Characteristics of Novel Anticoagulants and Potential Economic Implications

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Abstract

Deep vein thrombosis and pulmonary embolism—the components of venous thromboembolism (VTE)—are significant causes of morbidity and mortality and are a major burden on US healthcare systems. Current VTE prevention strategies are often suboptimal after total hip or total knee arthroplasty, possibly due to drawbacks of the established anticoagulants, resulting in residual VTE and associated (or related) costs of care. New anticoagulant agents under development may address some of the limitations of current options and possibly increase adherence to guidelines for thromboprophylaxis. This article will review the characteristics of the new oral anticoagulants, which may potentially translate into cost savings for the healthcare system.

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Deep vein thrombosis (DVT) and pulmonary embolism (PE)—the components of venous thromboembolism (VTE)—are a major burden on US healthcare systems: estimates put costs at nearly $500 million per year.[1] DVT and PE are significant causes of morbidity and mortality. Without prophylaxis, risk of a DVT or a PE event is especially high in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA),[2] with an incidence of venographic DVT without prophylaxis estimated at 40% to 60%.[2] Current standard prophylaxis with a low molecular weight heparin (LMWH) or warfarin for ≤4 weeks after surgery does not satisfactorily reduce the incidence of these events, with between 1.4% and 2.8% of patients still developing symptomatic DVT after THA or TKA, and PE occurring in 0.4% to 1.2% of patients.[3] The prognosis for patients with VTE is also characterized by the risk of recurrent events, such as post-thrombotic syndrome (PTS) or pulmonary hypertension after PE,[4] which result in an additional burden on US healthcare systems. About one-third to one-half of patients with DVT will develop PTS, in most cases within 1 to 2 years of acute DVT.[5] A detailed review of the published literature on the economic consequences of using conventional prophylaxis to prevent VTE after THA or TKA is included in the article by Baser in this supplement[6] and will not be described in detail here. This article will review the potential implications of the new oral anticoagulants on the costs of thromboprophylaxis after THA or TKA.

Cost Implications

The Global Orthopaedic Registry collected data on the incidence of VTE and prophylaxis from 6639 patients who underwent THA and 8326 who underwent TKA in 100 hospitals in 13 countries worldwide. Results indicated that current VTE prevention strategies were often suboptimal after THA and TKA,[7] resulting in increased VTE and increased costs of care. The reasons for this, and strategies to improve care, are discussed in detail in the article by Merli in this supplement.[8] New agents under development may potentially address the limitations of

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current options[9] and could facilitate adherence to guidelines for thromboprophylaxis.

Characteristics of the Ideal Anticoagulant, Which Should Translate Into Potential Cost Savings

A number of characteristics of the novel oral anticoagulants, such as rivaroxaban, apixaban, and dabigatran, would be expected to translate into cost savings after THA/TKA, as well as in other indications. The sections that follow illustrate such characteristics.

Administered Orally, 1 Tablet Once or Twice Daily

Poor adherence to medication accounts for substantial deterioration in disease, death, and increased healthcare costs—approximately 30% to 70% of medication-related hospital readmissions are due to poor adherence. These cost the healthcare system approximately $100 billion a year.[10] Appropriate medication adherence has been identified as a priority for healthcare reform.[11] A variety of factors may affect non-adherence; however, simplifying treatment is a strategy that may improve it, and 1 pill, once daily has been shown to maximize adherence.[10] Patients given a single-pill amlodipine/atorvastatin combination, rather than a 2-pill regimen, were approximately 3 times more likely to achieve adherence over 1 year of follow-up.[12] Similarly, simplifying therapy to a once-daily regimen instead of a more frequent regimen in virologically suppressed HIV-1–infected patients improved patient satisfaction and adherence.[13]

The ease of use of rivaroxaban has been identified as one of its most tangible benefits.[14] In clinical trials, rivaroxaban and dabigatran were given once daily after THA/TKA,[15-21] whereas apixaban was given twice daily after TKA.[22,23] An oral route of administration should also be significantly cost saving, since subcutaneous administration, as required with LMWH, can be costly. Home healthcare nurse visits during the post-hospital prophylaxis period cost an average of $100 per patient for enoxaparin.[24] Some patients feel comfortable self-injecting LMWH, but patient education by experienced nurse clinicians takes an average of 30 minutes, and experienced medical staff must be available on a 24-hour basis to provide support to patients who have concerns about self-injection.[25]

