New Anticoagulants for Thromboprophylaxis After Total Knee Arthroplasty

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Abstract

Total knee arthroplasty (TKA) is one of the most common orthopedic procedures in the United States. The number of TKAs is expected to rise significantly over the next 2 decades. One of the most common complications after TKA is venous thromboembolism (VTE), which is potentially fatal. The incidence of VTE is effectively reduced by prophylactic anticoagulants, and clinical guidelines have been developed to improve VTE management. However, current anticoagulants have limitations in terms of efficacy, safety, half-life, ease of administration, and patient adherence. Moreover, these anticoagulants require routine monitoring and dose adjustment, and potential bleeding complications represent an important concern. A new generation of anticoagulants, including recently approved rivaroxaban, is being developed to address the shortcomings of current agents. The efficacy and safety of these newer agents are comparable with those of existing ones. Rivaroxaban is the only new oral agent that is approved for use in TKA and that has demonstrated an efficacy superior to that of enoxaparin in phase 3 trials. To optimize the management of VTE prophylaxis after TKAs, orthopedic surgeons must have a thorough understanding of these new oral agents.

Total knee arthroplasty (TKA) is one of the most common orthopedic procedures in the United States (US). More than half a million surgeries are performed each year, and this figure is expected to rise to about 3.5 million surgeries per year by 2030.[1]

Patients who undergo TKA are at risk for a range of postsurgical complications, including wound-healing problems, wound and deep-tissue infection, and venous thromboembolism (VTE).[2] VTE is potentially fatal and among the most common of these complications. It has been estimated that, in the absence of effective chemoprophylaxis, the total incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) after major orthopedic surgery is as high as 41% to 85% and 1.5% to 10%, respectively.[3]

VTE is a major cause of postoperative morbidity and carries a significant risk for mortality.[3] The cost of managing VTE is estimated to be as much as $1.5 billion annually in the US. The cost of managing an initial DVT event is estimated to be $7712 to $10,804, and the cost of managing an initial PE event is estimated to be $9566 to $16,644.[4] Appropriate use of effective thromboprophylaxis reduces the cumulative incidence of symptomatic VTE to 2.3% within 3 months after TKA.[5]

Anticoagulants increase the risk for bleeding. With that in mind, clinicians need to consider the cost of managing any bleeding event when assessing the overall cost savings associated with anticoagulant prophylaxis.[6] Analyses of insurance claims from the Ingenix National Managed Care (Impact) Database revealed that, in patients who have had either TKA or total hip arthroplasty (THA), the increased monthly health care cost associated with a VTE event was comparable with that of a bleeding event ($2729 vs $2696).

The cost of a VTE event, however, was substantially lower than that of a major bleeding event ($2729 vs $4304).[6] The overall 3-month risks for any bleeding or major bleeding event were lower (4.0% and 1.9%, respectively) than the risk for VTE (6.7%). From a managed-care population perspective, the larger incremental cost associated with major bleeding compared with VTE was offset by the reduction in symptomatic events that would require additional treatment and hospitalization.[6] This study and others emphasize the importance of balancing bleeding risk and use of effective thromboprophylaxis in the overall consideration of health care economics.[6,7]

Morbidity and mortality are a function of the high incidence of VTE after TKA as well as the long-term sequelae of VTE, including recurrence, postthrombotic syndrome, and chronic thromboembolic pulmonary hypertension. It is therefore necessary to optimize thromboprophylaxis in patients undergoing TKA.

