Review Article

New antithrombotics: The impact on global health care

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Abstract

New and generic forms of widely used medications introduced in the antiplatelet, anticoagulant and fibrinolytic therapeutic classes will have a world-wide impact on prescribing, practice guidelines, and routine patient care. However, several uncertainties regarding these agents will remain even after the publication of their respective pivotal trials or regulatory approval. These questions include dosing in the frail, the elderly, and in those with renal and/or hepatic dysfunction, timing of administration in the peri-operative period, efficacy and safety in subgroup populations such as patients with cancer, the interchangeability of biosimilar products, and outcome differences between new agents in the absence of head-to-head clinical trials. Additionally, new generic forms of widely used agents have recently impacted the United States (US) and Canadian market place and more are under development. Clinicians should be vigilant concerning these agents and be prepared to inform patients and make decisions with their use.

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Background and epidemiology of thromboembolism

Arterial thromboembolism (ATE) and venous thromboembolism (VTE) are leading causes of morbidity and mortality world-wide [1]. While ATE typically forms under high shear conditions of blood flow and consists of platelets bound by small amounts of fibrin, VTE forms under low shear conditions [2]. In the US alone, it is estimated that over 850,000 acute myocardial infarctions (MI) occur annually, with an 18% and 35% recurrence rate within 6 years for men and women, respectively [3]. ATE is the most common cause of cardioembolic events including MI, ischemic stroke, and limb gangrene [1]. ATEs are considered “platelet rich”; thus, strategies to inhibit ATE formation have recently focused on blocking platelet function [4]. Additional strategies include anticoagulants for preventing cardioembolic events in patients with atrial fibrillation (AF) or mechanical heart valves [1,4].

VTE primarily contains fibrin and trapped red blood cells and consists of relatively few platelets as compared to ATE [2]. Therefore, anticoagulants are agents of choice for the prevention and treatment of VTE due to the large amounts of fibrin. Vitamin K antagonists (VKA), such as warfarin, are utilized for both prevention of ATE and prevention...
and treatment of VTE. Limitations to VKA therapy include: frequent monitoring, challenging standardization of laboratory processes, diet-drug and drug-drug interactions, narrow therapeutic range, and genetic polymorphisms that affect VKA metabolism and dose response [5]. In North America, a minority of VKA patients are monitored by anticoagulation clinics, leaving independent physicians to manage the vast majority of these patients. A large percentage of AF patients are undiagnosed and at risk for stroke. However, in many AF patients who are diagnosed, clinicians avoid prescribing VKA's due to their numerous limitations. These limitations provide a large window of opportunity for new, improved anticoagulants.

Several antithrombotics are in advanced stages of clinical trials and are expected to be available soon for use in North America [1,6]. This review covers antiplatelet and anticoagulant agents as well as generic agents that are emerging into clinical practice.

**New agents**

**Antiplatelet therapy**

A number of antiplatelet agents are in advanced stages of development. These medications primarily target adenosine diphosphate (ADP), thromboxane A2, or thrombin receptors on the platelet surface (Figs. 1 and 2) [1,6]. A majority of the ADP receptor antagonists specifically target P2Y12 while the thrombin receptor antagonists primarily target protease activated receptor-1 (PAR-1) [1].

Prasugrel is a new oral ADP receptor antagonist (P2Y12 platelet inhibitor) that has been recently approved in Canada, Mexico and the US. [7] In the US and Canada, prasugrel is indicated for the reduction of thrombotic cardiovascular events, including stent thrombosis, in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) including patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI), and those with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI [8]. However, uptake has been slow to displace clopidogrel possibly due to the drug’s limited labeling. Clopidogrel is indicated for ACS, recent MI, recent stroke, or established peripheral arterial disease [9].

Ticagrelor and cangrelor are also ADP receptor antagonists that are undergoing phase III trials. Ticagrelor is an oral twice daily administered agent that recently was approved in Europe. Cangrelor is an intravenous adenosine triphosphate (ATP) analogue. Both agents are potent and reversible inhibitors of P2Y12 receptor [6].

