PPIs With Warfarin Regimens: Balancing the Perks and Pitfalls

Patients on warfarin + antiplatelet/NSAID regimens are likely to benefit from the gastroprotective effect of PPIs. But for patients taking warfarin alone, it's a different story.

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PRACTICE CHANGER

Prescribe a proton pump inhibitor for patients taking dual antiplatelet/antithrombotic therapy to reduce the risk for upper gastrointestinal bleeding.

STRENGTH OF RECOMMENDATION

B: Based on a cohort study.[1]

A 60-year-old man establishes care with you. He has well-controlled osteoarthritis (as long as he takes his low-dose daily aspirin) and chronic atrial fibrillation, for which he takes warfarin. His international normalized ratio (INR) is consistently within the recommended target range of 2 to 3. He feels well and has never had GERD or a gastrointestinal (GI) bleed. Should you recommend a proton pump inhibitor (PPI) to decrease the likelihood of a future upper GI bleed?

Anticoagulation therapy creates a dilemma—the need to balance the benefit of preventing embolization with the risk for serious bleeding. Concurrent use of NSAIDs, aspirin, and other antiplatelet agents further increases the latter risk.[2]

Clinicians have long used PPIs to treat upper GI bleeds. They prevent acid secretion and are the most effective drugs for healing peptic ulcers.[3,4] But while previous case-control studies show that PPIs reduce the risk for upper GI bleeds in patients taking antiplatelet agents or NSAIDs, they do not show a statistically significant benefit for patients taking warfarin.[5,6] What's more, while one expert consensus report recommends that patients taking dual warfarin and antiplatelet agent/NSAID therapy take a PPI to decrease the risk for upper GI bleeding, other guidelines do not address this clinical question.[2,7,8]

STUDY SUMMARY

Study supports PPI use in a high-risk group

This retrospective cohort study sought to answer the question: "Does PPI co-therapy decrease the rate of serious upper GI bleeds in patients taking warfarin?" Researchers examined rates of hospitalization for upper GI bleeding in Medicare and Medicaid patients taking warfarin, with and without PPI co-therapy (tracked via prescription fill dates). They also evaluated concomitant use of NSAIDs and antiplatelet agents.

The authors excluded patients with a recent history of severe bleeding or certain illnesses that predispose patients to GI bleeding (eg, esophageal varices). Patients with risk factors for an upper GI bleed (eg, abdominal pain, peptic ulcer disease, anemia) were more likely to be taking PPI co-therapy. Researchers analyzed the effect of PPI co-therapy in patients with and without these additional risk factors.

Results. The study followed more than 75,000 person-years of active warfarin therapy (Medicaid, > 52,000 person-years; Medicare, > 23,000 person-years). Hospitalizations due to upper GI bleeding occurred at a rate of 127/10,000 person-years (incidence was similar in both the Medicaid and Medicare groups).

Among *all* patients taking warfarin (regardless of whether they were also taking an NSAID or antiplatelet agent), PPI co-therapy reduced the risk for hospitalization for upper GI bleeding by 24% (adjusted hazard ratio [HR], 0.76), which translates into

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29 fewer hospitalizations per 10,000 person-years. The number needed to treat (NNT) was 345 person-years, meaning that 345 patients taking warfarin would have to take a PPI for one year to prevent one hospitalization for an upper GI bleed. As one might expect, PPI co-therapy did not significantly reduce the risk for lower GI, other GI, or non-GI bleeding.

In patients taking both warfarin and concurrent antiplatelet agents or NSAIDs, PPI co-therapy reduced the risk for hospitalization for upper GI bleeding by about half (HR, 0.55). Hospitalizations decreased by 128/10,000 person-years (NNT, 78 person-years). For patients taking warfarin but *not* antiplatelet agents or NSAIDs, PPI co-therapy did not significantly reduce the risk for hospitalization due to upper GI bleeding (HR, 0.86).

Further research is warranted to determine if PPI therapy is beneficial to patients taking direct oral anticoagulants.

Additional risk factors for GI bleeds. Researchers also looked at patients who had additional risk factors for GI bleeds (other than the exclusion criteria). For patients taking both warfarin and an antiplatelet agent/NSAID, PPI co-therapy decreased the risk for upper GI bleeding regardless of whether the patients had other bleeding risk factors. Again, for patients who had additional bleeding risk factors, but were not taking an antiplatelet agent or NSAID, PPI therapy showed no statistically significant effect.

WHAT'S NEW

PPIs offer benefits, but not to warfarin-only patients

The statistically significant results in this large observational study suggest that PPI co-therapy is beneficial in reducing the risk for upper GI bleeding in patients taking warfarin *plus* an antiplatelet agent/NSAID, but that PPI co-therapy provides no benefit to patients taking warfarin exclusively.

CAVEATS

Not a randomized controlled trial

This study was observational, not a randomized control trial (RCT). Therefore, unknown confounding variables may have skewed results. For example, patients could have taken OTC medications that influenced or obscured results but were not included in the data analysis (misclassification bias).

At best, we can infer a correlation between PPIs and decreased risk for upper GI bleeds. We need RCTs to determine whether PPIs *cause* a risk reduction.

Don't overlook the risks of PPIs. This study assessed the ability of PPIs to prevent bleeds but did not address the risks of long-term PPI therapy. Adverse effects of PPIs include increased risk for pneumonia, infection with *Clostridium difficile*, hip and spinal fractures, anemia, and possibly chronic kidney disease and dementia.[9-11] In addition, cost-analysis studies of PPI therapy are limited and their results are inconsistent.[12] Therefore, it's best to make decisions regarding PPIs after discussing other risks and benefits.

What about DOACs? Another option is to prescribe a direct oral anticoagulant (DOAC; eg, dabigatran, rivaroxaban, or apixaban) instead of warfarin. DOACs are at least as effective as warfarin at preventing stroke in patients with atrial fibrillation and may even be safer.[13] Dabigatran 110 mg causes fewer "major bleeding" events than warfarin.[13] Compared to warfarin, rivaroxaban has been shown to result in fewer fatal bleeding events due to intracranial bleeds, although it is associated with more GI bleeding.[13] Apixaban is associated with fewer GI bleeds and lower bleeding rates overall, compared with warfarin.[13] Further research is warranted to determine if PPI therapy is beneficial to patients who are taking DOACs.

CHALLENGES TO IMPLEMENTATION

It's still a balancing act

When long-term anticoagulation is necessary, providers and patients must attempt to prevent thrombotic events while minimizing the risk for GI bleeds. PPIs may be beneficial in preventing upper GI bleeds in patients

taking dual warfarin and antiplatelet therapy, but the long-term consequences of PPI therapy should not be ignored. **CR**

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