Wider Therapeutic Window

Vitamin K antagonists (VKAs) have a narrow therapeutic window, and patients are frequently above or below the therapeutic international normalized ratio (INR) range,[26,27] putting them at risk for a bleeding event or for thrombosis.[28,29] Therefore, INR monitoring forms part of the management strategy to ensure safe and optimal anticoagulation control.[30] However, monitoring of warfarin control can be relatively expensive, with mean costs averaging (in 2003 dollars) $281 for patients with atrial fibrillation treated for 1 full year.[31] When examining the costs of complications of warfarin, a supratherapeutic INR level was associated with costs ranging from $75 for a hematoma to $33,487 for a transfused gastrointestinal bleed, while a subtherapeutic INR was associated with costs ranging from $543 for a delay in cardioversion to $11,917 for a recovered stroke.[32] The novel anticoagulants have a wider therapeutic index, thus eliminating the need for routine coagulation monitoring.[33] Therefore, it is expected that monitoring and related management and complications costs would be limited or avoided with the introduction of these agents.

Minimal Interaction With Food or Other Drugs

Warfarin is one of the most frequently used thromboprophylaxis agents in the United States. However, due to its pharmacokinetics and pharmacodynamics, there is considerable intra- and inter-patient variability in the dose response, and it is associated with multiple drug-drug and food-drug interactions.[30,34] LMWHs have a predicable dose response,[35] but enoxaparin should not be used with certain agents, including anticoagulants, platelet inhibitors, acetylsalicylic acid, salicylates, nonsteroidal anti-inflammatory drugs, dipyridamole, and sulfinpyrazone, as coadministration with these agents increases the likelihood of bleeding.[36] Enoxaparin does not interact with food. The minimal drug-drug interactions and lack of dietary restrictions that characterize the new oral agents, including rivaroxaban, dabigatran, and apixaban,[37] should simplify therapy and reduce the need for patient visits to providers. At the same time, these characteristics are likely to improve adherence, with an attendant reduction in VTE events. In patients with diabetes, hypertension, and hypercholesterolemia, for example, a high level of adherence to medication has been found to be associated with lower disease-related costs.[38]

Rapid Onset of Action

Rivaroxaban has a rapid onset of action, with a time to reach maximal plasma concentration of 2 to 4 hours.[39] Similarly, apixaban reaches its maximal concentration within 1 hour of oral administration.[40] Dabigatran also exhibits the short time of approximately 2 hours to maximal concentration.[41] This is also the case for other anticoagulants in development.[42] For rivaroxaban, apixaban, and dabigatran, a close correlation exists between their plasma concentration and their pharmacodynamic effects.[42] Enoxaparin has a similar time to maximal plasma concentration of approximately 3 hours.[43] Guidelines recommend administration of enoxaparin either preoperatively

or postoperatively in THA or TKA.[2] Preoperative initiation may require early admission, increasing the financial burden of the procedure.[35,44] This may suggest that the administration of novel anticoagulants that are initiated postoperatively would avoid the added cost of early admission. In addition, a small single-center study investigating the use of warfarin as thromboprophylaxis for lower limb arthroplasty found that 68% of patients experienced a delay in hospital discharge while waiting for their INR to stabilize.[45] This resulted in additional costs related to bed occupancy, a problem that could likely be reduced with the new anticoagulants.

Effectiveness in Reducing Thromboembolic Events

Better efficacy should translate into cost savings, as outlined in the article by Merli in this supplement.[8] From discharge summaries, Ollendorf et al found that mean costs of inpatient care were $17,114 for patients with DVT and $18,521 for patients with PE, compared with $9345 for patients with no VTE.[46] A study using data from a large healthcare claims database calculated much higher in-hospital mean billed charges for the index admission after THA: $36,705 in patients with no VTE, $62,558 in patients with in-hospital VTE, and $34,970 for post-discharge VTE.[47] Similarly, costs after TKA were $35,601 in patients with no VTE, $44,898 in patients with in-hospital VTE, and $31,774 for post-discharge VTE.[47] An analysis of the economic burden of VTE in hospitalized patients estimated the cost of managing an initial episode of DVT at $7712 to $10,804, while for an initial PE event, estimated cost was $9566 to $16,644.[48]

