

# The clinical implications of new oral anticoagulants: Will the potential advantages be achieved?

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## Introduction

With the advent of new oral anticoagulants a thorough assessment and evaluation of benefits weighed against potential risks must be conducted. In a practical sense, what will these new agents really offer to the healthcare system, to practitioners, and to patients?

Oral anticoagulation with the vitamin K antagonist (VKA), warfarin, continues to increase worldwide due to its efficacy in preventing stroke in patients with atrial fibrillation (AF) or recurrent thromboembolism in patients with thromboembolic disease (1). Despite warfarin's efficacy, its management remains problematic due to its complex pharmacokinetic and pharmacodynamic properties and narrow therapeutic range. Warfarin therapy requires vigilant coagulation monitoring, clinical surveillance, and continuous patient education (► Table 1). Due to these dosing complexities, warfarin is associated with a high rate of adverse events that creates barriers to more widespread use (2, 3).

The development of new anticoagulants has been pursued with the aim of finding effective, but safer and more convenient therapies. Many of the new agents attempt to meet the goals of an ideal anticoagulant (► Table 2) by targeting a specific step or factor in the coagulation pathway. Among agents that are most advanced in clinical re-

search, and rapidly becoming approved for specific indications, are the direct thrombin (factor IIa [FIIa]) inhibitors and the direct factor Xa (FXa) inhibitors (4–7). Ximelagatran, an oral, direct thrombin inhibitor, was the first to undergo extensive testing showing that it was at least as effective and safe as warfarin for stroke prevention in AF (8, 9) and for the secondary prevention of venous thromboembolism (VTE) in patients with established VTE (10). It also showed effectiveness in patients with acute coronary syndromes (11). Because of hepatic toxicity, however, the drug was removed from the market and is no longer in development.

## Results of phase III trials with FIIa and FXa inhibitors

Dabigatran etexilate is an oral, direct thrombin inhibitor, recently evaluated in a number of phase III VTE prevention trials after orthopaedic surgery, and is already approved in Europe and Canada for the prevention of VTE after elective total hip or knee replacement surgery (12–14). The dabigatran orthopaedic studies were all non-inferiority trials. Dabigatran etexilate was shown to be non-inferior to enoxaparin when the latter is dosed according to the European regimen for enoxaparin (40 mg once daily beginning pre-operatively) for the prevention of VTE in patients undergoing hip or knee replacement surgery (► Table 3). When compared to enoxaparin dosed according to the North American regimen (30 mg twice daily), however, dabigatran etexilate failed to show non-inferiority in knee arthroplasty (14). In one of the first of the large stroke prevention in AF trials, dabigatran etexilate was recently shown to be superior to warfarin at the 150 mg BID dose with a similar amount of major bleeding, and non-inferior to warfa-

rin at the 110 mg BID dose, with significantly less major bleeding (Table 3) (15). Studies are ongoing with dabigatran etexilate in acute coronary syndrome (ACS), and in the treatment of patients with VTE.

Similarly, two oral FXa inhibitors have completed phase III studies in major orthopaedic surgery (16–22), all of which were non-inferiority trials except for the RECORD 2 trial which was a superiority trial. Rivaroxaban is licensed in the European Union and Canada for the prevention of VTE after total hip and knee replacement surgery. ► Table 4 summarises the phase III results with rivaroxaban which has been

**Table 1: Limitations of the vitamin K antagonists.**

- Slow onset of action
- Slow offset of action (long duration of action, long elimination half-life)
- Narrow therapeutic range
- Multiple drug and dietary interactions
- Monitoring required to maintain therapeutic range
- Difficult to manage peri-procedural interventions
- Impaired quality of life for patient
- Labor intensiveness of management for healthcare provider
- Underuse of therapy due to fear of adverse events and complexity of management

**Table 2: Attributes of an ideal anticoagulant compared to current VKAs and parenteral anticoagulants.**

- Oral administration
- Rapid onset of action / Rapid offset of action
- Wide therapeutic range
- Predictable therapeutic effect with fixed or weight-based dosing
- No food or drug interactions
- No monitoring required (although, the ability to monitor if desired)
- Well defined pharmacokinetics in presence of renal or hepatic disease
- Easily reversible
- Cost effective

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shown to be superior to enoxaparin dosed according to either the European or North American regimens for the prevention of VTE in major orthopaedic surgery. An analysis of pooled data from these four studies further showed that rivaroxaban was superior to enoxaparin for the prevention of symptomatic VTE and all-cause mortality (20) (Table 4). Phase III studies of rivaroxaban for the prevention of stroke in AF, VTE prevention in medically ill patients, prevention of cardiovascular events in ACS, and the treatment of VTE are ongoing.