**Anticoagulants**

New anticoagulant agents may be categorized broadly into three groups: [4]

- Drugs that are thrombin inhibitors – direct or indirect
- Drugs that inhibit the initiation of coagulation
- Drugs that impact coagulation, specifically direct and indirect inhibitors of activated factor X (FXa) or IX (FIXa)

Approximately twenty new anticoagulants are in advanced stages of development, with apixaban and rivaroxaban in all likelihood being the next agents to gain US Food and Drug Administration (FDA) approval [4] (See Table 1 and Fig. 3). Rivaroxaban is also currently approved in Canada [10]. Dabigatran, a potent, oral, direct competitive inhibitor of activated coagulation factor IIa (i.e. thrombin), was approved by the FDA in October 2010 for use in the prevention of stroke due to non-valvular AF.
and systemic embolism in patients with non-valvular AF [11]. Dabigatran is in a class referred to as direct thrombin inhibitors (DTI). Dabigatran is also approved for use in Canada [12]. The FDA approved doses are 150 mg and 75 mg, both administered twice daily, with the latter more likely used in patients with severe renal impairment. Since the 75 mg dose has not yet been studied in clinical trials, the dosing has been a topic of discussion and debate.

Desirudin is another DTI approved for VTE prevention at a fixed subcutaneous (SC) dose. As compared to other DTIs, desirudin may have advantages related to dosing, administration, monitoring, and ease of transition to oral anticoagulants. In patients undergoing hip replacement surgery, desirudin was significantly more effective than unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in preventing thromboembolic events with similar safety [13,14]. The drug has also been studied in ACS [15,16]. Current investigations include the phase IV “Multi-Center Trial of Desirudin for the Prophylaxis of Thrombosis: an Alternative to Heparin-Based Anticoagulation (DESIR-ABLE)”. A recent study in suspected hepatic induced thrombocytopenia (with or without thrombosis) suggests that it may be a safer and cost effective alternative to argatroban [17].

Rivaroxaban and apixaban are both oral factor Xa inhibitors being studied in a wide array of patients including AF, VTE prevention, and VTE treatment [6]. The recent phase III, Apixaban Versus Acetylsalicylic acid to Prevent Strokes (AVERROES) study was stopped early because apixaban demonstrated superior efficacy to aspirin in AF patients who were unsuitable for warfarin [18]. Additionally, the APPRAISE 2 study was terminated in ACS patients due to increased bleeding with apixaban as compared to placebo because the increase in bleeding was not offset by clinically meaningful reductions in ischemic events [19]. Apixaban is being further studied in AF versus warfarin.

Phase II dose-ranging trials with intravenous oxatimabin, also a Xa inhibitor, were recently completed in Non-ST Elevation Acute Coronary Syndrome (SEPIA-ACS) [20] and non-urgent PCI. [21] A phase III trial in unstable angina/ non-ST elevation MI undergoing early invasive strategy (TAO) is currently underway [22].

Edoxaban is another oral factor Xa inhibitor, currently being investigated in the phase III study ENGAGE AF-TIMI 48 (Effective aNtiocoagulation with factor Xa next Generation in Atrial Fibrillation) for stroke prevention in patients with AF. Edoxaban has also completed a phase III trial, STARS E-3 (Studying Thrombosis After Replacement Surgery), for VTE prevention in total knee replacement (TKR) and was found to be superior to enoxaparin [23].

### Table 1

<table>
<thead>
<tr>
<th>Drug Features</th>
<th>Dabigatran Etexilate</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Factor IIa</td>
<td>Yes</td>
<td>No</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>628</td>
<td>460</td>
<td>No</td>
</tr>
<tr>
<td>Molecular weight in Daltons</td>
<td></td>
<td></td>
<td>436</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once or Twice daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>12-17</td>
<td>9-14</td>
<td>7-11</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>80</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Moderate (e.g. amiodarone) and Potent Inhibitors/Inducers of P-gp (e.g. quinidine, clarithromycin, rifampin); Caution should be exercised.</td>
<td>Potent Inhibitors/Inducers of CYP3A4 (e.g. ketoconazole) Caution should be exercised.</td>
<td>Potent Inhibitors/Inducers of CYP3A4 (e.g. ketoconazole, macrolide antibiotics) or P-gp (e.g. quinidine, clarithromycin, rifampin); Caution should be exercised.</td>
</tr>
<tr>
<td>Routine monitoring Antidote</td>
<td>None Developed Yet</td>
<td>None Developed Yet</td>
<td>None Developed Yet</td>
</tr>
<tr>
<td>Populations being studied in</td>
<td>Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment</td>
<td>VTE prophylaxis, atrial fibrillation, VTE treatment, and acute coronary syndromes</td>
<td>Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment, and acute coronary syndromes</td>
</tr>
<tr>
<td>Status</td>
<td>Approved in US for atrial fibrillation and in Canada and Europe for VTE prophylaxis after major orthopedic surgery</td>
<td>No approvals yet</td>
<td>Approved in Canada and Europe for VTE prophylaxis after major orthopedic surgery</td>
</tr>
</tbody>
</table>

