



Review Article

New antithrombotics: The impact on global health care

Charles E. Mahan ^{a,*}, John Fanikos ^b^a University of New Mexico Health Sciences Center, Albuquerque, New Mexico^b Brigham and Women's Hospital, Boston, Massachusetts

ARTICLE INFO

Article history:

Received 4 February 2011

Received in revised form 28 March 2011

Accepted 29 March 2011

Available online 6 May 2011

Keywords:

Antithrombotic

Anticoagulant

Antiplatelet

Biosimilar

Thromboprophylaxis

Arterial thromboembolism

Venous thromboembolism

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.

© 2011 Elsevier Ltd. All rights reserved.

Contents

Background and epidemiology of thromboembolism	518
New agents	519
Antiplatelet therapy	519
Anticoagulants	519
Generics of complex biologics and biosimilars	520
Impact of new agents	522
Current controversies	522
Conclusion	522
Dedication	523
Conflict of interest statement	523
Acknowledgement	523
References	523

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

* Corresponding author at: University of New Mexico Health Sciences Center & Clot Prevention Intervention Management Programs, LLC, Albuquerque, NM 87111. Tel.: +1 505 681 4279.

E-mail address: chmahan@yahoo.com (C.E. Mahan).

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

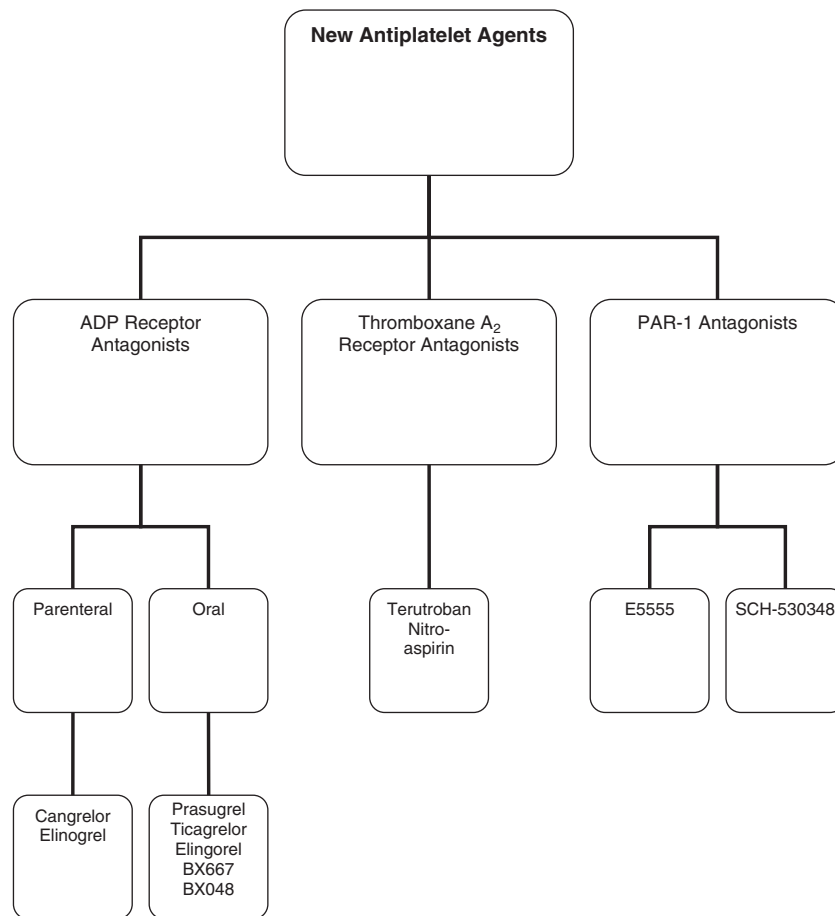


Fig. 1. New Antiplatelet Agents.

