The Medical Letter on Drugs and Therapeutics

New Oral Anticoagulants for Acute Venous Thromboembolism

Anticoagulants are the drugs of choice for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE).

Standard Treatment

Patients with acute VTE are often treated initially with a parenteral anticoagulant such as unfractionated heparin, low molecular weight heparin (LMWH), or fondaparinux (Arixtra, and generics); all are associated with similar rates of mortality, recurrent VTE, and major bleeding. For most patients, the oral vitamin K antagonist warfarin (Coumadin, and others) is started on the same day as parenteral therapy and titrated to maintain an INR between 2 and 3. After ≥5 days, the parenteral anticoagulant is stopped and warfarin is continued as monotherapy, usually for at least 3 months.[1]

Related articles pages 717, 729 and 741

New Oral Anticoagulants

Rivaroxaban (Xarelto), dabigatran etexilate (Pradaxa), apixaban (Eliquis), and edoxaban (not FDA-approved) have all been studied for treatment of acute VTE (**Table**), but only rivaroxaban is FDA-approved for this indication. Unlike warfarin, the newer drugs do not require INR monitoring and have no dietary restrictions, but they have shorter half-lives (increasing the risks associated with missed doses) and no specific antidote to reverse their anticoagulant effect.

Clinical Studies

Only a small minority of patients in any clinical trial of a new oral anticoagulant for treatment of acute VTE were ≥75 years old, had a creatinine clearance (CrCl) <50 mL/min, or had cancer.

Rivaroxaban (Xarelto)

A randomized open-label study (EINSTEIN) in 3449 patients compared rivaroxaban alone to standard therapy with the LMWH enoxaparin (Lovenox, and generics) plus a vitamin K antagonist for treatment of acute VTE. Rivaroxaban was non-inferior to standard therapy in reducing the rate of recurrent VTE. The rate of major or clinically relevant non-major bleeding, the primary safety endpoint, was the same in both groups.[2] A second randomized open-label study (EINSTEIN-PE) in 4832 patients with PE found that rivaroxaban was non-inferior to enoxaparin plus a vitamin K antagonist in reducing the rate of recurrent VTE with a similar rate of major or clinically relevant non-major bleeding.[3]

Dabigatran Etexilate (Pradaxa)

A 6-month, randomized, double-blind trial (RE-COVER) in 2539 patients compared dabigatran to warfarin for treatment of acute VTE after initial treatment with a parenteral anticoagulant. Twice-daily dabigatran was non-inferior to warfarin in preventing recurrent VTE or VTE-related death, the primary efficacy endpoint. Rates of major bleeding were similar in the two groups.[4]

Apixaban (Eliquis)

A 6-month, randomized, double-blind trial (AMPLIFY) in 5395 patients compared apixaban alone to enoxaparin plus warfarin for treatment of acute VTE. Twice-daily apixaban was non-inferior in preventing recurrent VTE or VTE-related death (the primary efficacy endpoint). Major bleeding, the primary safety outcome, occurred less frequently with apixaban (0.6% vs 1.8%).[5]

Edoxaban

In a randomized, double-blind trial of 8240 patients with acute VTE first treated with unfractionated heparin or LMWH, once-daily edoxaban (not FDA-approved) was non-inferior to warfarin in preventing recurrent VTE or VTE-related death (the primary endpoint). Patients taking edoxaban had a significantly lower rate of major or clinically relevant non-major bleeding (8.5% vs 10.3%).[6]

Conclusion

The new oral anticoagulants rivaroxaban (Xarelto), dabigatran etexilate (Pradaxa), and apixaban (Eliquis), and the investigational oral

Table. Oral Anticoagulants for Treatment of Venous Thromboembolism

Drug	Mechanism of Action	Usual Dosage	Cost[a] $
Warfarin generic	Vitamin K antagonist	2-10 mg[b] once/d	6.00
(Coumadin)			43.00
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	15 mg bid for 3 wks, then 20 mg once/d[c]	265.00
Apixaban (Eliquis)[d]	Direct factor Xa inhibitor	10 mg bid for 7 d, then 5 mg bid[e]	265.00
Dabigatran etexilate (Pradaxa)[d]	Direct thrombin inhibitor	150 mg bid[f]	265.00

[a] Approximate wholesale acquisition cost of 30 days' treatment at the lowest daily dose. Source: Analy$ource Monthly (Selected from FDB Medknowledge) December 5, 2013. Reprinted with permission by FDB, Inc. All rights reserved. ©2013. www.fdbhealth.com/policies/drug-pricing-policy. Actual retail prices may be higher.

[b] Monitor INR daily and adjust dose until in therapeutic range (2-3) for >24 hours.

[c] With food; avoid use with combined P-glycoprotein and strong CYP3A4 inhibitors or inducers, or in patients with CrCl <30 mL/min.

[d] Not FDA-approved for treatment of VTE.

[e] Not studied in patients with acute VTE who are taking strong CYP3A4 inhibitors or who have CrCl <25 mL/min or serum creatinine >2.5 mg/dL.

[f] Avoid use with P-glycoprotein inducers; not studied for acute VTE in patients who have CrCl <30 mL/min.

anticoagulant edoxaban all appear to be effective and safe for treatment of acute venous thromboembolism, but data in older and sicker patients are limited. They do not require INR monitoring and do not have dietary restrictions, but they have short half-lives that increase the risk of thrombosis with missed doses and no specific antidote to reverse their anticoagulant effect.

ARTICLE INFORMATION

Section Editors: Gianna Zuccotti, MD, MPH, Executive Editor; Jean-Marie Pflomm, PharmD, Editor

Previous Publication: This article was previously published: *The Medical Letter*. January 6, 2014;56(1433):3-4. http://www.medicalletter.org.

REFERENCES

1. Kearon C, Akl EA, Comerota AJ, et al; American College of Chest Physicians. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2)(suppl):e419S-e494S.

2. Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.

3. Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297.

4. Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.

5. Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

6. Büller HR, Décousus H, Grosso MA, et al; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.