VTE = Venous Thromboembolism; CYP3A4 = cytochrome p450 3A4 protein; P-gp = P-glycoprotein 1.

M118 is a “rationally designed” LMWH being studied in coronary artery disease patients undergoing PCI [24,25]. However, with the availability of new oral anticoagulants and antiplatelet agents the role of a new injectable LMWH will have to be established.

### Generics of complex biologics and biosimilars

In the US, the FDA recognizes that certain products are biologics, with similar versions to the innovator product called biosimilars or follow-on biologics (FOB). Biosimilars are non-identical biologic products comparable to the innovator product while biogenerics are biologic products that are deemed therapeutically equivalent, interchangeable, and substitutable with the innovator product. A clinical study or studies that include the assessment of immunogenicity as well as the agent’s pharmacokinetics and pharmacodynamic parameters must be performed for it to be deemed biogeneric.

Internationally, economics are a driving force for the introduction of biosimilars as several key agents lose patent protection over the next few years. The loss of patent protection removes a barrier for other companies, providing the opportunity to manufacture a medication with a financial gain. At lower sale prices, health care systems buy generic medications, including biosimilars or biogenerics, as a substitute for other more expensive innovator products, generating competition between manufacturers. The annual US market for biosimilars is expected to be $20 billion within the next five years [26]. Although debate exists on the subject, the FDA has classified the LMWHs as drugs and therefore they are not considered biologics [27]. Additionally, the FDA, through the Center for Drug Evaluation and Research (CDER)
Accelerated New Drug Application (ANDA), approved the first generic LMWH, enoxaparin produced by Sandoz Pharmaceuticals, in July of 2010. [28] Considerable controversy existed over the criteria for LMWH "sameness" with many experts advocating for the completion of head to head clinical trials. The FDA based their approval on equivalence of source material, production, physiochemical properties, biological and biochemical assays, and the in-vivo pharmacodynamic profile. Other pharmaceutical companies, including Teva and Amphastar, are also pursuing approval of their version of generic enoxaparin [28].

Despite being biologics, LMWHs, including enoxaparin, were initially approved under the Food, Drug and Cosmetic (FD&C) Act, a CDER controlled process [29]. Legislation on an abbreviated pathway for biosimilar interchangeables or the abbreviated biologic license application (ABLA), for generic versions of biologics, only became law as of March of 2010. Because LMWHs were approved as drugs originally, the FDA had the authority, based on scientific evidence, to deem an agent equally safe and effective as the innovator (i.e. original) enoxaparin. The FDA justified these actions because it had previously evaluated heparin and hetastarch in the same manner as the generic enoxaparin [29]. In the case of generic enoxaparin, one in vivo study was completed in healthy individuals assessing anticoagulant levels. The FDA could have required a generic LMWH follow the ABLA pathway as compared to the CDER pathway however, generic enoxaparin application reviews had been submitted and pending since 2005.

The advantages of the ABLA pathway include the demonstration of equivalent safety and efficacy through clinical head to head studies. These studies would have taken more time, money, and resources, raising barriers to generic manufacturer market entry. Advantages of the ANDA pathway are that the FDA follows a previous approval path for similar agents. The overall costs for bringing the generic enoxaparin to market are lower than the ABLA pathway. Disadvantages of the ANDA pathway may be that the evidence upon which the FDA based their decision may not have been robust enough to determine any true safety and efficacy differences between brand and generic enoxaparins.

