Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk
Lancet 2007;369:1621-6 (May 12)

Study Type: POEM
Purpose: Will celecoxib and esomeprazole be better than celecoxib alone for the prevention of recurrent ulcer bleeding in patients with previous NSAID-induced ulcer bleeding who need continued NSAID therapy?
Study Duration: 1 year
Trial Design: Single-center (Hong-Kong), prospective, randomized, double-blinded
Procedure: Patients with upper GI bleeds and taking NSAID who had ulcer bleeding on endoscopy. H.pylori + patients were treated with antibiotic/PPI regimen, all patients discontinued NSAID and started 8 weeks of PPI. Those who were not healed on endoscopy after this regimen were retreated with another 8 weeks. Those who were healed were randomized.

Treatment Groups: Celecoxib 200 mg twice a day with esomeprazole 20 mg twice a day vs Celecoxib 200 mg twice a day with placebo

Patients: n = 273, mean of 70 years, ~50% female, 10% smoke, 10% drink alcohol, patients need NSAID due to OA (85%) and RA history (3%)

Bleed history: 58% gastric ulcer bleed, 34% duodenal, 8% gastric and duodenal; ~ 20% had more than one episode, ~ 45% had a transfusion, ~50% H.pylori positive

Inclusion Criteria: ulcers were healed on endoscopy after a course of PPI, H.pylori negative, need for NSAID
Exclusion Criteria: unhealed ulcers, low-dose aspirin, anticoagulants or steroids before index bleed, GI surgery for bleed repair, erosive esophagitis, gastric outlet obstruction, terminal illness, cancer, renal failure

Primary outcome: Recurrent ulcer bleeding and erosions confirmed by endoscopy, decrease Hb at least 20 g/L in the presence of proven ulcers or erosions by endoscopy
Secondary outcome: Efficacy of treatment for arthritis

1. Are the results valid?
   • Randomized? Yes
   • Similar groups? Yes
   • Double-blinded? Yes
   • Patient accountability? Yes
   • Placebo-controlled? Yes

2. What were the results?

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Celecoxib + placebo (n=136)</th>
<th>Celecoxib + PPI (n=137)</th>
<th>P-value</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent bleeding</td>
<td>8.9% (n=12)</td>
<td>0%</td>
<td>.0004</td>
<td>8.9%</td>
<td>11</td>
</tr>
<tr>
<td>Those on ASA*</td>
<td>19%</td>
<td>0%</td>
<td>.03</td>
<td>19%</td>
<td>5</td>
</tr>
<tr>
<td>Those not on ASA</td>
<td>7.1%</td>
<td>0%</td>
<td>.004</td>
<td>7.1%</td>
<td>14</td>
</tr>
<tr>
<td>Lower GI bleed</td>
<td>1.6%</td>
<td>3.0%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th>Disease-activity score</th>
<th>Improvement</th>
<th>Improvement</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain scale</td>
<td>improvement</td>
<td>improvement</td>
<td>NS</td>
</tr>
</tbody>
</table>

• *Due to information concerning COX-2 inhibitors and MI risk, ~30% of patients in either group began ASA on their own.

3. Will the results help me?
   • 83% (n=10) of the recurrent bleeds recurred at their previous locations
   • adverse events were similar in both groups, except there were more GI bleeds in celecoxib group
   • comparing data of other trials and the incidence of bleeding due to celecoxib, it looks as though the longer you are on celecoxib, the greater your risk of bleed (4.9% rate in 6 mth trial, to 8.9% in this 13 month trial)

Conclusion: In patients’ high risk to bleed that need NSAID therapy, this study suggests the use of celecoxib and esomeprazole. There were no recurrent bleeds after a 13 month follow-up. The esomeprazole dose was 20 mg twice daily. They chose this dose to get better acid control over a 24 hour period (Aliment Pharmacol Ther 2004;19:1105). Prophylaxis with a PPI is therefore indicated in patients needing long-term COX-2 therapy and who are at high risk to have a GI bleed.

Can we substitute celecoxib with another traditional NSAID?
We do know that treatment with Diclofenac + PPI is as good as celecoxib alone for preventing recurrent ulcer bleeds (NEJM 2002;347:2104). Would celecoxib + PPI be better than Diclofenac + PPI? This combination has yet to be studied.
Can we generalize celecoxib + twice daily PPI like OTC Prilosec? You decide.