Apixaban, another FXa inhibitor, is currently emerging from phase III testing in orthopaedic surgery with ongoing trials in

stroke prevention in AF, treatment of VTE, VTE prophylaxis in medical patients and in cancer patients, and prevention of cardiovascular events in ACS. In the first phase III trial reported in major knee replacement surgery (21), according to prespecified non-inferiority criteria, apixaban failed to show non-inferiority to enoxaparin dosed using the North American regimen, based on relative risk reduction ( $p=0.06$ ), possibly due to the small number of events in the enoxaparin group (► Table 5). Apixaban did show less bleeding compared to enoxaparin at the dose used in the study, but major bleeding was not significantly different. The second phase III trial in knee replacement surgery, presented recently,

showed apixaban to be superior to enoxaparin when dosed according to a European regimen (22). A third phase III orthopaedic trial in hip surgery is nearing conclusion.

Current and future research focussing on oral FXa and FIIa inhibitors is promising. These agents could potentially alter the practice of anticoagulation as we know it. However, despite the limitations of warfarin, these novel agents have large expectations to meet, if they are to fulfil the unmet need for safe and effective oral anticoagulants. ► Table 6 summarises some of the potential advantages and disadvantages of the new oral FXa and FIIa inhibitors compared with warfarin.

**Table 3: Results of dabigatran etexilate in major orthopaedic surgery and atrial fibrillation (phase III trials).**

Study	Indication	Population, number, duration	Dabigatran dose	Comparator dose	Primary efficacy outcome measure	Primary safety measure	Primary efficacy measure results	Primary safety results
RE-MODEL <sup>12</sup>	VTE prevention	TKR, 2,076, 6–10 days, with f/u 3 mo	Dab 150 or 220 mg qd (1 <sup>st</sup> dose was half-dose starting 1–4 h post-op)	Enox 40 mg qd pre-op	Composite VTE and all-cause mortality	Major bleeding	150 mg: 40.5%, 213/526 $p=0.017$ 220 mg: 36.4%, 183/503 $p=0.0003$ Enox: 37.7%, 193/512 (Dab vs. Enox for non-inf)	150 mg: 1.3%, 9/703, $p=1.0$ 220 mg: 1.5%, 10/679, $p=0.82$ Enox: 1.3%, 9/694 (Dab vs. Enox for non-inf)
RE-NOVATE <sup>13</sup>	VTE prevention	THR, 3,494, 28–35 days	Dab 150 mg or 220 mg qd (1 <sup>st</sup> dose was half-dose starting 1–4 h post-op)	Enox 40 mg qd pre-op	Composite VTE and all-cause mortality	Major bleeding	150 mg: 8.6%, 75/874, $p<0.0001$ 220 mg: 6%, 53/880, $p<0.0001$ Enox: 6.7%, 60/897 (Dab vs. Enox for non-inf)	150 mg: 1.3%, 15/1163, $p=0.6$ 220 mg: 2%, 23/1146, $p=0.44$ Enox: 1.6%, 18/1154 (Dab vs. Enox for non-inf)
RE-MOBILIZE <sup>14</sup>	VTE prevention	TKR, 2,615, 12–15 days	Dab 150 or 220 mg qd (1 <sup>st</sup> dose was half-dose starting 6–12 h post-op)	Enox 30 mg bid post-op	Composite VTE and all-cause mortality	Major bleeding	150 mg: 34%, 219/649, $p<0.001$ 220 mg: 31%, 188/604, $p=0.02$ Enox: 25%, 163/643 (Enox better than Dab)	150 mg: 0.6%, 5/871 220 mg: 0.6%, 5/857 Enox: 1.4%, 12/868
RE-LY <sup>15</sup>	Stroke prevention	Atrial fibrillation, 18,113, 2 yrs	Dab 110 or 150 mg BID	Warfarin with INR 2–3	Stroke or systemic embolism	Major bleeding	110 mg: 1.53%, 182/6015, (RR 0.91; 95%CI 0.74–1.11; $p<0.001$ for non-inferiority) 150 mg: 1.11%, 134/6076, (RR 0.66; 95% CI 0.53–.82; $p<0.001$ for superiority)	Warf: 3.36%, 397/6022 110 mg: 2.71%, 322/6015, $p=0.003$ 150 mg: 3.11%, 375/6076; $p=0.31$

