An alternative to warfarin for patients with PE

Rivaroxaban appears to be as safe and effective as warfarin, without the need for lab monitoring.

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PRACTICE CHANGER

Consider treating patients with acute pulmonary embolism (PE) with rivaroxaban, a factor Xa inhibitor; it works as well as low-molecular-weight heparin (LMWH) followed by warfarin, but may cause fewer major bleeds.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single, nonblinded randomized controlled trial.

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

ILLUSTRATIVE CASE

A 55-year-old man is brought to the emergency department with shortness of breath, pleuritic chest pain, and hypoxia shortly after returning from an overseas business trip. High-resolution spiral computed tomography (CT) reveals a PE.

How should he be treated?

Pulmonary embolism (PE) is fairly common—with an annual incidence estimated at 69 per 100,000[2]—and the cause of significant morbidity and mortality. Up to 30% of patients with venous thromboembolism (VTE) die within a month of diagnosis, mostly from PE, and in about 25% of cases, PE presents as sudden death.[3]

Warfarin has a significant downside

Standard therapy consists of either unfractionated heparin or LMWH followed by warfarin, a vitamin K antagonist (VKA), for ≥3 months.[4] In addition to requiring frequent laboratory monitoring, warfarin has potentially significant interactions with many prescription drugs. Numerous trials have investigated novel anticoagulants for treatment of VTE in recent years. In one randomized controlled trial (RCT), rivaroxaban (Xarelto)was found to be noninferior to a VKA for treating acute deep vein thrombosis (DVT).[5]

STUDY SUMMARY

Major bleeding is less likely with rivaroxaban

The EINSTEIN PE investigators conducted a randomized, unblinded noninferiority trial to determine whether rivaroxaban was at least as effective as the standard therapy—enoxaparin, followed by a dose-adjusted VKA (warfarin [for US patients] or acenocoumarol) for acute symptomatic PE.[1] To be included, participants had to have PE confirmed by CT, ventilation perfusion scan, or pulmonary angiography, with or without accompanying DVT. Exclusion criteria included active bleeding, significant renal impairment (creatinine clearance <30 mL/min), >48 hours of heparin treatment, or more than one dose of a VKA.

Participants (N=4832 in 38 countries) were randomized to receive either rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once a day thereafter) or standard therapy. The intervention and control groups were similar. Just over half were male, with an average age of 58 years; three-quarters of the patients had an intermediate to extensive PE

burden; and 90% were hospitalized for initial treatment. The researchers listed the etiology as unprovoked in 64% of the cases, followed by recent surgery or trauma and immobilization (17% and 16%, respectively).

After VKA initiation, the international normalized ratio (INR) was checked at least monthly. Patients in the control groups were within the target range (INR 1-2) 62% of the time, which is similar to other studies of anticoagulation in patients with VTE. Adherence to rivaroxaban was at least 80% in more than 94% of patients. Treatment lasted 3, 6, or 12 months, with the duration determined before randomization by the treating physician.

There was no difference in dropout rates (10.7% of rivaroxaban patients withdrew for any reason, vs 12.3% of the controls). Fewer than 0.5% of participants were lost to follow-up.

Symptomatic recurrent VTE, the primary outcome, occurred in 50 patients receiving rivaroxaban vs 44 of those on standard therapy (2.1% vs 1.8%; *P*=.003 for noninferiority using an intention-to-treat analysis). Major bleeding, defined as overt bleeding causing death, a drop in hemoglobin of ≥2 points, needing a transfusion, or bleeding in a critical site, occurred less often in the rivaroxaban group (1.1% vs 2.2%, *P*=.003, NNT=91). There was no significant difference in overall bleeding rates between the 2 groups.[1]

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WHAT'S NEW

Rivaroxaban is easier to use—and on label

This trial found rivaroxaban to be at least as effective as enoxaparin followed by a dose-adjusted VKA for acute symptomatic PE, with fewer major bleeding events. What's more, rivaroxaban—which now has US Food and Drug Administration approval for the prevention and treatment of PE and DVT[6]—does not require laboratory monitoring.

CAVEATS

Questions about study population, duration remain

This was an open-label study—neither patients nor investigators were blinded to the group assignments after randomization. The investigators suspected more recurrent VTE in those receiving rivaroxaban, which could have biased their findings in favor of the standard treatment. However, actual rates of recurrence were similar.

Study participants were <60 years old, on average, which may limit extrapolation to an older population. This trial lasted 12 months; the effects of longer treatment with rivaroxaban are unknown. Bayer HealthCare and Janssen Pharmaceuticals, who jointly manufacture rivaroxaban, funded the study.

CHALLENGES TO IMPLEMENTATION

Cost and lack of antidote may limit use

Rivaroxaban is more expensive than warfarin: A one-month supply costs approximately $260, while a month's supply of warfarin plus lab monitoring runs less than $100.[7] What's more, factor Xa inhibitors, unlike VKAs, do not have a readily available pharmacologic antidote. JFP

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