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# Scientific Update™

## New Perspectives in Long-term Anticoagulation: An Innovative Approach to Improve Patient Management

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Discussed by: GORDON MOE, MD

**Long-term anticoagulant therapy for the prevention and treatment of venous and arterial thromboembolic diseases is a standard and required treatment for many patients. However, significant limitations exist in the current forms of anticoagulation therapy that preclude a full therapeutic application from the perspective of both physician and patient. This issue of *Cardiology Scientific Update* reviews contemporary data on the burden of venous arterial thromboembolic diseases, the limitations of vitamin K antagonists, and the promising novel approaches to anticoagulation in the management of patients with these diseases.**

### The burden of thromboembolic disease: a challenge for clinicians and healthcare systems

Atrial fibrillation (AF) remains the most common sustained arrhythmia in clinical practice worldwide and affects >1% of the population.[1,2] In the last 2 decades, the prevalence of AF has increased dramatically[3] and is described as a "growing epidemic."[4] Indeed, the prevalence of AF in the United States (US) is expected to increase to above 5.3 million by the year 2050.[5] The presence of AF is associated with poor clinical outcomes, including stroke and death;[6,7] for example, the risk of ischemic stroke increases 5-fold in patients with AF, with a 1.5- to 1.9-fold increase in the risk of mortality across all age groups.[8] The percentage of strokes attributable to AF increases sharply with age, from 1.5% at 50-59 years of age to 23.5% at 80-89 years of age.[8,9] Reports suggest that patients with ischemic stroke caused by AF are 2.23 times more likely to be bedridden than those who suffer stroke from other causes.[10] Considerable evidence exists that stroke in AF patients has a worse outcome than in patients without AF, including higher mortality, severity, and recurrence rates, and greater functional impairment and dependency.[11] A large number of patients with AF also experience heart failure and the presence of heart failure also increases 1-year mortality in these patients.[12]

In a survey carried out in 5 European countries, in-patient care and interventional procedures were found to be the main driver of costs in patients with AF, accounting for >70% of total annual costs.[13] Stroke associated with AF accounts for one-fifth of stroke hospitalizations in Europe. In the United Kingdom (UK), there were 534 000 people with AF during 1995. The direct cost of healthcare for these patients was £244 million (~$391 million CDN; 1995 exchange rate), or 0.62% of total National Health Service expenditures. Hospitalizations and drug prescriptions accounted for 50% and 20% of this expenditure, respectively. Long-term nursing home care after hospital admission cost an additional £46.4 million (~ $74 million CDN; 1995 exchange rate). Therefore, from the perspective of the patient, embolic stroke is the most catastrophic complication of AF, and its prevention is one of the most challenging but dynamic areas of AF investigation.

In 2000, the direct cost of hospital admission for stroke due to AF rose to €376 million ($530 million CDN; 2000 exchange rate).[14] Several analyses have now demonstrated that the mortality and stroke risks from AF are not reduced by rhythm control when compared with rate control (Table 1).[15-19] Anticoagulation using vitamin K antagonists (VKAs; eg, warfarin) reduces the risk of stroke in patients with AF by



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**Table 1: Risk of mortality and ischemic stroke in randomized, controlled trials of rhythm versus rate control in atrial fibrillation (AF)**

| | N | Follow-up (years) | Mortality (%) | | Ischemic stroke (%) | |
|---|---|---|---|---|---|---|
| | | | Rhythm | Rate | Rhythm | Rate |
| STAF[15] | 200 | 1 | 4.0 | 8.0 | 5.0 | 2.0 |
| RACE[16] | 522 | 2.3 | 6.8 | 7.0 | 7.9 | 5.5 |
| HOT CAFE[17] | 205 | 1.7 | 2.9 | 1.0 | 2.9 | 0 |
| AFFIRM[18] | 4 060 | 3.5 | 23.8 | 21.3 | 7.1 | 5.5 |

~60%.[20,21] Current management guidelines recommend anticoagulation for patients with AF who are at intermediate and high-risk for thromboembolic events and without contraindications (Tables 2 and 3).[22-25] High-risk factors include mitral stenosis, prosthetic heart valves, and history of stroke and transient ischemic attacks. Moderate-risk factors include age >75 years, hypertension, diabetes, and heart failure. Systemic anticoagulation therefore currently plays an important role in the long-term management of AF, since reducing the incidence of stroke in this population will reduce the burden of the disease both for patients and the healthcare system.