In this review, we summarize some of the most clinically relevant data on the newer, recently approved anticoagulants and on the agents being developed for thromboprophylaxis

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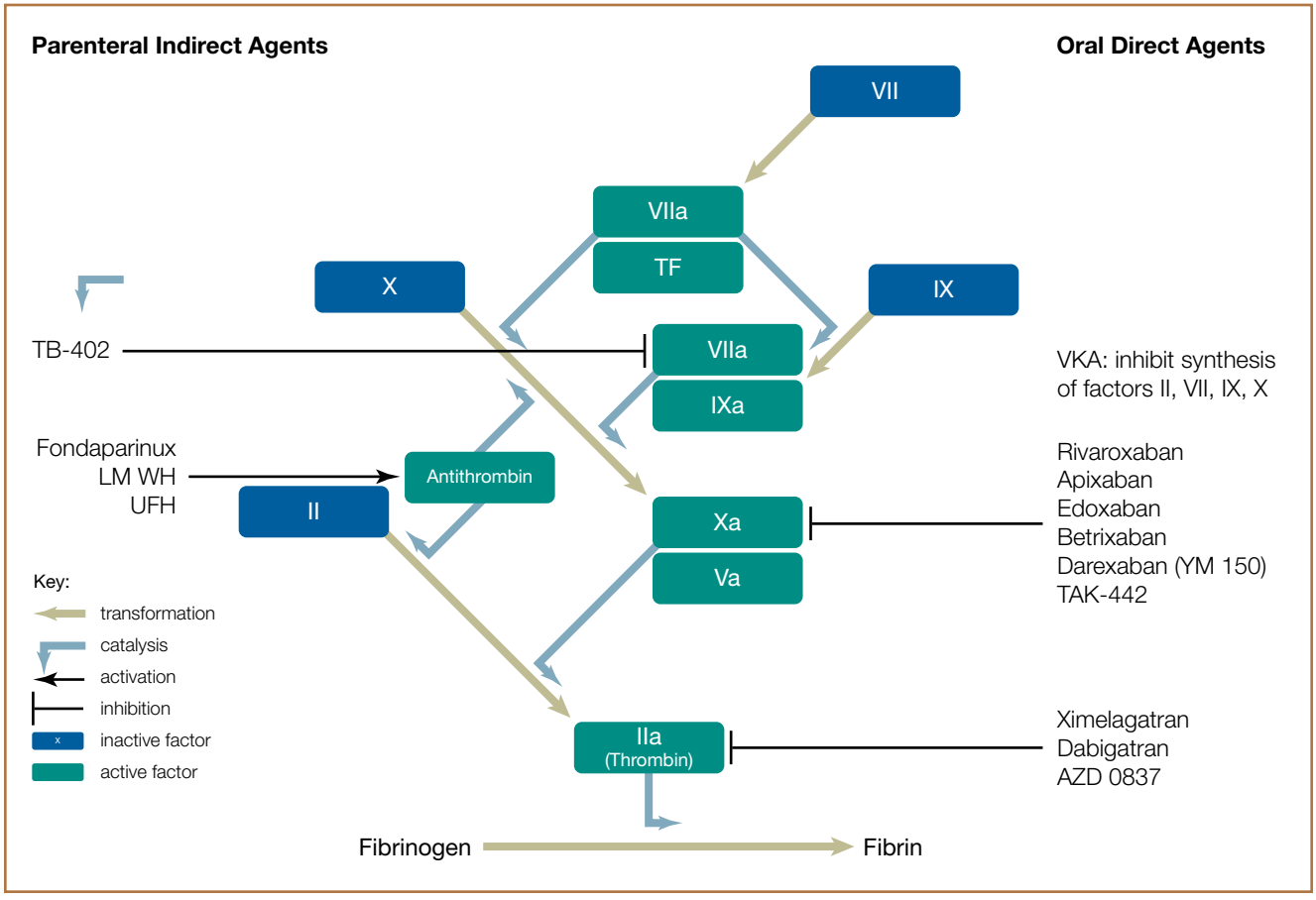

Figure. Targets for anticoagulants in use and in development as thromboprophylaxis after total knee arthroplasty.[14,20,39] LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

after TKA. In addition, we discuss current practice guidelines, pharmacology, clinical trial data, and application of these new anticoagulants in real-life orthopedic practices.

