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Concomitant Oral Anticoagulant and Nonsteroidal Anti-Inflammatory Drug Therapy in Patients With Atrial Fibrillation

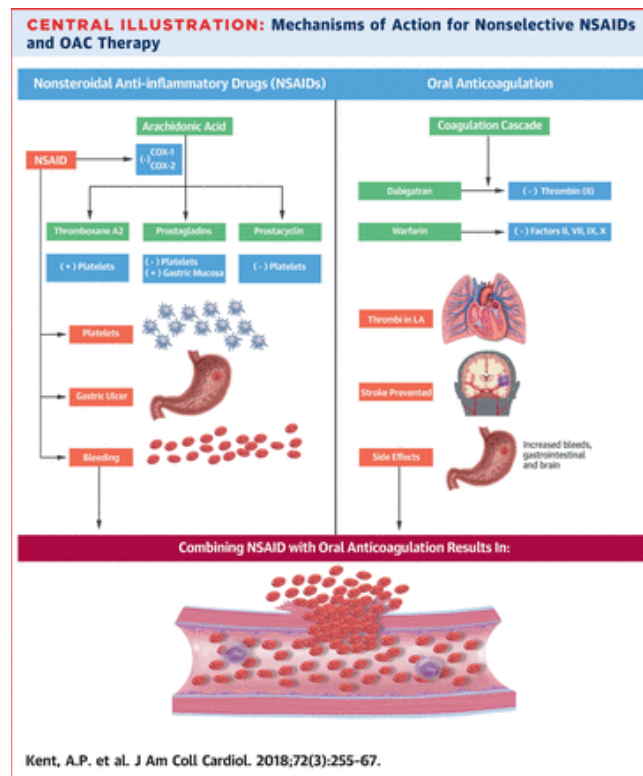
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Abstract

Background Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used medications that can potentially increase the risk of bleeding and thrombosis.

Objectives This study quantified the effect of NSAIDs in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial.

Methods This was a post hoc analysis of NSAIDs in the RE-LY study, which compared dabigatran etexilate (DE) 150 and 110 mg twice daily (b.i.d.) with warfarin in patients with atrial fibrillation. Treatment-independent, multivariate-adjusted Cox regression analysis assessed clinical outcomes by comparing NSAID use with no NSAID use. Interaction analysis was obtained from treatment-dependent Cox regression modeling. Time-varying covariate analysis for NSAID use was applied to the Cox model.

Results Among 18,113 patients in the RE-LY study, 2,279 patients used NSAIDs at least once during the trial. Major bleeding was significantly elevated with NSAID use (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.40 to 2.02; $p < 0.0001$). NSAID use did not significantly alter the risk of major bleeding for DE 150 or 110 mg b.i.d. relative to warfarin ($p_{\text{interaction}} = 0.63$ and 0.93 , respectively). Gastrointestinal major bleeding was significantly elevated with NSAID use (HR: 1.81; 95% CI: 1.35 to 2.43; $p < 0.0001$). The rate of stroke or systemic embolism (stroke/SE) with NSAID use was significantly elevated (HR: 1.50; 95% CI: 1.12 to 2.01; $p = 0.007$). The use of NSAIDs did not significantly alter the relative efficacy on stroke/SE for DE 150 or 110 mg b.i.d. relative to warfarin ($p_{\text{interaction}} = 0.59$ and 0.54 , respectively). Myocardial infarction rates were similar with NSAID use compared with no NSAID use (HR: 1.22; 95% CI: 0.77 to 1.93; $p = 0.40$). Patients were more frequently hospitalized if they used an NSAID (HR: 1.64; 95% CI: 1.51 to 1.77; $p < 0.0001$).

Conclusions The use of NSAIDs was associated with increased risk of major bleeding, stroke/SE, and hospitalization. The safety and efficacy of DE 150 and 110 mg b.i.d. relative to warfarin were not altered. (Randomized Evaluation of Long Term Anticoagulant Therapy [RE-LY]; NCT00262600)

Key Words

anticoagulation atrial fibrillation bleeding NSAID stroke prevention

Footnotes

The RE-LY clinical trial was funded by Boehringer Ingelheim GmbH & Co KG, Ingelheim, Germany. The post hoc analysis did not have a funding source. Dr. Connolly has received grants and personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Sanofi, and Bayer; has received personal fees from Portola; has received grants from Boston Scientific; and has received an institutional research grant from Boehringer Ingelheim. Dr. Yusuf has received grants, honoraria, and travel reimbursements for speaking engagements from Boehringer Ingelheim, Bayer, and Bristol-Myers Squibb; and has received a research grant from Boehringer Ingelheim. Dr. Eikelboom has received consulting fees and/or honoraria and grant and/or in-kind support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Pfizer, Janssen, and Sanofi. Dr. Oldgren has been a consultant (including steering and data monitoring committees) and has received lecture fees from Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daichii-Sankyo, and Sanofi; and has been a member of the advisory board for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Sanofi. Dr. Wallentin has received institutional research grants from AstraZeneca, Bristol-Myers Squibb/Pfizer, Merck & Co., Roche, GlaxoSmithKline, and Boehringer Ingelheim; and has received consulting fees from Abbott. Dr. Ezekowitz has received consulting fees from Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Portola, Daiichi-Sankyo, and Armethion; and has received grant support from Boehringer Ingelheim and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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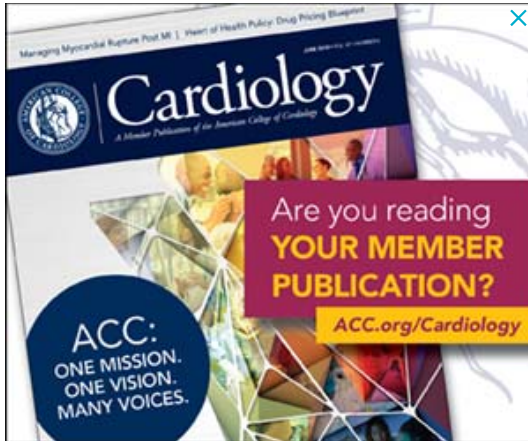
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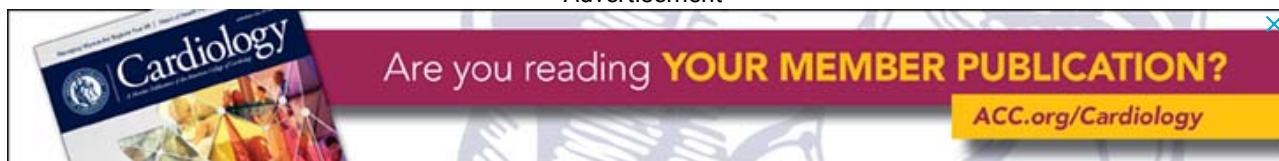
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