Dab, dabigatran etexilate; Enox, enoxaparin; VTE, venous thromboembolism (includes deep-vein thrombosis and pulmonary embolism); TKR, total knee replacement; THR, total hip replacement; bid, twice daily; qd, once daily; h, hour; pre-op, pre-operatively; post-op, post-operatively; f/u, follow up; CI, confidence interval.

## The advantages and disadvantages of new oral anticoagulants

The potential superior efficacy and/or safety profiles found in phase III studies may not be the only attributes that the new

oral anticoagulants possess over warfarin. These agents have a rapid onset of action, leading to a faster onset of anticoagulant effect compared with warfarin. Peak plasma dabigatran concentrations are attained after approximately 1.5 hours (23). Peak plasma levels for rivaroxaban are achieved at 3 to 4 hours and at about 3 hours for api-

xaban (24,25) (see ► Table 7). This enables these agents to produce an anticoagulant response in the same time frame as the low-molecular-weight heparins and fondaparinux, without the requirement for subcutaneous administration. In addition, dabigatran, apixaban and rivaroxaban all have shorter half-lives than warfarin, there-

**Table 4: Results of rivaroxaban in major orthopaedic surgery (phase III trials).**

Study	Indication	Population, number, duration	Rivaroxaban dose	Comparator dose	Primary efficacy outcome measure	Primary safety measure	Primary efficacy measure results	Primary safety results
RECORD-1 <sup>16</sup>	VTE prevention	THR, 4,541, 31–39 days	Riv 10 mg qd	Enox 40 mg qd pre-op	Composite VTE and all-cause mortality	Major bleeding	Riv: 1.1%, 18/1595 Enox: 3.7%, 58/1558 p<0.001 for superiority	Riv: 0.3%, 6/2209 Enox: 0.1%, 2/2224 p=0.18
RECORD-2 <sup>17</sup>	VTE prevention	THR, 2,509, 31–39 days	Riv 10 mg qd for 31–39 days	Enox 40 mg qd for 10–14 days pre-op followed by placebo	Composite VTE and all-cause mortality	Major bleeding	Riv: 2%, 17/864 Enox: 9.3%, 81/869 p<0.0001 for superiority	Riv:<0.1%,1/1228 Enox:<0.1%,1/1229 p=1
RECORD-3 <sup>18</sup>	VTE prevention	TKR, 2,531, 10–14 days	Riv 10 mg qd	Enox 40 mg qd pre-op	Composite VTE and all-cause mortality	Major bleeding	Riv: 9.6%, 79/824 Enox: 18.9%, 166/878 p<0.001 for superiority	Riv: 0.6%, 7/1220 Enox: 0.5%, 6/1239 p= 0.77
RECORD-4 <sup>19</sup>	VTE prevention	TKR, 3,148, 10–14 days	Riv 10 mg qd	Enox 30 mg bid pre-op	Composite VTE and all-cause mortality	Major bleeding	Riv: 6.9%, 67/965 Enox: 10.1%, 97/959 p=0.012 for superiority	Riv: 0.7%, 10/1526 Enox: 0.3%, 4/1508 p=0.11
Pooled RECORD 1,2,3,4 <sup>20</sup>	VTE prevention	RECORD-1,2: THR 3,4: TKR, 12,729; 35 days	Riv 10 mg qd	RECORD 1,2,3: Enox 40 mg qd RECORD 4: Enox 30 mg bid	Composite of symptomatic VTE and all-cause mortality	Major bleeding	Riv: 0.8% (515/6183) Enox: 1.6% (101/6200) p< 0.001 for superiority	Riv: 0.4% (27/6183) Enox: 0.3% (17/6200) p= 0.076

Riv, rivaroxaban; Enox, enoxaparin; VTE, venous thromboembolism (includes deep-vein thrombosis and pulmonary embolism); N, number of patients; 1°, primary; TKR, total knee replacement; THR, total hip replacement; bid, twice daily; qd, once daily; h, hour; wk, week; pre-op, pre-operatively; post-op, post-operatively; tx, treatment.