The European Medicines Agency (EMEA) and Health Canada consider LMWHs as biologics and thus similar products to the innovator or brand products would be called "biosimilars." [30] There appears to be some debate as to whether the term "biogeneric" should be utilized [27]. While the EMEA and Canada have more experience with biosimilars, [31,32] the US is currently building the infrastructure to help ensure safety and efficacy of these new agents. Biosimilars cannot be immediately assumed to have the same bioactivity and safety as the original innovator product. For example, pure red-cell aplasia was related to the previous release of biosimilars of erythropoietin outside of the US [33]. Pharmacovigilance, which is proactive monitoring of quality, safety, will be important to determine that generic biologics (i.e. LMWH in the US) and biosimilar products are meeting patient needs safely and effectively [26]. The FDA held a hearing on biosimilar legislation on November 2–3, 2010, with many key issues still being debated despite the current availability of the generic enoxaparin within the US [34,35].

Lastly, a generic version of the synthetic pentasaccharide, fondaparinux, is also being pursued. [36] This agent currently has minimal

![Diagram of TF/VIIa, IXa, TAFIa, tPA, and PAI-1]

**Fig. 3.** New anticoagulant and fibrinolytic therapies. TF = Tissue Factor. NAPc2 = Nematode Anticoagulant Peptide c2. TAFIa = Thrombin Activatable Fibrinolysis Inhibitor. PAI-1 = Plasminogen Activator Inhibitor - Type 1.
market share and does not carry an FDA indication for ACS or medical prophylaxis within the US; thus, its impact on the market place is uncertain. The agent does carry indications for prophylaxis in hip replacement, knee replacement, hip fracture, and abdominal surgery as well as for treatment of acute PE and DVT without PE.

Impact of new agents

New agents approved for use will likely have higher drug acquisition costs than current strategies. Economic analyses will be helpful to determine if overall costs are cost-neutral or cost-dominant due to reduced need for monitoring, or improved efficacy and safety. Preliminary cost-analyses appear to favor new agents over current standards of care, despite higher acquisition costs, although further analysis is needed [37–41]. The market to replace warfarin with new anticoagulants is estimated to be in the range of $10 to $20 billion globally [42,43]. Although a smaller market, the utilization of these new agents for VTE prevention in the medical and surgical patient will be important as recent studies demonstrate appropriate prophylaxis is delivered in only 13–34% of patients admitted to US hospitals [44–47]. This leaves a large opportunity to improve prophylaxis selection, dose, duration and reduce unnecessary morbidity and mortality. Despite the National Quality Forum (NQF) and The Joint Commission (TJC) developing new, important VTE quality measures, [48] current reporting in the US is only in approximately 60 hospitals out of more than 5000 acute care hospitals. [49,50] While the Centers for Medicare & Medicaid Services (CMS) considered adapting the new VTE measures, they have delayed implementation until a future date. [51] Mandating these VTE measures at the national level within the US would significantly reduce morbidity, mortality, and healthcare costs associated with the disease. New anticoagulants will likely have an impact on current TJC national patient safety goals and VTE measures and therefore require specialized handling and monitoring at the hospital level [52].

The US government and FDA are viewing the introduction of biosimilars as a potential cost savings initiative, especially in light of the recently passed health care reform [26]. In the near future, we will likely have multiple antiplatelet agents and anticoagulants from which to choose for various patient populations. The FDA and health care systems and/or providers will likely be diligently tracking efficacy and safety with FOB’s. Harmonization of key organizations such as the FDA and Health Canada, EMEA, International Union of Angiology, American College of Chest Physicians, the Anticoagulation Forum, and NATF on critical clinical points would be beneficial to meet this need. Off label use of newly approved agents may be of concern to the FDA and Health Canada and should be minimized to ensure patient safety.

Current controversies

Key controversies that remain are:

• Superiority of agents
• Optimal duration of prophylaxis
• Will patients with more than one indication for antithrombotic therapy require dual or triple antithrombotics with the new, more potent anticoagulants?
• Future of biosimilars

Without head-to-head clinical trials, the differences in new agents, such as half-lives, drug interactions, safety in special populations (e.g. frail elderly, renal, obesity, etc), will play an important role in which agent takes the lead in the market. Although less monitoring will be required, the impact on patient care is currently unclear and warrants further investigation. These new oral agents seem promising to displace warfarin, LMWHs, and fondaparinux in AF, VTE treatment and VTE prevention in orthopedic surgery. Because warfarin has an antidote, the absence of a reversal agent for these new anticoagulants remains a concern among practitioners. All of these factors (pharmacodynamic differences, special populations, reduced monitoring, and reversibility) will influence how each agent impacts healthcare.