## Is there room for improvement in long-term anticoagulation therapy? The patient's perspective

For the prevention of stroke risk in AF, warfarin has been commercially available for over 50 years and is the sole oral anticoagulant currently used in many parts of the world. With an estimated 2 million people in the US initiating warfarin therapy each year, the efficacy and safety of warfarin and related oral anticoagulants are central issues in stroke prevention. Much has been written about the disadvantages of VKAs. Although VKAs are highly effective in preventing thromboembolism in rigorous trial settings, their use in everyday clinical practice may be challenging. The limitations of this drug class may lead to suboptimal utilization and an increase in adverse events. VKA limitations include the following:

- slow onset of action
- narrow therapeutic window[26]
- the need for frequent monitoring
- wide variability in dose response
- drug-drug and drug-food interactions[27]
- efficacy compromised by inadequate dosing.

Indeed, VKAs are among the most common classes of drugs implicated in adverse events.[28] Patient adherence to and/or persistence with warfarin is also considered a problem and several studies indicate that it is a major factor in the instability of anticoagulant control.[29,30] In patients with AF managed by general practitioners in the US, there is a relatively low likelihood of patients remaining on treatment, with only

**Table 2: The $CHADS_2$ index: stroke risk score for AF[22,23]**

| | Score, points | Prevalence (%) |
|---|---|---|
| Congestive heart failure | 1 | 32 |
| Hypertension | 1 | 65 |
| Age >75 years | 1 | 28 |
| Diabetes mellitus | 1 | 18 |
| Prior Stroke or TIA | 2 | 10 |
| High risk | ≥2 | 1–9 |
| Moderate risk | 1 | 13–40 |
| Low risk | 0 | 18–51 |

| | Score points | Risk of stroke (% per year) | |
|---|---|---|---|
| Approximate risk threshold for anticoagulation (risk/benefit ratio) | 0 | 1.9 | |
| | 1 | 2.8 | 3% per year |
| | 2 | 4.0 | |
| | 3 | 5.9 | |
| | 4 | 8.5 | |
| | 5 | 12.5 | |
| | 6 | 18.2 | |

TIA = transient ischemic attack

50% taking the medication at 3 years.[31] These observations suggest that not all benefits observed in clinical trials may be achievable in day-to-day clinical practice. A prospective, cohort study was carried out in 3 anticoagulation clinics to determine the effect of adherence to anticoagulation control; patients were found to have substantial difficulties maintaining

**Table 3: Antithrombotic therapy for AF: ACC/AHA/ESC guidelines 2006[23]**

| Weak RFs | Moderate RFs | High RFs |
|---|---|---|
| • Female sex | • Age ≥75 | • Previous stroke, TIA or SE |
| • Age 65-75 | • Hypertension | • Mitral stenosis |
| • CAD | • HF/LVSD | • Prosthetic valve |
| • Thyrotoxicosis | • Diabetes | |

| Risk category | Recommended therapy |
|---|---|
| No risk factors | ASA, 81-325 mg |
| One moderate-risk factor | ASA, 81-325 mg or **warfarin** (INR 2.0-3.0, target 2.5)[a] |
| Any high-risk factor or >1 moderate-risk factor | **Warfarin** (INR 2.0-3.0, target 2.5) |
| Prosthetic valve | **Warfarin** (INR 2.5-3.5, target 3.0) |

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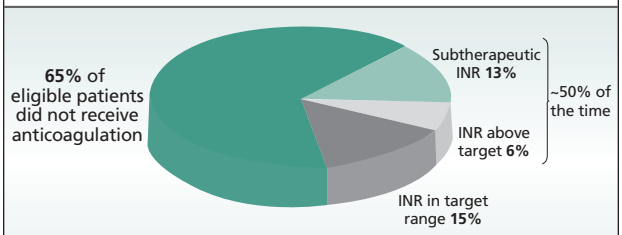
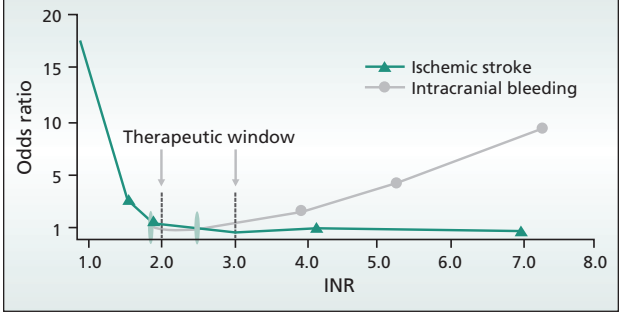
ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; RF = risk factor; AF = atrial fibrillation; CAD = coronary artery disease; LVSD = left ventricular systolic dynfunction; SE = side effects; HF = heart failure; ASA = acetylsalicylic acid; INR = international normalized ratio.
[a] If mechanical value, target INR >2.5.