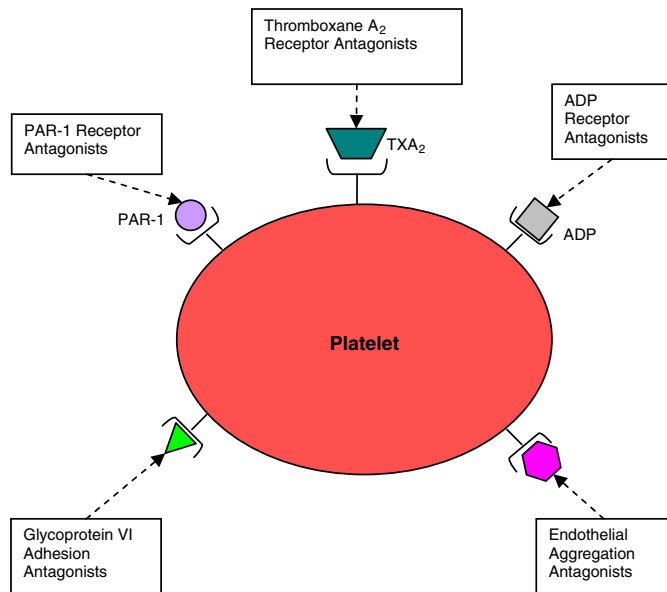


Fig. 2. New Antiplatelet Agent Platelet Targets.

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 heparin induced thrombocytopenia (with or without thrombosis) suggests that it may be a safe 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 otamixaban, also a Xa inhibitor, were recently completed in Non-ST Elevation Acute Coronary Syndrome (SEPIA-ACS1) [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 anti-coagulation 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
Characteristics and background of new anticoagulants.

Drug Features	Dabigatran Etexilate	Apixaban	Rivaroxaban
Target	Factor IIa	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Molecular weight in Daltons	628	460	436
Dosing	Once or Twice daily	Twice daily	Once daily
Bioavailability (%)	6	60	80
Half-life (hours)	12-17	9-14	7-11
Renal excretion (%)	80	25	65
Drug Interactions	Moderate (e.g. amiodarone) and Potent Inhibitors/ Inducers of P-gp (e.g. quinidine, clarithromycin, rifampin). Caution should be exercised.	Potent Inhibitors/ Inducers of CYP3A4 (e.g. ketoconazole). Caution should be exercised.	Potent Inhibitors/ Inducers of CYP3A4 (e.g. ketoconazole, macrolide antibiotics) or P-gp (e.g. quinidine, clarithromycin, rifampin) Caution should be exercised.
Routine monitoring	No	No	No
Antidote	None Developed Yet	None Developed Yet	None Developed Yet
Populations being studied in	Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment	Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment, and acute coronary syndromes	Medical and surgical VTE prophylaxis, atrial fibrillation, VTE treatment, and acute coronary syndromes
Status	Approved in US for atrial fibrillation and in Canada and Europe for VTE prophylaxis after major orthopedic surgery	No approvals yet	Approved in Canada and Europe for VTE prophylaxis after major orthopedic surgery

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 biologics 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 five 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 biologics, 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)