**Table 5: Results of apixaban in major orthopaedic surgery (phase III trial).**

Study	Indication	Population, number, duration	Apixaban dose	Comparator dose	Primary efficacy outcome measure	Primary safety measure	Primary efficacy outcome measure results	Primary safety results
ADVANCE-1 <sup>21</sup>	VTE prevention	TKR; 3195; 12 days	Apix 2.5 mg bid	Enox 30 mg bid	Composite VTE and all-cause mortality	Major bleeding	Apix: 9%, 104/1157 Enox: 8.9%, 100/1130 RR 1.02 (CI 0.78–1.32)	Apix: 0.7%, 11/1596 Enox: 1.4%, 22/1588 p=0.053
ADVANCE-2 <sup>22</sup>	VTE prevention	TKR; 1,973; 12 days	Apix 2.5 mg bid	Enox 40 mg qd	Composite VTE and all cause mortality	Major bleeding	Apix: 15%, 147/976 Enox: 24%, 243/997 (RRR 0.62; 95%CI 0.51–0.74; p<0.0001)	Apix 0.60% Enox 0.93% P=not significant

Apix, apixaban; Enox, enoxaparin; VTE, venous thromboembolism (includes deep-vein thrombosis and pulmonary embolism); TKR, total knee replacement; bid, twice daily; CI, confidence interval.

fore their effects will wear off more quickly than warfarin's.

This rapid onset and offset of action may eliminate the need for a two-anti-coagulants regimen for the treatment of VTE, and also an anticoagulant "bridge" for pre- and post-invasive procedures in patients on warfarin. The elimination of a subcutaneous or intravenous heparin bridge would decrease the burden of clinical care and potentially decrease hospitalisations or length of stay, leading to cost savings.

Another advantage of these new anticoagulants is that they do not require routine coagulation monitoring. They exhibit a linear, predictable therapeutic effect with a fixed or weight-based dose (5, 24, 26, 27). The lack of monitoring requirement could alleviate healthcare practitioners' workloads relative to the management of warfarin and, because their therapeutic effect is predictable and more stable than warfarin, may lead to fewer adverse events (both from under- and over-anticoagulation) requiring emergency room visits and hospitalisations. It may also be more convenient to the patient, potentially resulting in improvements in quality of life and eliminating some of the barriers that limit widespread oral anticoagulant use.

Warfarin has numerous food and drug interactions leading to non-therapeutic international normalised ratios (INRs). Newer agents have few, if any, interactions with food. However, they are not completely free of drug interactions. The risk of drug-drug interactions with dabigatran is low because the cytochrome P-450 system is not involved in its metabolism (23). However, the absorption of dabigatran is reduced by approximately 25% with the co-administration of proton pump inhibitors (23, 26, 28). Rivaroxaban and apixaban are both partially metabolised in the liver via a portion of the CYP450 pathway. Rivaroxaban is metabolised via the CYP3A4 and 2J2 pathways and apixaban is partially metabolised by the liver via CYP3A4 (5, 25, 29). As various medications are metabolised via this pathway, it could be the source of potential medication interactions.

Despite the advantages of these new agents, there are also potential disadvantages.

