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Can extended anticoagulation prophylaxis after discharge prevent thromboembolism?

A meta-analysis confirmed the benefit of thromboprophylaxis with a direct oral anticoagulant for high-risk nonsurgical patients after hospital discharge.

PRACTICE CHANGER

Treat seriously ill patients with a direct oral anticoagulant (DOAC) for 6 weeks after hospital discharge to reduce venous thromboembolism (VTE) events, improve mortality, and lower costs.

STRENGTH OF RECOMMENDATION

A: Meta-analysis of randomized clinical trials[1]

Bhalla V, Lamping OF, Abdel-Latif A, et al. Contemporary meta-analysis of extended direct-acting oral anticoagulant thromboprophylaxis to prevent venous thromboembolism. *Am J Med.* 2020;133:1074-1081.e8. doi: 10.1016/j.amjmed.2020.01.037

ILLUSTRATIVE CASE

A 67-year-old man with a history of type 2 diabetes, hypertension, and chronic congestive heart failure (ejection fraction = 30%) was admitted to the intensive care unit with a diagnosis of acute hypoxic respiratory failure. He was discharged after 10 days of inpatient treatment that included daily VTE prophylaxis with low-molecular-weight heparin (LMWH). Should he go home on VTE prophylaxis?

Patients hospitalized with nonsurgical conditions such as congestive heart failure, chronic obstructive pulmonary disease, sepsis, inflammatory bowel disease, or active cancers are at increased risk for VTE due to inflammation and immobility. In a US study of 158,325 hospitalized nonsurgical patients, including those with cancer, infections, congestive heart failure, or respiratory failure, 4% of patients developed deep vein thrombosis (DVT), 1.5% developed pulmonary embolism (PE), and 0.2% developed both DVT and PE, at a median time of 74 days after discharge.[2] Prophylaxis in medical inpatients reduces VTE incidence in the hospital by 50% to 75%, but the period of increased VTE risk after discharge is not well understood in medical patients.[3] American College of Chest Physicians guidelines provide recommendations for the duration of prophylactic anticoagulation after major orthopedic surgeries but make no recommendation for medical patients.[3] American Society of Hematology 2018 guidelines recommend against extending VTE prophylaxis after hospital discharge, including for patients with risk factors or chronic immobility.[4]

However, use of DOACs for short-term VTE prophylaxis as an alternative to LMWH in hospitalized patients is supported by a meta-analysis showing equivalent efficacy, safety, and cost-effectiveness.[1] The current study examined DOACs for extended post-discharge use.[1]

STUDY SUMMARY

Significant benefit of DOACs demonstrated across 4 large trials

This meta-analysis of 4 large randomized con-

trolled trials examined the safety and efficacy of 6 weeks of postdischarge DOAC thromboprophylaxis compared with placebo in 26,408 high-risk nonsurgical hospitalized patients.[1] Patients at least 40 years old were admitted with diagnoses that included New York Heart Association (NYHA) class III or IV congestive heart failure, active cancer, acute ischemic stroke, acute respiratory failure, or infectious or inflammatory disease. Study patients also had risk factors for VTE, including age 75 and older, obesity, chronic venous insufficiency, history of VTE, history of NYHA class III or IV congestive heart failure, history of cancer, thrombophilia, hormone replacement therapy, or major surgery within the 6 to 12 weeks before current medical hospitalization.

Patients were excluded if DOACs were contraindicated or if they had active or recent bleeding, renal failure, abnormal liver values, an upcoming need for surgery, or an indication for ongoing anticoagulation. Patients in 3 studies received 6 to 10 days of enoxaparin as prophylaxis during their inpatient stay. (The fourth study did not specify length of inpatient prophylaxis or drug used.) After discharge, patients were assigned to placebo or a regimen of rivaroxaban 10 mg daily, apixaban 2.5 mg twice daily, or betrixaban 80 mg daily for a range of 30 to 45 days. The primary outcome was the composite of total VTE and VTE-related death. A secondary outcome was the occurrence of nonfatal symptomatic VTE, and the primary safety outcome was the incidence of major bleeding.

The primary outcome occurred in 2.9% of the patients in the DOAC group compared with 3.6% of patients in the placebo group (odds ratio [OR] = 0.79; 95% CI, 0.69-0.91; number needed to treat [NNT] = 143). The secondary outcome occurred in 0.48% of patients in the DOAC group compared with 0.77% of patients in the placebo group (OR = 0.62; 95% CI, 0.47-0.83; NNT = 345). Major bleeding resulting in a decrease in hemoglobin concentration of more than 2 g/L, requiring transfusion of at least 2 units of packed red blood cells, reintervention at a previous surgical site, or bleeding in a critical organ or that was fatal, occurred in 0.58% of patients in the DOAC group compared with 0.3% of patients in the placebo group (OR = 1.9; 95% CI, 1.4-2.7; number needed to harm [NNH] = 357). Nonmajor bleeding was increased in the DOAC group compared with placebo (2.2% vs 1.2%; OR = 1.8; 95% CI, 1.5-2.1; NNH = 110).

The NNT to prevent a fatal VTE was 899 patients. After extrapolating original data on fatal PE and major bleeding to a national level, cost-benefit analysis preferred extended DOAC use, with a direct medical cost balance of $1.2 million per life saved.

WHAT'S NEW

Mortality and morbidity benefit with small bleeding risk

Based on this study, for every 300 high-risk patients hospitalized with nonsurgical diagnoses who are given 6 weeks of DOAC prophylaxis, there will be 2 fewer cases of VTE and VTE-related death. In this same group of patients, there will be approximately 1 major bleeding event and 3 less serious bleeds.

Patients with preexisting medical conditions such as congestive heart failure, cancer, and sepsis and those admitted to an intensive care unit are at increased risk for DVT after discharge.[5] Extending DOAC prophylaxis in nonsurgical patients with serious medical conditions for 6 weeks after discharge reduces the risk of VTE or VTE-related death by 0.7% compared with placebo. Treatment in this population does incur a small increased risk of major bleeding by 0.3% in the DOAC group compared with placebo.

A recent meta-analysis sheds light on the benefits of extended postdischarge thromboprophylaxis in nonsurgical patients at high risk for VTE.

CAVEATS

Results cannot be generalized to all patient populations

Many high-risk patients have chronic kidney disease, and because DOACs (including apixaban, rivaroxaban, and dabigatran) are renally cleared, there are limited data to establish their safety in patients with creatinine clearance ≤ 30 mL/min. Benefits seen with DOACs cannot be extrapolated to other anticoagulation agents, including warfarin or LMWH.

In accordance with new guidelines, some of the patients in this study would now receive antiplatelet therapy, eg, poststroke pa-

tients, cancer patients, and—with the ease of DOAC use—patients with atrial fibrillation. If these patients were excluded, it is not known whether the benefit would remain. Patients included in these trials were at particularly high risk for VTE, and the benefits seen in this study cannot be generalized to a patient population with fewer VTE risk factors.

CHALLENGES TO IMPLEMENTATION

High cost and lack of updated guidelines may limit DOAC thromboprophylaxis

Cost is a concern. All the new DOACs are expensive; for example, rivaroxaban costs a little less than $500 per month.[6] Obtaining insurance coverage for a novel indication may be challenging. The American Society of Hematology and others have not yet endorsed extended posthospital thromboprophylaxis in nonsurgical patients, although the use of DOACs has expanded since the last guideline revisions. JFP

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