 for non inferiority**	**Any clinical bleeding:** Rivaroxaban (38/1711(8.1%) Warfarin: 139/1718(8.1%) P=0.77
EINSTEIN-EXT, 2010 Continued treatment N=1196	Continued treatment 20 mg/d for an additional 6-12 mo after completing therapy in acute DVT study vs Placebo	**Recurrent, symptomatic VTE:** Placebo: 42/594(7.1%) Rivaroxaban: 8/602(1.3%) **P<0.001 for superiority**	**Major bleeding**: Placebo: 0/590(0%) Rivaroxaban: 4/598(0.7%) P=0.11
EINSTEIN-PE, 2012 Symptomatic PE N=4832	Rivaroxaban 15 mg bd 3 wk followed by 20 mg/d for 3, 6, or 12 mo vs Enoxaparin bridging to warfarin for 3, 6, or 12 mo	**Recurrent, symptomatic VTE:** Warfarin: 4/2413(1.8%) Rivaroxaban: 0/2419(2.1%) **P=0.003 for non inferiority**	**Any clinical bleeding:** Warfarin 274/2405(11.4%) Rivaroxaban: 49/2412(10.3%) P=0.23
ROCKET AF,2011 Atrial fibrillation N=14,264	Rivaroxaban 20 mg /d vs Warfarin	**Composite VTE per year**: Warfarin 306/7090 (2.4%) Rivaroxaban: 269/7081(2.1%), **P<0.001 for non inferiority**	**All clinical bleeding events per year:** Warfarin: 1449/7125(14.5%) Rivaroxaban: 1475/7111(14.9%) P=0.44

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Table 3: Dabigatran Phase 3 clinical trials

Trial	Study design	Primary efficacy	Safety
RE-LY, 2009 **Atrial fibrillation** N=18,113	Warfarin vs Dabigatran 150 mg bd and 110 mg bd	**Composite VTE per year**: Warfarin 199/6022(1.69%) Dabigatran, 150 mg 134/6076(1.11%) **P<0.001 for superiority** Dabigatran, 110 mg 182/6015(1.53%) **P<0.001 for non inferiority**	**Major bleeding per year:** Warfarin 397/6022(3.36%) Dabigatran, 150 mg bid 375/6076(3.11%) P=0.31 Dabigatran, 110 mg bid 322/6015(2.71%) P=0.003
RE-MODEL, 2007 **Postop TKA** N=2076	Enoxaparin,40 mg vs Dabigatran 150 mg /d 220 mg /d	**Composite VTE and mortality**: Enoxaparin, 40 mg 193/512(37.7%) Dabigatran, 150 mg 213/526 (40.5%) **P=0.017 for non inferiority** Dabigatran, 220 mg 183/503(36.4%) **P=.0003 for non inferiority**	**Major bleeding**: Enoxaparin 9/694(1.3%) Dabigatran, 150 mg/d 9/703(1.3%) P value not significant Dabigatran, 220 mg/d (10/679(1.5%) P value not significant
RE-NOVATE I, 2007 **Postop THA** N=3494	Enoxaparin,40 mg vs Dabigatran 150 mg /d 220 mg /d	**Composite VTE and mortality**: Enoxaparin, 40 mg 60/897(6.7%) Dabigatran, 150 mg 75/874(8.6%) **P<.0001 for non inferiority** Dabigatran, 220 mg 53/880(6.0%) **P<.0001 for non inferiority**	**Major bleeding:** Enoxaparin, 40 mg/d 18/1154(1.6%) Dabigatran, 150 mg/d 15/1163(1.3%) P=0.60 Dabigatran, 220 mg/d 23/1146(2.0%) P=0.44
RE-NOVATE II,2011 **Postop THA** N=2055	Enoxaparin, 40 mg vs Dabigatran 220 mg /d	**Composite VTE and mortality**: Enoxaparin, 40 mg 69/785(8.8%) Dabigatran, 220 mg 61/792(7.7%0 **P=0.43 for superiority**	**Major bleeding**: Enoxaparin, 40 mg/d 9/1003(0.9%) Dabigatran, 220 mg 14/1010(1.4%) P=0.40
RE-MOBILIZE 2009 **Postop TKA** N=2615	Enoxaparin 30 mg bd vs Dabigatran 150 mg/d 220 mg /d	**Composite VTE and mortality**: Enoxaparin, 30 mg 163/643(25.3%) Dabigatran, 150 mg 219/649(33.7%) **P=0.0009 for inferiority** Dabigatran, 220 mg 188/604(31.1%) **P=0.0234 for inferiority**	**Major bleeding**: Enoxaparin, 30 mg 12/868(1.4%) Dabigatran, 150 mg 5/871(0.6%) P value not significant Dabigatran, 220 mg 5/857(0.6%0 P value not significant
RE-COVER, 2009 **Acute VTE** N=2564	Warfarin vs Dabigatran150 mg bd 06 months	**Composite VTE and related mortality:** Warfarin 27/1265(2.1%) Dabigatran, 150 mg bd 30/1274(2.4%) **P<0.001 for non inferiority**	**Major bleeding:** Warfarin 24/1265(1.9%) Dabigatran, 150 mg bid 20/1274(1.6%) P value not significant

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