**Table 6: Potential advantages and disadvantages of new FXa and FIIa inhibitors compared to the VKAs.**

Advantages	Disadvantages
<ul style="list-style-type: none"> <li>● Oral administration</li> <li>● Rapid onset of action               <ul style="list-style-type: none"> <li>– May replace parenteral anticoagulants for selected conditions</li> <li>– Eliminates need for two anticoagulant regimen (i.e. heparin and warfarin)</li> </ul> </li> <li>● Predictable therapeutic effect with fixed or weight-based dosing               <ul style="list-style-type: none"> <li>– No routine coagulation monitoring required</li> </ul> </li> <li>● Limited or no food or drug interactions</li> <li>● Short half-life               <ul style="list-style-type: none"> <li>– Effect wears off more quickly than VKAs</li> </ul> </li> <li>● No need for bridging AC for invasive procedures</li> <li>● More convenient for patient               <ul style="list-style-type: none"> <li>– No routine coagulation monitoring; no dietary limitations; limited drug interactions</li> </ul> </li> <li>● More convenient for physician               <ul style="list-style-type: none"> <li>– No routine coagulation monitoring</li> </ul> </li> <li>● Potential for greater use               <ul style="list-style-type: none"> <li>– Barriers removed that limit more widespread use</li> </ul> </li> <li>● More cost effective               <ul style="list-style-type: none"> <li>– No routine coagulation monitoring</li> <li>– Fewer adverse events requiring emergency room visits and hospitalizations</li> </ul> </li> <li>● Possible superior efficacy</li> <li>● Possible superior safety               <ul style="list-style-type: none"> <li>– Stable therapeutic levels avoids excessive AC seen with VKAs</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● No routine coagulation monitoring               <ul style="list-style-type: none"> <li>– Cannot titrate dose</li> <li>– Determination of failure of therapy vs. poor compliance</li> </ul> </li> <li>● Short half-life               <ul style="list-style-type: none"> <li>– Anticoagulation effect declines quickly if compliance poor</li> <li>– Poor compliance may affect efficacy more than with VKA</li> </ul> </li> <li>● No antidote</li> <li>● No monitoring lab marker available to measure drug activity if needed</li> <li>● Potential dose adjustment required for renal or hepatic dysfunction</li> <li>● Cost</li> </ul>

The short half-lives of new agents in combination with the fact that they do not require routine coagulation monitoring, makes the issue of medication adherence extremely important. Although rarely a problem in clinical trials, adherence is a real problem in everyday treatment, leading to increased rates of morbidity, mortality, and in turn, overall healthcare costs (30–32). Studies show that approximately 50% of patients across varying gender, age, ethnicity and medical disorders, fail to follow their prescribed medication regimens (33). Poor adherence to warfarin is noted to be associated with poor anticoagulation control. Risk factors for non-adherence to warfarin therapy were related to higher level of higher education, employment status, impaired mental health, and cognitive impairment (34). Poor adherence may be a particular problem in patients with AF, who often experience no symptoms, and may not fully understand the importance of

their medication. Anticoagulation management clinics are useful in monitoring and managing adherence and they achieve high rates of time in therapeutic range (35).

Despite the challenge that practitioners face on a daily basis, warfarin's long, effective half-life of approximately 40 hours, may work to the providers' advantage in non-adherent patient populations, and therefore, a degree of non-adherence may have a negligible effect on anticoagulation levels (36) compared with an anticoagulant with a short half-life. If a non-adherent patient misses one or two doses of warfarin, its anticoagulant protective effects may still be present which may not be the case with a drug with a short half-life.

Routine INR monitoring in patients on warfarin may be deemed as cumbersome for both the patient and practitioner. Although the lack of monitoring required with FIIa and FXa inhibitors compared with warfarin reduces the number of clinic

**Table 7: Summary of pharmacokinetics and pharmacodynamics of warfarin and novel oral anticoagulants (23–29).**

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	VKOR and factors II, VII, IX, X	Factor IIa (thrombin)	Factor Xa	Factor Xa
Time to peak concentration	72–96 h	1.5–3 h	2–4 h	1–3 h
Vol. of dist.		60–70 l	50 l	Reported as low
Half-life	40 h	12–14 h	9–13 h	9–14 h
Metabolism	Liver-CYP2C9	Conjugation	Liver-CYP3A4 and CYP2J2	Partially through CYP3A4
Elimination	Bile and urine	80% renal, 20% faecal	66% faecal, 33% renal	75% faecal, 25% renal
Administration	Once daily	Once or twice daily	Once daily	Twice daily
Monitoring	INR	Not needed	Not needed	Not needed
Antidote or potential therapy for bleeding	Vitamin K, FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa	FFP, PCC or rFVIIa
Assay	PT/INR	Experimental	Experimental	Experimental
Drug interactions	CYP 2C9	PPIs decrease absorption and potent P-gp inhibitors	Potent CYP 3A4 inhibitors and P-gp inhibitors	Potent CYP 3A4 inhibitors

VKOR, vitamin K oxidase reductase; CYP, cytochrome P450; PCC, prothrombin complex concentrates; PPIs, proton pump inhibitors; P-gp, P-glycoprotein; h, hour.