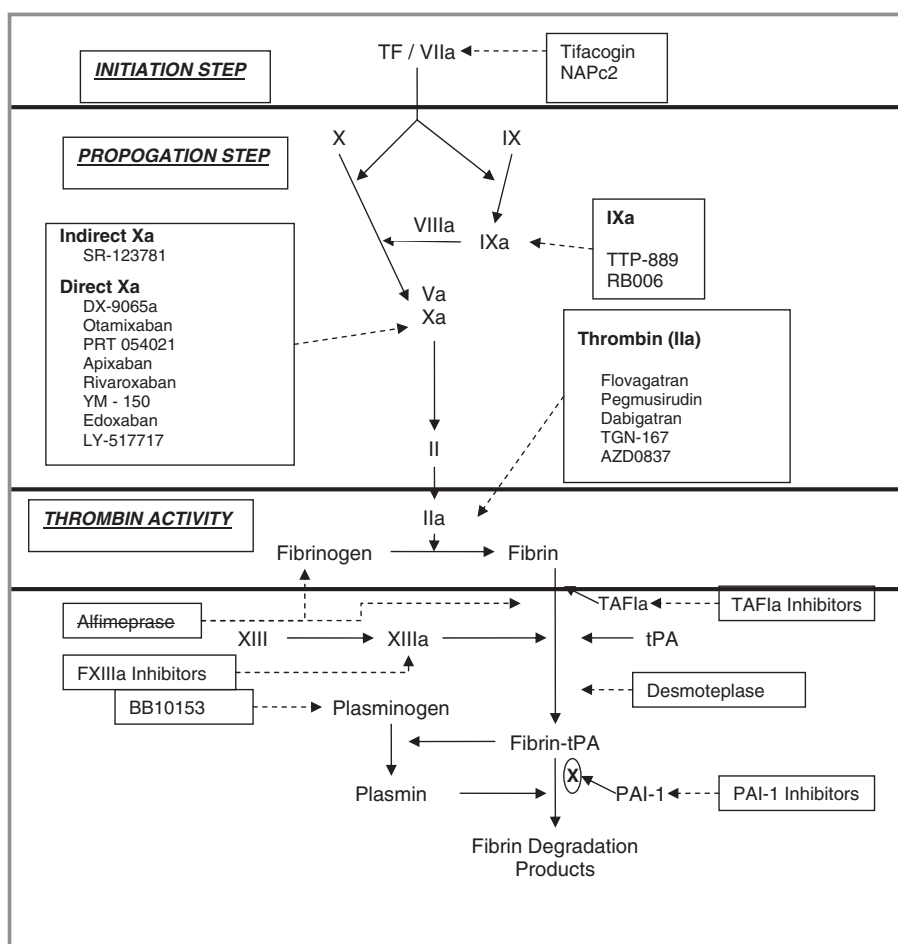


Fig. 3. New anticoagulant and fibrinolytic therapies. TF = Tissue Factor. NAPc2 = Nematode Anticoagulant Peptide c2. TAFIa = Thrombin Activatable Fibrinolysis Inhibitor. PAI-1 = Plasminogen Activator Inhibitor- Type 1.

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, physicochemical 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 interchangeable 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 (EMA) 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 EMA 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

