

Adverse events associated with nonsteroidal anti-inflammatory drug use among patients taking oral anticoagulants

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Ratings: Methods – 4/5 Usefulness – 4/5

(110-mg bid; 150-mg bid) with warfarin in patients with atrial fibrillation (AF).¹ The study was a post hoc, treatment-independent, multivariate-adjusted COX regression analysis of the RE-LY data.¹

Setting

International, multicentre study (951 centres in 44 countries)

Subjects

Patients who used NSAIDs at least once compared with those who had not

Outcomes

Primary outcomes included any major bleeding, gastrointestinal (GI) major bleeding, intracranial hemorrhage (ICH), stroke, systemic embolism, myocardial infarction (MI), hospitalization, and all-cause mortality. The median duration of the follow-up period was 2 years.

INTRODUCTION

Background

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in the emergency department (ED), though they carry an increased risk of hemorrhage and thrombotic events.

Objectives

Kent and colleagues sought to examine the risk of adverse events associated with the use of NSAIDs among patients taking oral anticoagulants (OACs).

METHODS

Design

The RE-LY study was a phase III randomized controlled trial (RCT) that compared two doses of dabigatran

RESULTS

Of 18,113 patients included in the RE-LY study, 2,279 (12.9%) patients used NSAIDs at least once during the trial. This post hoc analysis compared the group of patients who used NSAIDs (NSAIDs, $n = 2,279$) versus the patients who did not (No NSAIDs, $n = 15,834$). The analysis did not include selective COX-2 inhibitors due to a small sample size. The mean age was 72 in each group ($p = 0.85$). The average CHADS₂-VASc score was

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3.6 in each group ($p = 0.54$). There were baseline differences between the groups, including more antiplatelet (44.9% v. 41.2%, $p < 0.01$) and proton pump inhibitor (16.8% v. 13.8%, $p < 0.01$) use in the NSAID group. There were also fewer prior MI in the NSAID group (13.1% v. 17.1%, $p < 0.01$). There were no differences in rates of a previous stroke.

An adjusted analysis demonstrated an association between NSAIDs and major bleeding (hazard ratio [HR] 1.68, 95% confidence interval [CI] 1.40–2.02) and GI major bleeding (HR 1.81, 95% CI 1.35–2.43). Rates of major bleeding associated with NSAID use were increased among each of the treatment arms. When compared with warfarin, the association between NSAIDs and increased major and GI bleeding was not significantly different from dabigatran 110 mg and 150 mg ($p = 0.93$ and 0.63). NSAID use was also associated with ischemic stroke (HR 1.55, 95% CI 1.11–2.16), systemic embolism (HR 2.43, 95% CI 1.08–5.46), and hospitalization (HR 1.64, 95% CI 1.51–1.77). There were no significant differences in rates of MI, ICH, or all-cause mortality.

APPRAISAL

Strengths

- Primary study was a high quality RCT
- Large number of patients
- Multiple adjustments for confounding variables
- Evaluation of all patient-important outcomes
- Outcome measures were based on objective and unbiased criteria
- Long duration of follow-up
- Low number lost to follow-up (only 20 patients out of 18,113 in the original trial)

Limitations

- Post hoc analysis
- Not an ED specific study, though patient populations are likely similar
- Does not examine patients on Factor Xa inhibitors or anticoagulated for venous thromboembolism
- Relationship between exposure and outcome is not addressed (e.g., type of NSAID, indication, dose and duration)
- COX-2 inhibitors not examined in this study

CONTEXT

Pain management in older ED patients can be challenging. Painful conditions such as osteoarthritis are common, but rates of comorbid renal and cardiovascular disease are similarly high.² Studies have shown that up to 11.6% of adults regularly take NSAIDs for pain, and use is twice as common among those with cardiovascular disease.²

Prior studies have demonstrated increased rates of bleeding and thromboembolism with NSAIDs, though relatively few studies have examined the relationship among patients taking concomitant OAC therapy.² One recently presented abstract demonstrated similar results in a post hoc analysis of the ARISTOTLE trial (apixaban v. warfarin in AF).³

BOTTOM LINE

The use of NSAIDs in combination with OAC therapy with either warfarin or dabigatran in patients with AF was associated with an increased risk of major bleeding, including GI and non-GI bleeding, stroke and systemic embolic events, ischemic stroke, and hospitalization. Emergency physicians should exercise caution when prescribing NSAIDs to patients on OACs, and alternative pain management options should be considered. Emergency physicians should also counsel patients on the risks associated with the use of NSAIDs when prescribing OACs for new onset AF in the ED.

Keywords: Adverse effects, emergency department, nonsteroidal anti-inflammatory drugs, oral anticoagulants

Competing interests: None declared.

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