Clinical Practice Guidelines for Thromboprophylaxis

Clinical practice guidelines for VTE prevention have been published by the American College of Chest Physicians (ACCP) for more than 20 years, with the most recent update in 2012.[3,8] These evidence-based recommendations have helped to define the optimal use of thromboprophylaxis in patients undergoing TKA and are widely used throughout North America and the rest of the world.[9] In 2007, the American Academy of Orthopaedic Surgeons (AAOS) published its first set of clinical practice guidelines for VTE prevention in patients undergoing TKAs and THAs.[10] AAOS released an updated version in 2011.[11]

There are some important differences between these guidelines. The ACCP guidelines are for preventing both DVT and PE, whereas the AAOS guidelines specifically address preventing death from PE after total joint arthroplasty (TJA). As a result, there were initially some significant areas of disagreement. The AAOS guidelines have been criticized for not considering the incidence of asymptomatic DVT as a meaningful endpoint in studies of prophylactic treatment and for considering PE and fatal PE as the only valid outcomes. In contrast, the ACCP guidelines recognize a link between asymptomatic DVT and PE. The implications of this decision are described in a comprehensive review by Eikelboom and colleagues.[9] Both ACCP and AAOS guidelines meet the standards of the Surgical Care Improvement Project (SCIP) of the Centers for Medicare and Medicaid Services (CMS). Most hospitals have adopted one or the other to fulfill their compliance requirement with CMS.

For thromboprophylaxis after TKA, the ACCP guidelines recommend routine low-molecular-weight heparin (LMWH; enoxaparin or dalteparin), the pentasaccharide fondaparinux (an indirect non-oral factor Xa inhibitor), or the vitamin K antagonist (VKA) warfarin.[3] They did not recommend aspirin as a sole agent for thromboprophylaxis; however, aspirin and sequential compression devices are included in the recommendations.[3,10]

The latest AAOS guidelines suggest pharmacologic agents and/or mechanical compressive devices (grade of recommendation: moderate) for thromboprophylaxis. The AAOS suggests, however, that evidence is still unclear as to which prophylactic strategies are optimal, and it does not recommend for or against specific prophylactics in patients who have

undergone TKA (grade of recommendation: inconclusive).[11]

Controversy also exists regarding the appropriate duration of thromboprophylaxis. The AAOS guidelines recommend using a LMWH or fondaparinux for 7 to 12 days after surgery or warfarin for 2 to 6 weeks after surgery.[10] However, they also cite the fact that evidence is not sufficient for specific time recommendations (grade of recommendation: consensus) and therefore suggest that patients and physicians discuss the duration of prophylaxis.[11]

Data from the Global Orthopaedic Registry (GLORY) suggested that adherence to the guideline standards of thromboprophylaxis was poor in real-world clinical practice. Poor adherence was particularly prevalent in the US. Thus, there remain unmet goals for optimizing thromboprophylaxis using evidence-based criteria.[12]

Other issues arising with thromboprophylaxis include administration of other drugs to patients who are anticoagulated after TKA. Concomitant administration of other agents that could affect coagulation is not recommended. These medications include nonsteroidal anti-inflammatory drugs, clopidogrel bisulfate (Plavix), and aspirin. In some clinical trials in cardiology, low-dose (82-mg) aspirin has been permitted. In the most recent ACCP guidelines,[3] aspirin is included as an acceptable option for thromboembolic prophylaxis after TJAs. It is crucial that patients be stratified by risk for venous thromboembolism and risk for major bleeding after surgery. The most efficacious and safest chemoprophylaxis should be administered.

As for using anticoagulants in conjunction with paraxial anesthesia, the guidelines put forth by the American Society of Regional Anesthesia and Pain Medicine (ASRA) should be strictly followed.[13] In general, management of these new agents should be in keeping with the well-established guidelines that have been in clinical use for LMWHs.