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 (pharma-

dynamic 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

- Weitz JI, Hirsh J, Samama MM. New antithrombotic drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):234S–56S.
- Freiman DG. The structure of thrombi. In: Colman RW, Hirsh J, Marder V, et al, editors. Hemostasis and thrombosis: basic principles and clinical practice. 2nd ed. Philadelphia, PA: JB Lippincott; 1987. p. 1123–35.
- American Heart Association. American Stroke Association: Heart Disease and Stroke Statistics 2006 Update. Dallas, TX: Author; 2010. Available at: http://www.americanheart.org/downloadable/heart/113535864858055-1026_HS_Stats06-book.pdf. Accessed November 3rd, 2010.
- Mahan CE, et al. Contemporary Hospitalists' Guide to Anticoagulation. In: Deitelzweig Steven B, Amin Alpesh, editors. Brave New World: Antithrombotics on the Horizon. Handbooks in Health Care Co.; July 15, 2009. Chapter 12.
- Ansell J, Hirsh J, Hylek E, Jacobson A, Crowley M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133(6 Suppl):160S–98S.
- Paikin JS, Eikelboom JW, Cairns JA, Hirsh J. New antithrombotic agents—insights from clinical trials. *Nat Rev Cardiol* Sep 2010;7(9):498–509.
- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm171497.htm> Prasugrel FDA approval: Accessed 11/3/2010.
- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm> Pradaxa (Dabigatran) approval accessed 11/3/2010.
- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm> Pradaxa (Dabigatran) approval accessed 11/3/2010.
- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm> Pradaxa (Dabigatran) approval accessed 11/3/2010.
- Eriksson BI, Ekman S, Lindbratt S, et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. *J Bone Joint Surg Am* Mar 1997;79(3):326–33.
- Eriksson BI, Wille-Jørgensen P, Kalebso P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med* Nov 6 1997;337(19):1329–35.
- Antman EM. Hirudin in acute myocardial infarction. Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial. *Circulation* Sep 1 1996;94(5):911–21.
- A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb investigators. *N Engl J Med* Sep 12 1996;335(11):775–82.
- <http://www.clinicaltrials.gov/ct2/results?term=desirudin> accessed 1/17/2011.
- Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* Mar 3 2011;364(9):806–17.
- <http://www.clinicaltrials.gov/ct2/show/NCT00831441?term=appraise+2&rank=1> APPRAISE 2 accessed 3/17/2011.
- <http://www.clinicaltrials.gov/ct2/show/NCT00317395> Otamixaban SEPIA-ACS1 accessed 11/3/2010.
- <http://www.clinicaltrials.gov/ct2/show/NCT00133731?term=otamixaban&rank=5> Otamixaban in Non-urgent PCI accessed 11/3/2010.
- <http://www.clinicaltrials.gov/ct2/show/NCT01076764?term=otamixaban&rank=1> Otamixaban UA/ non-STEMI Phase III accessed 11/3/10.
- <http://www.clinicaltrials.gov/ct2/results?term=du-176b> Edoxaban accessed 11/3/2010.
- <http://www.momentapharma.com/pipeline/novel.html> M118 Accessed 11/3/2010.
- <http://www.clinicaltrials.gov/ct2/results?term=m118> M118 accessed at 11/3/2010.
- Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol* Mar 2008;19(3):411–9.
- Kalodiki E, Fareed J, Tapson VF, et al. A consensus conference on complex biologics and low molecular weight heparins. *Int Angiol* Apr 2010;29(2):193–6.
- <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm> accessed 11/3/2010.
- <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm> accessed 3/17/2011.
- Kalodiki E, Leong W. SASAT (South Asian Society on Atherosclerosis & Thrombosis) proposal for regulatory guidelines for generic low-molecular weight heparins (LMWHs). *Clin Appl Thromb Hemost* Feb 2009;15(1):8–11.
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&murl=menus/regulations/regulations.jsp&mid=WCO-b01ac058002958c&jsenabed=true#Overarchingbiosimilarguidelines EMEA accessed 11/3/2010.
- <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/consultation/seb-pbu/2008-1-eng.php> Health Canada Biosimilar Information accessed 11/3/2010.
- Bennett CL, Luminari S, Nissenon AR, et al. Pure red-cell aplasia and epoetin therapy. *N Engl J Med* Sep 30 2004;351(14):1403–8.
- FDA biologics meeting initial feedback accessed 11/9/10 <http://www.fdalawyers-blog.com/biologics/>.
- FDA Biosimilar Hearing November accessed 11/3/10 <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm>.
- Fondaparinux generic accessed 11/3/10 <http://www.alchemia.com.au/irm/content/products.html>.
- Wolowacz SE, Roskell NS, Plumb JM, et al. Economic evaluation of dabigatran etexilate for the prevention of venous thromboembolism in patients aged over 75 years or with moderate renal impairment undergoing total knee or hip replacement. *Thromb Haemost* Feb 2010;103(2):360–71.
- Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation <http://www.ncbi.nlm.nih.gov/libproxy.unm.edu/pubmed/21041570>. *Ann Intern Med* Jan 4 2011;154(1):1–11. [Electronic publication ahead of print 2010 Nov 1].
- Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E. Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal. *Health Technol Assess* Oct 2009;13(Suppl 3):43–8.
- McCullagh L, Tilson L, Walsh C, Barry M. A cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin sodium as thromboprophylaxis after total hip and total knee replacement in the Irish healthcare setting. *Pharmacoeconomics* 2009;27(10):829–46.
- Holmes M, Carroll C, Papaioannou D. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal. *Health Technol Assess* Sep 2009;13(Suppl 2):55–62.
- http://www.clevelandclinic.org/afic/mid_grant.pdf Afib market \$17 Billion with estimated 20% growth annually through 2016.
- <http://www.uk.reuters.com/article/idUKLDE65A1GN20100804> Accessed 11/3/2010 Afib Financial Market.
- Amin A, Spyropoulos AC, Dobesh P, et al. Are hospitals delivering appropriate VTE prevention? The venous thromboembolism study to assess the rate of thromboprophylaxis (VTE start). *J Thromb Thrombolysis* Apr 2010;29(3):326–39.
- Amin A, Stenkowski S, Lin J, Yang G. Thromboprophylaxis rates in US medical centers: success or failure? *J Thromb Haemost* Aug 2007;5(8):1610–6.
- Amin AN, Stenkowski S, Lin J, Yang G. Preventing venous thromboembolism in US hospitals: are surgical patients receiving appropriate prophylaxis? *Thromb Haemost* Apr 2008;99(4):796–7.
- Yu HT, Dylan ML, Lin J, Dubois RW. Hospitals' compliance with prophylaxis guidelines for venous thromboembolism. *Am J Health Syst Pharm* Jan 1 2007;64(1):69–76.
- "NQF Web site." Accessed 11/3/2010, from http://www.qualityforum.org/News_And_Resources/Press_Releases/2008/NATIONAL_QUALITY_FORUM_ENDORSES_CONSENSUS_STANDARDS_FOR_QUALITY_OF_HOSPITAL_CARE.aspx.
- The Joint Commission, Internal Personal Communication from the Joint Commission to Charles Mahan via email, 11/9/2010.
- Table 115, Hospitals, Beds, and Occupancy Rates, according to Type of Ownership and Size of Hospital: United States, Selected Years 1975–2007 (PDF), Health United States, 2009. 2009.
- CMS considered adapting VTE Measures; 11/3/2010. Accessed 11/3/2010, from <http://www.cms.gov/apps/media/press/release.asp?Counter=3041&intNumPerPage=10&checkDate=&checkKey=&srchType=1&numDays=3500&srchOpt=0&srchData=&keywordType=All&chckNewsType=1%2C+2%2C+3%2C+4%2C+5&intPage=&showAll=&pYear=&year=&desc=false&cbOrder=date>.