While extended prophylaxis is well-established in certain surgical groups such as major orthopedic, or major abdominal cancer surgery, clinical trial data for prophylaxis in the medical patient only support up to 14 days of LMWH thromboprophylaxis [53–56]. Current studies in medical and surgical patients are assessing durations of 30 to 35 days and 14 to 35 days, respectively [57,58]. Thus outpatient prescriptions of these newer oral agents may be more common than with current injectable LMWHs and fondaparinux. In orthopedic patients, less monitoring of the agents will also be an advantage over warfarin for VTE prevention.

A large percentage of patients are currently on dual and triple antithrombotic therapy, including multiple antiplatelet agents (e.g. aspirin and clopidogrel/prasugrel) as well as warfarin for indications such as MI, ACS, mechanical heart valves, or stroke prevention in AF. The impact of more potent anticoagulants than warfarin with the same or reduced bleeding episodes, such as with dabigatran, may allow for fewer antiplatelet agents, although this will require future studies.

New agents (e.g. dabigatran, rivaroxaban, apixaban) will need to be avoided in such groups as: severe renal impairment, severe hepatic disease and those patients with poor compliance [1,6,59]. P-glycoprotein, a membrane associated protein responsible for drug transport, impacts the absorption of novel agents. Dabigatran and rivaroxaban are substrates of P-glycoprotein 1 (P-gp 1) transporter, which is located in the gastrointestinal tract and kidneys [6]. Similarly, rivaroxaban and apixaban are metabolized by the hepatic cytochrome 3A4 system. Strong inducers and inhibitors of these systems should be avoided or used with caution. It is currently unknown how individual patient genetic variants and polymorphisms will affect drug levels. Studies to determine these effects are underway which may better guide the clinician as to best monitoring practices.

It may also not be practical or desirable to change patients over to new agents from warfarin if the patients are currently stable on warfarin. Overall costs, not just drug acquisition price, of the drug versus warfarin will be a primary driver at the health plan level of how quickly these agents penetrate the market place. Many hospitals will likely continue previous therapy of these agents if the patient has been stabilized on them as an outpatient. While drug interactions appear to be significantly less than warfarin, they will still need to be taken into consideration with new agents.

Clinical studies will be helpful for the peri-operative management of these new anticoagulants as overlap with parenteral agents may not be required due to quicker onsets and offsets than warfarin [60]. Bleeding treatment also remains unclear at this time with new and emerging agents.

FOBs will play an important role in the near future on cutting health costs internationally. The market dominance of small molecule products is ending with more pharmaceutical research monies being focused on the development of new biotech agents by 2013. By 2014, top blockbuster drug positions will be dominated by FOBs [61] and by 2016, primary savings will likely come from the introduction of new FOBs. Technology advances and, ultimately, clinical trials are still needed to ensure that FOBs are equally as safe and effective as the original product.

Conclusion

ATE and VTE continue to have a tremendous impact on international health systems with a huge unmet need for new medical and pharmacologic improvements. The antithrombotic market will have many additions in the near future and education surrounding these new agents and appropriate use will be critical. A balanced approach between industry, the FDA, key thrombosis organizations, consumers, and health care systems would be helpful in developing both
consensus statements and education on antithrombotic issues to maximize patient care. To ensure biosimilar and generic biologics efficacy and patient safety, registry data and pharmacovigilance of health systems will be important as new biosimilars are introduced to the North American market place.

Dedication

We would like to dedicate this publication to the North American Thrombosis Forum (NATF) and the patients who have lost their lives to, or been harmed from, thromboembolism. The NATF strives to reduce both morbidity and mortality associated with thromboembolism.

Conflict of interest statement

Within the last year, Dr. Mahan has received honoraria as a consultant and speaker from Eisai and Sanofi-Aventis Pharmaceuticals and as a consultant from Polymedix and Leo Pharmaceuticals. He has also received travelling fellowship funds from the North American Thrombosis Forum. Dr. Mahan is an unpaid consultant for Johnson and Johnson Pharmaceutical Research & Development and Ortho-McNeil Janssen Scientific Affairs.

Acknowledgement

NATF coordinated a roundtable discussion with experts on September 26th, 2010. The following are some key points discussed during this roundtable session.

References