Current Anticoagulants and Their Limitations

LMWHs and unfractionated heparin (UFH) bind to antithrombin and catalyze the inactivation of thrombin and factor Xa (**Figure**).[14] UFH also binds to cells and other plasma proteins, resulting in unpredictable pharmacokinetic (PK) and pharmacodynamic (PD) properties and necessitating frequent monitoring and dose adjustment. This lack of specificity may contribute to bleeding or nonhemorrhagic adverse events, such as heparin-induced thrombocytopenia and osteoporosis. LMWHs have more specificity for factor Xa; their PK and PD characteristics are more predictable, and they can often be administered without routine monitoring.[14] The greatest concern when using LMWHs is bleeding complications after surgery. Dose adjustments are necessary in patients with compromised renal function, and many clinicians make dose adjustments based on weight in selected cases.

Fondaparinux is a synthetic pentasaccharide that acts as an indirect inhibitor of factor Xa activity (**Figure**). Compared with LMWHs, fondaparinux has a longer half-life, and it may be administered once-daily as a fixed dose without the need for anticoagulant monitoring. Similar to UFH and LMWHs, fondaparinux is administered subcutaneously (SC) and lacks the convenience of oral administration.[14] The VKA warfarin, which has been the principal oral anticoagulant for more than 60 years, has complex PK and PD properties, and its dose response is highly susceptible to genetic factors, drug–drug interactions, and food–drug interactions.[14,15] In addition, warfarin has a narrow therapeutic window, making routine coagulation monitoring and dose adjustment essential[15]; it also has a slow onset (and offset) of action.

The efficacy of aspirin in the prevention of VTE after TKA has been much debated. There are only a few randomized controlled trials comparing aspirin to other antithrombotic agents. These studies have conflicting data of varying quality; for this reason the beneficial effect of aspirin on VTE prevention after TKA has remained unproven.[3,16]

The bleeding risk associated with anticoagulants depends on many factors.[17] The risk for major bleeding with LMWH prophylaxis after THA and TKA is estimated to be 3% to 5%.[17] The unpredictable PK and PD properties of warfarin also increase the risk for bleeding, particularly in the outpatient setting when monitoring and dose adjustment are difficult. The perceived risk for bleeding complications associated with effective chemoprophylaxis represents a major barrier to optimal use of thromboprophylaxis and to compliance with practice guidelines.[18,19]

New and Experimental Anticoagulants

Over the past 5 years, several new anticoagulants have been approved for clinical use in Europe and Canada or have entered clinical development. These new agents have advantages over existing therapies in terms of efficacy and safety profile, half-life, and ease of administration (**Table I**).[20-23] Broadly speaking, these new medications fall into 2 categories: direct thrombin inhibitors (DTIs) and factor Xa inhibitors.

Direct Thrombin Inhibitors

Thrombin catalyzes the production of fibrin in the final step in the clotting cascade. It is therefore an ideal target for anticoagulation (**Figure**).[20] Two intravenous DTIs, argatroban and bivalirudin, are approved as thromboprophylactic in patients with heparin-induced thrombocytopenia.

Ximelagatran was the first oral DTI to receive marketing authorization (in the European Union [EU]) for thromboprophylaxis in TKA and THA. It was later taken off the market because of reported hepatotoxicity and potential cardiovascular complications.[24]

Dabigatran is a new oral DTI. It was recently approved for stroke prevention in patients with atrial fibrillation, and it is also approved for VTE prophylaxis after TKA and THA in Canada and the EU. There have been no reported cardiovascular complications or hepatotoxicity associated with long-term administration of this agent.

The RE-MODEL trial was a randomized, double-blind study of 2076 patients undergoing TKAs. Oral dabigatran (150 or 220 mg QD) was shown to be equally effective as the standard EU enoxaparin regimen (40 mg SC QD).[25] However,

Table I. **Properties of Anticoagulants in Use and in Development as Thromboprophylaxis After Total Knee Arthroplasty**[20-23]

