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This series is coordinated by Sumi Sexton, MD, Associate Medical Editor.

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Patients with Initial Unprovoked DVT or PE Benefit from Long-Term Low-Dose Aspirin

Clinical Question

Does aspirin reduce the likelihood of recurrent venous thromboembolism (VTE) when used after the discontinuation of anticoagulation?

Bottom Line

Aspirin improves long-term cardiovascular and thrombotic outcomes in patients who have had an initial unprovoked episode of VTE. The risk of bleeding was no higher in the aspirin group, perhaps because those at risk of bleeding were "uncovered" during the initial period of anticoagulation. (Level of Evidence = 1a)

Synopsis

This was an individual patient meta-analysis. In most meta-analyses, authors are limited to using published, aggregated data, but by combining data from different studies at the individual patient level, there is greater statistical power to detect important clinical effects. The authors of this report combined data from two previous trials: WARFASA with 403 patients and ASPIRE with 822 patients. The trials had similar designs and populations (nonpregnant adults with a first unprovoked deep venous thrombosis [DVT] or pulmonary embolism [PE]). There were 56 withdrawals from these studies before the end of the study period because of revoked consent (31), no qualifying VTE episode (12), and loss to follow-up (13). The WARFASA study followed patients for up to two years, and ASPIRE for up to four years.

The intervention in each study was aspirin, 100 mg, given once daily or matching placebo, and analysis was by intention to treat. The anticoagulation protocol was low-molecular-weight heparin (Lovenox) initially followed by warfarin (Coumadin) for most patients. The rate of recurrent VTE was approximately one-third lower in the aspirin group (5.1% vs. 7.5% per year; $P = .008$; number needed to treat [NNT] = 42 per year), with a similar hazard ratio of 0.66 for DVT and PE. The rate of myocardial infarction, stroke, or cardiovascular death was also lower (5.7% vs. 8.7% per year; $P = .002$; NNT = 33 per year), and there was no difference in the risk of major bleeding (0.4% per year in the placebo group vs. 0.5% in the aspirin group). The combined outcome of any adverse event (major vascular event, major bleeding, or death from any cause) was lower in the aspirin group as well (6.5% vs. 9.8% per year; $P = .002$; NNT = 30). The benefit of aspirin was greatest in the first year, but a consistent and significant benefit was seen in years 2 through 4.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Government

Setting: Outpatient (any)

Reference: Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation*. 2014;130(13):1062-1071.

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Sterile Gloves Not Necessary for Minor Skin Surgery

Clinical Question

Do sterile gloves yield lower wound infection rates than clean nonsterile gloves during minor skin surgery?

Bottom Line

Infection rates in patients undergoing uncomplicated minor skin surgery were not different when sterile gloves, rather than simply clean gloves, were worn. A previous study (Perelman VS, et al. *Ann Emerg Med*. 2004;43(3):362-370) similarly found no difference in infection rates between sterile and nonsterile gloves in patients undergoing uncomplicated laceration repair in the emergency department. (Level of Evidence = 1b) ▶

Synopsis

These investigators enrolled 493 consecutive patients presenting to a general practice in Australia for minor skin excisions. Exclusion criteria included needing skin flaps, excision of a sebaceous cyst, and a history of latex allergy. Eligible patients randomly received (concealed allocation assignment) treatment by physicians wearing sterilized gloves or standard, boxed, nonsterilized gloves to perform the excision. Treating physicians were aware of the type of gloves they were wearing, and it is possible that they were more scrupulous with cleaning when wearing the nonsterile gloves. Follow-up was performed by a physician or nurse masked to treatment group assignment, with only 3% of cases lost. Using intention-to-treat analysis, infection occurred in 9.3% of patients treated with sterile gloves and 8.7% of patients treated with nonsterile gloves, a nonsignificant difference. The study was 80% powered as a noninferiority trial to detect a 7% difference in infection rates, if one existed.

Study design: Randomized controlled trial (single-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (primary care)

Reference: *Heal C, Sriharan S, Buttner PG, Kimber D. Comparing non-sterile to sterile gloves for minor surgery: a prospective randomised controlled non-inferiority trial. Med J Aust. 2015;202(1):27-31.*

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Amoxiclav Causes Diarrhea in 1 of 8 Persons Who Take It

Clinical Question

How frequently do harms of amoxicillin (with or without clavulanate) occur?

Bottom Line

The risk of diarrhea is significantly higher with amoxicillin/clavulanate (amoxiclav; Augmentin) than placebo, with a number needed to treat to harm (NNTH) of 8, which is not dissimilar from the number needed to treat for conditions such as otitis media. Contrary to popular

belief, the risks of nausea, vomiting, and rash are not increased, but the risk of candidiasis is (NNTH = 23). (Level of Evidence = 1a)

Synopsis

Meta-analyses and systematic reviews are increasingly common in the literature, but most focus on benefit and give little attention to harm. This study is a good example of looking carefully at the harms instead. In this case, the authors searched for randomized, placebo-controlled trials of amoxicillin or amoxiclav for any indication. They did a careful search, had two authors review each article and abstract data, and evaluated study quality. Overall, the risk of bias was low, which is good. They found 45 studies of adults or children, but only 25 studies provided data regarding harms that were usable for the quantitative data synthesis.

The most common conditions being treated with amoxicillin were a respiratory infection or an ear, nose, and throat infection. Studies reported between zero and 10 harms, most commonly gastrointestinal and skin adverse effects. There was no increase in the likelihood of diarrhea overall (10 studies with 4,284 patients), but it was increased with amoxiclav (odds ratio [OR] = 3.3; 95% confidence interval [CI], 2.2 to 4.9). The pooled prevalence of diarrhea was 17.5% with amoxiclav and 5.6% with placebo (NNTH = 8). Only three studies (two of amoxicillin, one of amoxiclav) with 456 patients reported rates of candidiasis, and the likelihood was significantly increased (OR = 7.8; 95% CI, 2.2 to 27). The pooled rates were 4.4% in the amoxicillin groups and 0% in the placebo groups (NNTH = 23). Rates of nausea, vomiting, and rash were similar between the amoxicillin/amoxiclav groups and the placebo groups.

Study design: Meta-analysis (randomized controlled trials)

Funding source: Government

Setting: Various (meta-analysis)

Reference: *Gillies M, Ranakusuma A, Hoffmann T, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015;187(1):E21-E31.*

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