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The benefits—and limits— of PPIs with warfarin regimens

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

PRACTICE CHANGER

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

STRENGTH OF RECOMMENDATION

B: Based on a cohort study

Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology*. 2016;151:1105-1112.¹

ILLUSTRATIVE CASE

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 gastroesophageal reflux disease (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 benefits of preventing embolization with the risks of serious bleeding. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and other antiplatelet agents further increases the risk of the latter.²

Physicians have long used PPIs to treat upper GI bleeds. They prevent acid secretion

and are the most efficacious drugs for healing peptic ulcers.^{3,4} However, while previous case-control studies show that PPIs reduce the risk of upper GI bleeds in patients taking antiplatelet agents or NSAIDs, they do not show a statistically significant benefit for patients taking warfarin.^{5,6} Further reflecting the confusion and uncertainty surrounding this issue is that while one expert consensus report recommends that patients taking dual warfarin and antiplatelet agent/NSAID therapy take a PPI to decrease the risk of upper GI bleeding,² other guidelines regarding anticoagulant therapy do not address this clinical question.^{2,7,8}

STUDY SUMMARY

Study lends support to 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 for 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 a severe bleed or certain illnesses that would predispose a patient to GI bleeding (such as esophageal varices). Patients with risk factors for an upper GI bleed



INSTANT POLL

Do you typically prescribe a proton pump inhibitor for your patients taking warfarin?

- Yes
- No

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(such as abdominal pain, peptic ulcer disease, anemia, etc.) 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 over 75,000 person-years of active warfarin therapy (more than 52,000 person-years in the Medicaid cohort and more than 23,000 person-years in the Medicare cohort). 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).

Looking at *all* patients taking warfarin (regardless of whether or not they were also taking an NSAID or antiplatelet agent), PPI co-therapy reduced the risk of hospitalization for upper GI bleeding by 24% (adjusted hazard ratio [HR]=0.76; 95% confidence interval [CI], 0.63 to 0.91), which translates into 29 fewer hospitalizations per 10,000 person-years. The number needed to treat (NNT) was 345 person-years, meaning 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 of 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 of hospitalization for upper GI bleeding by about half (HR=0.55; 95% CI, 0.39-0.77). Hospitalizations decreased by 128/10,000 person-years (95% CI, -66 to -173), yielding an NNT of 78 person-years. For patients taking warfarin but *not* antiplatelet agents or NSAIDs, PPI co-therapy did not significantly decrease the risk of hospitalization for upper GI bleeding (HR=0.86; 95% CI, 0.70-1.06).

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 of upper GI bleeding whether or not 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 patients taking warfarin alone

The statistically significant results in this large observational study suggest that PPI co-therapy is beneficial in reducing the risk of 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

Study was good, but it wasn't a randomized controlled trial

This study is observational, and not a randomized control trial (RCT). Therefore, unknown confounding variables may have skewed results. For example, patients could have taken over-the-counter 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 of upper GI bleeds. We need RCTs to determine whether PPIs *cause* a lower risk.

Don't overlook the risk 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 an increased risk of pneumonia, infection with *Clostridium difficile*, hip and spine fractures, anemia, and possibly chronic kidney disease and dementia.⁹⁻¹¹ In addition, cost-analysis studies of PPI therapy are limited and inconsistent.¹² Therefore, it's best to make decisions regarding PPIs after discussing other risks and benefits.

What about DOACs? Another consideration is the option to prescribe a direct oral anticoagulant (DOAC), such as 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 Rivaroxaban has been shown to result in fewer fatal bleeding events than warfarin due to fatal intracranial bleeds, although it is associated with more GI bleeding.¹³ Compared with warfarin, apixaban is

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

associated with fewer GI bleeds and lower bleeding rates overall.¹³ Further research is warranted to determine if PPI therapy is beneficial to patients taking DOACs.

CHALLENGES TO IMPLEMENTATION

It's still a balancing act

When chronic anticoagulation is necessary, physicians and patients must attempt to prevent thrombotic events while minimizing the risk of 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.

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