- [52] NPSG on Anticoagulation - TJC Website; 11/3/2010. Accessed 11/3/2010, from http://www.jointcommission.org/NR/rdonlyres/82B717D8-B16A-4442-AD00-CE3188C2F00A/0/08_HAP_NPSGs_Master.pdf.
- [53] Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* Jun 2008;133(6 Suppl):381S–453S.
- [54] Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ* Feb 11 2006;332(7537):325–9.
- [55] Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* Aug 17 2004;110(7):874–9.
- [56] Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* Sep 9 1999;341(11):793–800.
- [57] Weaver WD, White HD, Wilcox RG, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy. GUSTO-I investigators. *JAMA* Mar 13 1996;275(10):777–82.
- [58] Newby LK, Califf RM, Guerci A, et al. Early discharge in the thrombolytic era: an analysis of criteria for uncomplicated infarction from the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial. *J Am Coll Cardiol* Mar 1 1996;27(3):625–32.
- [59] Gomez-Outes A, Lecumberri R, Pozo C, Rocha E. New anticoagulants: focus on venous thromboembolism. *Curr Vasc Pharmacol* Jul 2009;7(3):309–29.
- [60] Spyropoulos AC. Bridging therapy and oral anticoagulation: current and future prospects. *Curr Opin Hematol* Sep 2010;17(5):444–9.
- [61] <http://www.pharmtech.findpharma.com/pharmtech/Manufacturing/The-Biosimilars-Market-Today-And-Tomorrow/ArticleStandard/Article/detail/685049> accessed 1/17/2011.