Drug	Therapeutic Target	Monitoring Required	Half-Life, h (Except TB-402)	Bioavailability, %	Mode of Elimination	Food–Drug Interactions
LMWH	Factors IIa, Xa	No	3-6	~90	Renal	None
Warfarin	Vitamin K	Yes	36-42	~100	Renal	Multiple
Fondaparinux	Factors IIa, Xa	No	17-21	~100	Renal	None
Rivaroxaban	Factor Xa	No	11-13[a]	80-100	Fecal (50%) Renal (50%)	CYP3A4 inhibitors/ inducers P-gp inhibitors/ inducers NSAIDs
Dabigatran	Factor IIa	No	12-14	6.5	Renal (85%)	P-gp inhibitors/ inducers NSAIDs
AZD0387	Factor IIa	No	9	22-52	NR	CYP3A4 inhibitors
Apixaban	Factor Xa	No	8-11[b]	34-88	Fecal (56%) Renal (~25%)	Minimal
Betrixaban	Factor Xa	No	19	47	NR	NR
Edoxaban	Factor Xa	No	9-11	50	NR	NR
YM150	Factor Xa	No	NR	25-82	NR	NR
TAK-442	Factor Xa	No	NR	NR	NR	NR
TB-402	Factor VIII	NR	19.5-22.9 d	NR	NR	NR

Abbreviations: h, hours; LMWH, low-molecular-weight heparin; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein.
[a]In elderly patients.
[b]Twice-daily dosing.

data from the RE-MOBILIZE trial demonstrated that once-daily oral dabigatran (220 or 150 mg) was inferior to the standard US enoxaparin regimen (30 mg SC BID) after TKA.[26] Dabigatran has not been submitted for approval as a thromboprophylactic agent for TKA patients in the US.

AZD0837 is an oral DTI in development as a modification of ximelagatran that does not have the same hepatotoxicity that ximelagatran did. Preliminary phase 2 dose-finding studies have shown antithrombotic effects and safety comparable to those of warfarin.[20,27]

Factor Xa Inhibitors

Factor Xa catalyzes the conversion of prothrombin to thrombin. This is a crucial step in the coagulation cascade that eventually promotes the formation of fibrin. The pentasaccharide fondaparinux inhibits factor Xa indirectly by binding to antithrombin, whereas the new oral factor Xa inhibitors have a direct mode of action (**Figure**).[20] The new factor Xa inhibitors that have been studied as potential thromboprophylactics after TKA include apixaban, betrixaban, edoxaban, TAK-442, YM150, and rivaroxaban.

In 2 large randomized, double-blind phase 3 trials, ADVANCE-1 and ADVANCE-2, the efficacy of oral apixaban was compared with that of enoxaparin in preventing VTE in patients who underwent TKA. Although apixaban 2.5 mg twice-daily proved superior to enoxaparin 40 mg once-daily, it did not achieve noninferiority compared with enoxaparin 30 mg every 12 hours.[28,29] A meta-analysis of these trials found a lower rate of major bleeding events for apixaban compared with enoxaparin.[30]

Phase 2 trial data have been reported for betrixaban, edoxaban, and TAK-442. In patients who underwent TKA, betrixaban demonstrated antithrombotic activity and appeared to be well tolerated. Edoxaban demonstrated significant dose-dependent reductions in VTE with no increases in major or clinically relevant bleeding events.[31,32] TAK-442 demonstrated efficacy similar to that of, and tolerability equivalent to that of, enoxaparin 30 mg SC twice-daily.[33] The safety and efficacy of YM150 are being investigated in a pair of phase 2 studies, NCT00595426 and NCT00408239. Results are not yet available.

In July 2011, rivaroxaban was approved in the US as the first novel oral anticoagulant for VTE prophylaxis after TKA and THA. Rivaroxaban 10 mg once-daily for up to 2 weeks proved superior to enoxaparin in 2 randomized, double-blind phase 3 trials, RECORD 3 and RECORD 4. Rivaroxaban significantly reduced the incidence of total VTE in comparison with both enoxaparin 40 mg SC once-daily and enoxaparin 30 mg SC twice-daily.[34,35] RECORD 4 was the first study in which the efficacy of a new oral anticoagulant (rivaroxaban) used after

Table II. Mechanism of Action and Dosing Details for Anticoagulants in Use and in Development as Thromboprophylaxis After Total Knee Arthroplasty[40]

