Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding

Study Type: POEM
Purpose: For patients with GI bleed from aspirin, do we add a proton pump inhibitor or switch to clopidogrel?
Study Duration: 1 year
Trial Design: Double-blinded, placebo-controlled, randomized, intention-to-treat, one hospital site in Hong Kong. Screened patients who presented on aspirin with a upper GI bleed, endoscopy performed, biopsy performed at 3 sites. Those h.pylori positive were treated with antibiotics and proton pump inhibitors (PPI). After 8 weeks, repeat endoscopy was performed, those healed were randomized.
Drug: Clopidogrel 75 mg daily + esomeprazole placebo versus ASA 80 mg daily + esomeprazole 20 mg twice a day
Patients: 320 patients out of 492 screened, mean age 72 years, ~67% male,
There were more smokers in the clopidogrel group (13% vs 8.2%), more alcohol assumption (8.1% vs 5%); Most ulcers were gastric oriented, however, more in the ASA/esomeprazole had duodenal ulcers (8% increase), ~50% in each group had a cardiac history
Inclusion: patients admitted to the hospital with GI bleed and user of aspirin, confirmed bleed via endoscopy, negative h.pylori, successfully treat h.pylori before study
Exclusion: NSAID use, anticoagulants, other anti platelets, steroids, history of gastric surgery, allergy to ASA or clopidogrel, erosive esophagitis, gastric-outlet obstruction, renal failure requiring dialysis, terminal illness or cancer,
Outcome Events: Primary: recurrent ulcer bleed determined by hematemesis or melena, ulcers or bleeding erosions on endoscopy, decrease Hb at least 2 gm. Secondary: lower GI bleeds

1. Are the results valid?
a. randomized? Yes
b. double-blinded? Yes
c. were groups similar? Yes, but there are some differences noted above, no statistical information
d. all patients accounted for? Yes
e. allocation concealment? Yes

2. What were the results?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel</th>
<th>ASA/Esomeprazole</th>
<th>ARI</th>
<th>P-value</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ulcer bleed</td>
<td>8.4%</td>
<td>0.7%</td>
<td>7.9%</td>
<td>.001</td>
<td>13</td>
</tr>
<tr>
<td>lower GI bleed</td>
<td>4.6%</td>
<td>4.6%</td>
<td>0</td>
<td>NS</td>
<td>---</td>
</tr>
</tbody>
</table>

Adverse Effects
Dyspepsia 7.5% 2.5% 5% ? 20

Extragastrointestinal bleeding - 3 patients in clopidogrel group (2 intracranial bleeds, one hematuria) and none in the ASA/esomeprazole
No real difference in recurrent ischemic events.

3. Will the results help me?
* The author’s raise concern about the GI safety of clopidogrel mainly due to the fact that those who had recurrent bleeds were NOT h.pylori positive
* They screened for NSAID use (national pharmacy computer database). Only 2 patients with recurrent bleeds used NSAIDs.
* 71% of the recurrent bleeds were in the same location. There is a theory that clopidogrel may inhibit platelet-derived growth factors and retard healing.
* The authors did not mention the few differences noted in the study patients. See above. Would patients in the clopidogrel group be more at risk to have a GI bleed?
* Esomeprazole is dosed 20 mg twice a day. Maybe the main difference is the benefit of esomeprazole.

Conclusion: The use of clopidogrel as an alternative antiplatelet for patients who have GI bleeds with aspirin is not recommended. For every 100 patients with a GI bleed to aspirin, utilizing clopidogrel instead of aspirin would cause 8 GI bleeds over adding esomeprazole to aspirin. These lesions mainly occur in the same location. I am left with a thought - it may not be the risk of clopidogrel, but actually the benefit of esomeprazole.
One issue to think about is that 20 mg twice a day of esomeprazole is $260.00 per month. This raises the cost of cardiovascular prevention way up and the benefit may make not be worth the cost.