visits, this may also deny the physician the opportunity for patient education and the earlier detection of problems, such as bleeding or thrombosis. It also denies the practitioner the ability to tailor the intensity of anticoagulant therapy for patient specific factors. With an increasing number of patients on single or dual antiplatelet therapy, or for those patients with an increased bleeding risk, it may be an advantage to monitor the intensity of anticoagulation therapy and adjust if necessary. Patient-specific tailoring of therapeutic anticoagulant levels based on a simple coagulation measurement is not an option with the newer agents. Bleeding events can often be prevented by the practitioner in a patient on a VKA by noticing a trend in elevated INRs and intervening before a significant bleed occurs. If a practitioner detects supratherapeutic levels of the INR with or without bleeding, a reduced dose can be given, a dose can be skipped, or vitamin K can be given to reverse the elevation. With newer agents, no antidote exists which may be problematic for patients who are at a high risk of bleeding or for those who pres-

ent with a bleed. Reversal options for direct thrombin or FXa inhibitors include fresh frozen plasma or factor concentrates, both requiring an inpatient hospital admission as well as increased costs. Agents that do not require monitoring do not allow for pre-emptive intervention if one notes an elevated level of anticoagulation.

Another disadvantage of not having a monitored drug involves the management response when therapy has appeared to fail. Currently, if a patient develops a thromboembolic event on warfarin, the INR is measured to determine if the event is truly a failure of therapy, or whether the patient was subtherapeutic (due to non-compliance or other factors influencing the INR). In the latter case, dosing can be adjusted to increase the INR and patient education can be provided if thought to be necessary. With the use of a non-monitored drug, such determinations cannot be made.

Other potential disadvantages include dosing adjustment for renal and/or hepatic dysfunction. Warfarin does not require dosing adjustments for renal impairment, and the INR provides a guide to dose-

adjust for hepatic impairment. Up to 80% of absorbed dabigatran is eliminated unchanged via the renal route with the remaining drug excreted in the faeces (23, 26, 28). Pharmacokinetic data indicates that for patients with moderate renal dysfunction (CRcl 30–50 ml/min) caution is warranted and the dose may be decreased, but for those patients with significant renal dysfunction (CRcl < 30 ml/min), use is contraindicated (28). Rivaroxaban has a dual mechanism of excretion, approximately two-thirds are metabolised to inactive metabolites, with half then being excreted renally and the other half eliminated by the hepatobiliary route in the faeces. The final one-third of the active drug undergoes direct renal elimination as unchanged active substance in the urine, mainly via active renal secretion (25). As a patient's renal function declines, the clearance of rivaroxaban is reduced and the max peak concentration is increased (24, 28, 29). Apixaban also has a dual mechanism of excretion, with approximately 25% excreted renally and the remainder eliminated by the hepatobiliary route in the faeces (27, 28). These new agents may need to be dose-adjusted for renal and/or hepatic insufficiencies or not used at all. Such patient populations are currently excluded from the recent clinical trials and consequently this may lead to initially unknown effects in populations with impairment.

Warfarin is available as a generic medication that is relatively inexpensive for third-party payers and patients to afford. Newer agents will be under new patent, sold as a brand name medication, and could be significantly more expensive. Like some other costly medications, third party payers may require prior approval providing that patients meet pre-specified criteria to receive such new, expensive oral anticoagulants. Patients who are unable to afford their medications may sometimes not take them, or skip days to extend the supply. A recent survey questioned 700 physicians and found that their biggest concern was that their patients were not filling their prescriptions or were skipping their pills due to financial stress (37). In 2008, these physicians wrote more prescriptions for generic medications vs. branded medications than in previous years.

## Implications for clinical practice

How will clinicians translate such emerging data, the pros and the cons of the novel oral anticoagulants, into everyday, real-world use? At first, with limited indications, the impact of new agents may be minimal and will depend on an orthopaedic surgeon's level of comfort in using such agents. A patient selection process may be put into place, involving carefully selected candidates for these new agents. Enoxaparin or warfarin will likely continue to be the mainstay of treatment until more phase III data outcomes are published in the AF and VTE populations, and show that the new agents are as safe and effective as warfarin. Warfarin will also remain as the mainstay of treatment for patients with mechanical heart valves, since studies in this population have not been started. Warfarin may also hold favour with patients who are considered non-compliant with therapy, and as an option for those patients that "fail" or develop an event while on one of the new agents. Lastly, patients on warfarin who are clinically defined as "non-responders" or who have difficulty maintaining a stable INR on warfarin may be ideal candidates for a new oral anticoagulant. Certainly, convenience of therapy will be a major motivating factor to change to a new, non-monitored anticoagulant drug.

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