Drug	Mechanism of Action	Prodrug	Mode of Administration
LMWH	Inhibition of factors IIa and Xa	No	Subcutaneous
Warfarin	Inhibition of vitamin K	No	Oral
Fondaparinux	Indirect inhibitor of factor Xa by binding to antithrombin	No	Subcutaneous
Rivaroxaban	Inhibition of factor Xa	No	Oral
Dabigatran	Indirect inhibition of factor IIa	Yes	Oral
AZD0387	Indirect inhibition of factor IIa	Yes	Oral
Apixaban	Direct inhibition of factor Xa	No	Oral
Betrixaban	Direct inhibition of factor Xa	No	Oral
Edoxaban	Direct inhibition of factor Xa	No	Oral
YM150	Direct inhibition of factor Xa	No	Oral
TAK-442	Direct inhibition of factor Xa	NR	Oral
TB-402	Partial inhibition of factor VIII producing an antithrombotic effect	NR	Subcutaneous

Abbreviations: LMWH, low-molecular-weight heparin; NR, not reported.

TKA was found superior to that of the standard enoxaparin regimen used in the US.[35] Compared with patients who received enoxaparin, those who received rivaroxaban did not have a significantly higher rate of major bleeding events.[34,35]

That rivaroxaban has superior efficacy and equivalent safety in comparison with enoxaparin was confirmed in a meta-analysis of 8 randomized, controlled trials of these 2 medications used for thromboprophylaxis after TKA and THA. Included in the meta-analysis were data from RECORD 3, RECORD 4, and the other phase 3 RECORD trials.[36]

Besides demonstrating superior clinical efficacy, rivaroxaban (vs other agents) has shown potential to reduce the total health care costs associated with drug administration, monitoring, and overall VTE treatment. Furthermore, as rivaroxaban reduces the incidence of symptomatic VTE, its use may lead to additional cost savings.[37]

Although rivaroxaban has a good safety profile, clinicians should exercise caution when administering it to patients with moderate renal impairment (estimated creatinine clearance, 30-50 mL/min).[38] The medication may accumulate in patients with moderate to severe renal impairment, as about 36% of rivaroxaban is excreted unchanged by the kidneys.[38] In addition, rivaroxaban is a P-glycoprotein (P-gp) substrate and is partially metabolized by CYP3A4/5 and CYP2J2; clinically significant drug–drug interactions are possible when rivaroxaban is combined with P-gp and CYP3A4 inducers or inhibitors.[38] Drugs that inhibit the CYP3A4 enzyme and drug transport system include: ketoconanzole, ritonavir, lopinavir, and similar classes. Drugs that induce the CYP3A4 enzyme and drug transport system include: carbamazepine, phenytoin, rifampin, and St. John's wort. Epidural or spinal hematomas have occurred in patients who received neuraxial anesthesia or underwent spinal puncture while being treated with rivaroxaban. Such patients should frequently be monitored for signs and symptoms of neurologic impairment and, if impairment is noted, urgently treated.[38]

Other New Agents

TB-402 is a novel anticoagulant in a pharmacologic class of its own. This monoclonal antibody has a prolonged antithrombotic effect as a result of its partial factor VIII inhibition (**Figure**) and long half-life.[39] In a recently completed phase 2 dose-finding study in patients who underwent TKA, the rate of VTE was lower for a single dose of TB-402 than for enoxaparin 40 mg given daily for 10 days (these medications had similar safety profiles).[39]

Summary

Table II summarizes the mechanisms of action and dosing modes of all the current and new anticoagulants.[39]

Given the projected significant increase in number of TKAs performed in the US, safe and effective anticoagulants are essential for reducing the morbidity and mortality associated with VTE. Current thromboprophylactics have limitations. The efficacy and safety of newer agents are comparable with those of existing therapies. Rivaroxaban is the only new oral agent that is approved for use in TKA and that has demonstrated an efficacy superior to that of enoxaparin in phase 3 trials. Orthopedic surgeons must have a thorough understanding of these new oral agents in order to administer the most efficacious and safest thromboprophylaxis after TKA.

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