Clinical Use of Evidence-Based Medicine - Clinical Questions

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Is Low-Dose Aspirin a Better Choice in Patients with Coronary Artery Disease and Bleeding Risks?

Patient
An 80-year-old man with a past medical history significant for coronary artery disease and upper gastrointestinal (GI) bleeding presented complaining of substernal chest pain. He was previously instructed to take an 81 mg aspirin daily to lessen the risk of recurrent GI bleeding when compared to a 325 mg aspirin.

Clinical Question
In a patient with a history of GI bleeding and coronary artery disease, does an 81 mg aspirin daily decrease the risk of GI bleeding compared to a 325 mg aspirin daily?

Search Strategy
1. Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE) (searched October 2006 via Wiley Interscience)
   a. “Aspirin” or “ASA”
   b. “Bleed”
   c. Combine (a) and (b)
   i. No applicable results found
2. ACP Journal Club (searched October 2006)
   a. “Aspirin”
   b. “Gastrointestinal or GI”
   c. “Bleed”
   d. Combine (a) (b) and (c)
   i. One article that met ACP criteria for inclusion but was a relatively poor quality systematic review
3. PubMed (searched October 2006)
   a) “Aspirin” (MeSH heading)
   b) “Hemorrhage” (MeSH heading)
   c) “Coronary disease” (MeSH heading)
   d) “Dose” or “Dosage”
   e) Combine (a) (b) (c) and (d)
   f) Limit (e) to “therapy, narrow” (clinical queries) and English
   i. 45 studies, one of which addressed our question

Study Characteristics
- CURE Trial background
  o Comparison of ASA alone versus ASA plus clopidogrel in patients with acute coronary syndrome (ACS) without ST-segment elevation
  o Multi-center, multi-national, randomized controlled trial
  o Large study population – 12,562 patients
  o Inclusion criteria
    ■ Symptoms of ACS in past 24 hours
    ■ No ST-segment elevation >1mm
    ■ EKG evidence of ischemia or cardiac enzymes twice the upper limit of normal
  o Interventions
    ■ Random assignment to clopidogrel or placebo
    ■ ASA given to all patients at a dose decided by the local investigator (recommended 75mg–325mg per study protocol)
  o Primary end points: cardiovascular death, myocardial infarction, stroke, or refractory ischemia at 1 year
  o Secondary end points: bleeding events
    ■ Life-threatening bleed—fatal, decrease in he-
moglobin ≥5g/dL, hypotension with need for inotropes, requiring surgery, symptomatic intracranial hemorrhage, or transfusion ≥4 units of red blood cells

- Major bleed — disabling, intraocular with vision loss, transfusion of 2 or 3 units of red blood cells
- Minor bleed — Did not meet criteria for major or life-threatening bleed and did not require modification of drug regimen

- Secondary analysis from the CURE trial — Our selected study
  - Post-hoc analysis of the CURE trial
    - Patients divided into 3 groups based on ASA dose:
      - ≤100 mg (low dose): 5320 patients
      - 101-199 mg (intermediate dose): 3109 patients
      - ≥200 mg (high dose): 4110 patients
    - Analyzed primary and secondary outcomes by clopidogrel use and ASA dose

Validity of Evidence
- Assignment of patients to 3 ASA dose groups was not randomized
- Study participants were not blinded
- Patients were followed for 12 months with dose and compliance with ASA therapy recorded at each visit
- Intention to treat analysis performed
- At the start of the study, the groups differed
  - ASA dose varied by geographic location
  - High-dose ASA group included more males, diabetics, and patients who had undergone coronary artery bypass grafting
  - High-dose ASA group was treated more often with heparin, GP IIb/IIIa inhibitors, anti-platelet agents, and percutaneous or surgical revascularization
- Analysis was adjusted for known differences between the groups; however, no data was given for history of GI bleeding, dietary variances, or concurrent use of acid suppression medications
- Overall, this study has several methodological flaws

Results
- High-dose ASA group had statistically significant higher rate of MI, cardiovascular death, and stroke in the high-dose ASA group
  - Adjusted hazard ratio for high-dose versus low-dose ASA 1.3 (1.08-1.52)
  - Adjusted hazard ratio for intermediate-dose versus low-dose ASA 1.0 (95% CI 0.82-1.23)
- High-dose ASA group had increased incidence of major bleeding
  - Adjusted hazard ratio for high-dose versus low-dose ASA 1.7 (1.22-2.59)
- High-dose ASA group had increased incidence of life-threatening bleeding
  - Adjusted hazard ratio for high-dose versus low-dose ASA 1.64 (1.04-2.59)
- Rates of surgical, gastrointestinal, and puncture site bleeding all increased significantly with increasing ASA dose

Applying the Evidence to the Patient
- The patient would likely meet inclusion criteria for this study
- The treatment is feasible
- Treatment decisions must also account for patient preference

Summary
This post-hoc analysis of the large, randomized controlled trial (CURE trial) shows a statistically significant increase in the risk of primary end points including CVA, cardiovascular death, and myocardial infarction with the use of high-dose aspirin therapy. Additionally, there was an increased incidence of major and life-threatening bleeding events in the high-dose aspirin group. This study should be interpreted with caution given its significant limitations: patients were not randomized based on ASA dose; patients and doctors were not blinded to the ASA dosage; study population groups were not equal at baseline; groups were treated differently depending on geographic location. Finally, given the nature of a cohort study, we would hope to see a larger magnitude of treatment effect to overcome the unknown confounding variables. There is currently no high quality evidence on the risk of bleeding with high-dose ASA versus low-dose ASA. The current evidence does not support using high-dose ASA therapy in patients with known coronary artery disease and a history of gastrointestinal bleeding.

Bottom Line
Based on this study, high-dose aspirin therapy appears to result in an increased risk of major bleeding with no benefit in cardiac outcomes. Therefore, we would not recommend changing this patient’s current aspirin dose. Further studies are needed to clarify the risk benefit ratio of high-dose aspirin in patients with gastrointestinal bleeding and coronary artery disease.

Reference
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