**Figure 1: Adequacy of anticoagulation in patients with AF in primary care practice[34]**




**65%** of patients are not treated; those treated are out of INR target range around **50%** of the time

**Figure 2: INRs and outcomes in AF[26,36]**




adequate adherence with warfarin regimens, and this poor adherence had a significant effect on anticoagulation control.[32] The benefits of VKAs are dependent on maintaining the international normalized ratio (INR) in the therapeutic range and the optimal balance between adverse events and efficacy is usually achieved with an INR of 2.0-3.0.[25] INR values >3.5 indicate an increase in the risk of hemorrhage whereas values <2.0 signify inadequate thromboprophylaxis and are associated with an increase in stroke risk.[33] Among patients with nonvalvular AF, anticoagulation that results in an INR ≥2.0 reduces not only the frequency of ischemic stroke but also its severity according to the modified Rankin as well as the risk of death from stroke.[33] Among patients who were taking warfarin, an INR <2.0 at admission, as compared with an INR ≥2.0, independently increased the odds of a severe stroke in a proportional-odds logistic-regression model (odds ratio, 1.9; 95% confidence interval [CI], 1.1 to 3.4) across 3 severity categories and the risk of death within 30 days (hazard ratio, 3.4; 95% CI, 1.1 to 10.1). An INR of 1.5–1.9 at admission was associated with a mortality rate similar to that for an INR <1.5 (18% and 15%, respectively). In a retrospective review of 660 AF patient medical records, managed by general internists and family practitioners, only 34.7% of eligible patients with AF received warfarin.[34] The INR values were out of the target range approximately one-half of the time, and the response to these values was not always appropriate (Figure 1). Given that clinicians have difficulty maintaining anticoagulation intensity with VKAs within a narrow therapeutic range over time implies that, on average, patients spend about one-third of their time outside the therapeutic range (INR 2.0-3.0).[35] A significant inverse relationship exists between the percentage of time in the therapeutic range (TTR) and adverse outcomes such as major hemorrhage and thromboembolic events (Figure 2).[26,36] Long-term anticoagulation is very important in AF patients at risk of stroke; clearly, there is a need for antithrombotic agents that are not only at least as effective as VKAs in decreasing the risk of thromboembolic events, but also more practical and with an improved safety profile.

The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial[37] was designed to assess whether clopidogrel plus acetylsalicylic acid (ASA) was noninferior to oral anticoagulation therapy for the prevention of vascular events and could offer a practical alternative to warfarin in patients with AF. Patients with AF plus one or more risk factors for stroke were randomly allocated to receive oral anticoagulation therapy (target INR 2.0-3.0; n = 3371) or clopidogrel (75 mg per day) plus ASA (75-100 mg per day recommended; n = 3335). The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3.93%) and 234 in those on clopidogrel plus ASA (annual risk 5.60%; relative risk 1.44; 95% CI, 1.18-1.76; *P*=0.0003). Dual antiplatelet therapy therefore did not constitute an alternative to VKAs in the prevention of stroke in AF (SPAF).

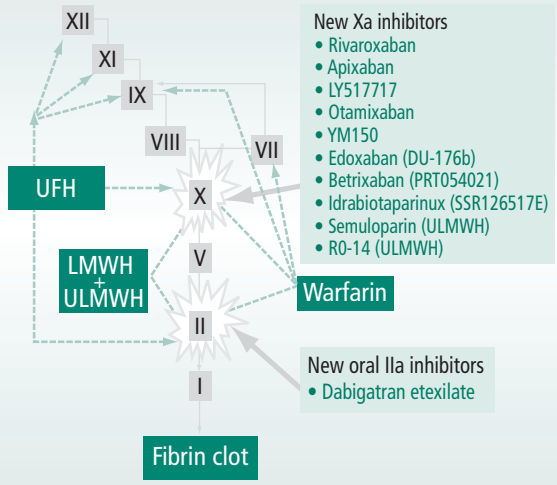
## Meeting patients' needs with a once-weekly reversible anticoagulant: what is on the horizon?