More effective anticoagulants should also result in reductions in the long-term complications of VTE, particularly PTS, which would save the US healthcare system significant sums. The average lifetime cost of complications after THA has been estimated to be $3069 per patient.[49] Changing from the use of LMWH would also mean a reduction in the incidence of heparin-induced thrombocytopenia (HIT). While LMWH is associated with lower rates of HIT after orthopedic surgery than unfractionated heparin (UFH),[50] a meta-analysis comparing the risk of HIT with the use of UFH or LMWH, mostly in studies after orthopedic surgery, still found that LMWH was associated with an absolute risk of 0.2%.[51] In addition, surgery itself is an important risk factor for HIT.[52,53] Patients admitted to a tertiary-care hospital with HIT incurred costs amounting to $41,133 more than those of control patients.[54]

Comparable Rate of Bleeding Events

Rates of bleeding after orthopedic surgery were comparable between the new agents and the current standard of care, enoxaparin.[23,44,55] Due to its unpredictable pharmacodynamics, warfarin can be associated with an increase in bleeding.[56] While healthcare providers should exercise caution when administering warfarin as monotherapy after joint arthroplasty,[57] guidelines still recommend it[2] and it is still used.[45,58] However, 1 study showed that after THA, warfarin was associated with more bleeding events and a much greater cost for treating these events compared with enoxaparin.[59] Therefore, cost saving would likely occur when comparing the new anticoagulants with warfarin.

No Individual Dose Adjustment Required

Variable dosing, requiring routine monitoring of INR for VKAs, can be costly in terms of resources and time for healthcare systems as well as for patients. The per-patient-per-month cost of an outpatient anticoagulation service was $51.25 in 2000.[60] A more recent systematic review of 29 studies found the costs of 1 INR to vary between $6 and $146.[61] Monitoring costs for tracking anticoagulation control will be eliminated with the new anticoagulants.

Prescription Costs

Barriers to adopting new pharmaceutical agents often include acquisition costs. New agents have sometimes appeared to be an expensive option at first, but may be otherwise cost-effective. As the new oral anticoagulants will involve significant outpatient use, the pricing of these agents will likely be lower compared with pricing on injectables such as LMWH and fondaparinux. Changing from UFH to a more costly LMWH for the treatment of VTE resulted in savings from reductions in the use of hospital facilities[62,63] and shortened hospital stays.[64] Economic analyses comparing the new agents with traditional treatment options will be needed to evaluate their cost-effectiveness and cost-benefit ratio (see the article by Kwong in this supplement[65]).

Resources

As stated earlier, patients receiving VKAs require anticoagulation monitoring, and anticoagulation clinics have effectively enabled patients to maintain good control.[66] However, such clinics are obviously associated with considerable costs.[32] If resources currently spent on anticoagulation clinics were to be redirected to the delivery of the new generation antithrombotic agents, rates of preventative therapy and adherence could potentially increase.[67] Such clinics could be transformed into thrombosis centers, which could coordinate antithrombotic therapy,[68] give counsel-

ing on antithrombotic drugs, and possibly be involved with D-dimer assaying.[69]

Conclusions

Future economic analyses of all the new anticoagulants will determine their place and value on the cost-benefit scale. Currently, comparisons of clinical results must be indirect, and conclusions must be drawn with caution until head-to-head comparisons are performed.[70] In a recent article, the authors described an indirect comparison between dabigatran and rivaroxaban after THA/TKA and concluded that their analysis did not provide grounds for any claims about superiority of one drug over the other.[71] Another indirect comparison concluded that rivaroxaban might be more effective than dabigatran for the prevention of VTE, but might also slightly increase the risk of bleeding.[72] A recent analysis of cost savings in the Irish healthcare setting found that when both rivaroxaban and dabigatran were compared with enoxaparin, rivaroxaban was the less costly and more effective option after THA and TKA.[73] However, there are many methodological problems in the use of indirect comparisons for evaluating healthcare interventions,[74] and the economic principles of cost-effectiveness analysis are often not adhered to,[75] so robust analyses will require close scrutiny.

Before the new agents are widely adopted, providers will need to feel comfortable that they are truly effective and safe. Their use and selection will be guided by the results of ongoing clinical trials and real-life observational and comparative-effectiveness trials, as well as by their pharmacologic and pharmacodynamic characteristics. Healthcare providers will need to be fully aware of such data and specific product characteristics to appropriately select and use these new agents.[76] A number of recent review articles have summarized the efficacy, safety, and clinical implications of these new oral anticoagulants, and may be helpful resources.[9,33,76-79]

Because the new anticoagulants may improve anticoagulation control, especially if appropriate adherence and persistence rates can be maintained (compared with health system investments in anticoagulation clinics or patient education), discussions about the economics of anticoagulation have never been more relevant.[80]

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