The major burden of thromboembolic disease centres on the management of venous thromboembolism (VTE) and SPAF. VTE is often asymptomatic, misdiagnosed, and unrecognized at death, and there is a lack of routine postmortem examinations. In a study estimating the total burden of VTE within the European Union,[35] the incidence of deep-vein thrombosis (DVT) – measured as attack rates (first lifetime and recurrent) — is 148 per 100 000 person-years (PY),[38] and 65 per 100 000 PY for community-acquired DVT. The pulmonary embolism (PE) attack rate was 95 per 100 000 PY, 28 for community-acquired PE and 67 for hospital-acquired PE. Deaths due to VTE exceed the combined deaths due to acquired immunodeficiency syndrome, breast and prostatic cancer, and transportation accidents.[38] The postthrombotic syndrome[39] and pulmonary hypertension[40] represent long-term complications of VTE and are important sources of morbidity. Long-term anticoagulation plays a key role in the treatment and secondary prevention of thromboembolic events in DVT/ PE and SPAF, but the VKA limitations apply.

These well-characterized risks of VTE treatment and the growing rate of AF, in part, have spurred the development of new therapeutic agents. Mechanisms of action for many of the new anticoagulants currently under investigation are shown in Figure 3A. In the area of VTE, drugs are being

**Figure 3: Anticoagulants of the future[41-53]**

**A** Coagulation cascade




**B** Phase III trial programs in VTE and AF

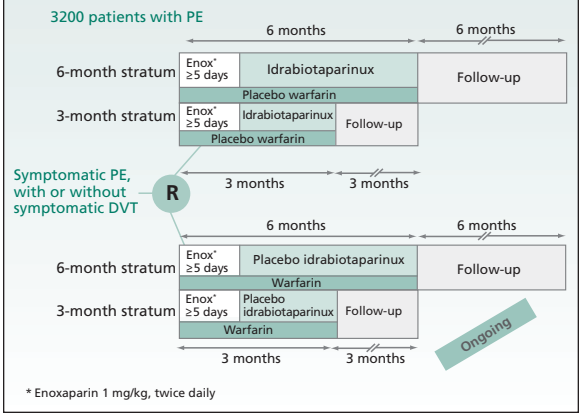
| | Indication | Trial name |
|---|---|---|
| Apixaban | Treatment of VTE | AMPLIFY program |
| | Stroke prevention in AF | ARISTOTLE (AVERROES vs ASA) |
| Dabigatran | Treatment of VTE | RECOVER<br>RECOVER II<br>RE-MEDY<br>RESONATE |
| | Stroke prevention in AF | RE-LY |
| Rivaroxaban | Treatment of VTE | EINSTEIN program |
| | Stroke prevention in AF | ROCKET-AF |

UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism; ULMWH = ultralow-MWH

developed that target the specific steps of coagulation, including the initiation and propagation of thrombin activity. Initiation of coagulation is inhibited primarily by agents that target the factor VIIa/tissue factor complex, although many of the therapies under development in this class are for intravenous use and may not necessarily constitute long-term options for SPAF. Activated factor X (factor Xa) has a central role in the amplification of thrombin generation and thrombus formation, making it an attractive therapeutic target in thromboprophylaxis.[41] In recent years, drugs whose use is specific to the inhibition of factor Xa have been evaluated for the treatment of DVT and PE, and in SPAF (Figure 3B).[41-53] Idraparinux (SR34006) is a long-lasting antithrombin-dependent anti-factor Xa pentasaccharide. Idrabiotaparinux (SSR126517E) is a biotinylated form of idraparinux and an indirect factor Xa inhibitor that offers long-acting anticoagulant effects. This drug can be administered as once-weekly subcutaneous injections, thereby resulting in better adherence,[43] with no need for biological monitoring and few concerns for drug-food or drug-drug interactions.[44,45] In term of bioequipotency, 3 mg of idrabiotaparinux is equivalent to 2.5 mg idraparinux after a single injection. In terms of pharmacokinetics, idrabiotaparinux has almost 100% bioavailability when administered subcutaneously, ie, rapid absorption after subcutaneous administration (peak concentration in 1-3 hours), as well as linear, dose-dependent pharmacokinetics, a small volume of distribution, and low systemic plasma clearance. Importantly, the addition of biotin enables immediate and specific reversibility of the anticoagulant effect by the administration of avidin, an injectable protein with a short half-life and no prothrombotic effect.[46] In the Bioequipotency Study of SSR126517E and Idraparinux in Patients With Deep Venous Thrombosis of the Lower Limbs (EQUINOX) trial,[47] idrabiotaparinux was compared with idraparinux and revealed a similar pharmacodynamic, efficacy, and safety profile, but with the added advantage of reversibility by avidin. Idraparinux and idrabiotaparinux will soon have been tested in more than 2500 patients with VTE and AF.[48-51] In brief, the Van Gogh study program (SR34006 Compared to Placebo in Patients Who Have Completed 6 Months of Treatment for Symptomatic Pulmonary Embolism or Deep Vein Thrombosis and SR34006 Compared to Vitamin K Antagonist [VKA] in the Treatment of Pulmonary Embolism) addressed the role of idraparinux in the management of PE and DVT.[50,51] Overall, the Van Gogh phase III studies demonstrated that idraparinux:

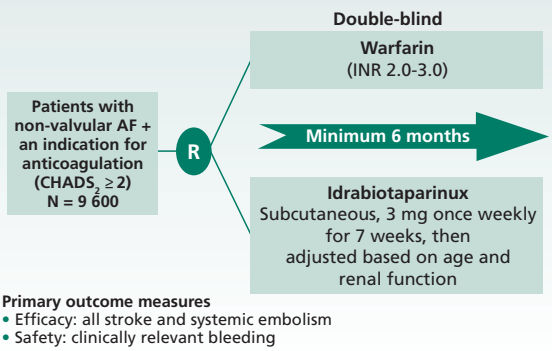
- had a similar efficacy to standard therapy in DVT
- was less efficacious than standard therapy in PE
- had less clinically relevant bleeding at 3 months and similar bleeding at 6 months versus low-molecular-weight heparin (LMWH)/VKA
- had a potential extended protective effect in VTE for an additional 6 months after cessation of therapy.

**Figure 4: Design of the CASSIOPEA study[52]**




PE = pulmonary embolism; DVT = deep-vein thrombosis

**Figure 5: Design of the BOREALIS-AF study[53]**




R = randomization

The ongoing Clinical Study Assessing SSR126517E Injections Once-Weekly in Pulmonary Embolism Therapeutic Approach (CASSIOPEA) study[52] is specifically designed to address the efficacy and safety of idrabiotaparinux in patients with PE. The study design is shown in Figure 4; the primary endpoint will be the recurrence of fatal and nonfatal venous thromboembolic events (DVT or PE) at 3 months.

The Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation (AMADEUS) study program is targeting the management of SPAF.[49] In the AMADEUS study, patients with AF at risk for thromboembolism were randomly assigned to receive either subcutaneous idraparinux (2.5 mg weekly) or adjusted-dose VKA (target INR of 2-3). The primary efficacy outcome was the cumulative incidence of all stroke and systemic embolism. The principal safety outcome was clinically relevant bleeding. The trial was stopped after randomization of 4576 patients (2283 received idraparinux, 2293 received VKAs) and a mean follow-up period of 10.7 months because of excess clinically relevant bleeding with idraparinux. However, in terms of efficacy, there were 18 cases of thromboembolism with idraparinux and 27 cases with VKAs (0.9 vs 1.3 per 100 PY; hazard ratio 0.71, 95% CI, 0.39-1.30; $P$=0.007), thereby satisfying the non-inferiority criterion. There were 62 deaths with idraparinux and 61 with VKAs (3.2 vs 2.9 per 100 PY; $P$=0.49).[49] The excess bleeding appeared over time and was highest in elderly patients with renal insufficiency. Therefore, in patients with AF at risk for thromboembolism, long-term treatment with idraparinux was no worse than VKAs in terms of efficacy, but caused significantly more bleeding. Analyses of pharmacokinetics/outcome helped to select the dose for the ongoing Evaluation of Weekly Subcutaneous Biotinylated Idraparinux Versus Oral Adjusted-dose Warfarin to Prevent Stroke and Systemic Thromboembolic Events in Patients With Atrial Fibrillation (BOREALIS-AF) trial.[53] The study design of BOREALIS-AF is shown in Figure 5. In this trial, the dose of idrabiotaparinux was adjusted based on age and renal function after 7 weeks of therapy. The primary endpoint will be a composite of all strokes or systemic embolic events.

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