Upper Gastrointestinal Bleeding
Peptic Ulcer Disease
Pharmacotherapy Issues in Acute Management and Secondary Prevention

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Objectives

• To discuss the acute management of upper GI bleeding peptic ulcers with a focus on antisecretory therapy.
• To discuss secondary prevention strategies following acute stabilization of acute GI bleeding peptic ulcers.

Epidemiology

• ~15,000 admissions annually in Canada
• 55% caused by peptic ulcer disease
  - Helicobacter pylori
  - ASA/NSAIDs/COX-2 Inhibitors
• 80% will stop spontaneously
• 6-7% mortality rate
  - 0.6% if <60 years of age and no co-morbidity
  - 15% if >60 years of age and/or co-morbidity

Economic Implications

Marshall et al. (Am J Gastroenterol 1999;94:1841-6)

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Total Cost</th>
<th>LOS (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-39</td>
<td>$1830</td>
<td>2.96</td>
</tr>
<tr>
<td>40-59</td>
<td>$2435</td>
<td>3.82</td>
</tr>
<tr>
<td>60-74</td>
<td>$2713</td>
<td>4.73</td>
</tr>
<tr>
<td>75-85</td>
<td>$5364</td>
<td>7.62</td>
</tr>
<tr>
<td>Mean (n=116)</td>
<td>$2690</td>
<td>4.26</td>
</tr>
</tbody>
</table>

Helicobacter pylori

NSAID-Induced Peptic Ulcer Disease

• 15-30% of all PUD is NSAID-induced
• NSAID use increases risk of PUD 3-5X
• 60% of NSAID users experience heartburn, pain, dyspepsia
• symptoms >4 weeks have increased risk of gastric ulceration
• 66% of all NSAID users will have endoscopic evidence of gastric lesions but clinical ulcers is 2-4% annually
Risk Factors for NSAID-Induced Gastropathy
Wolfe et al. (NEJM 1999;320:1888-98)

Definite:
• Age
• Prior history of ulcer
• Duration of NSAID therapy
• Concomitant corticosteroid therapy
• Concomitant warfarin therapy
• Concomitant ASA/NSAID
• NSAID dose
• Serious systemic illness (CHF, RA, CAD, others)

Possible:
• Concomitant H. pylori infection?
• Smoking
• Alcohol

Acute Gastrointestinal Bleeding Peptic Ulcer

Prognostic Factors: Clinical
Barkun et al. (Aliment Pharmacol Ther 1999;13:1565-84)

• Hemodynamic instability
• Hematochezia from upper GI source
• >60 years of age
• Units of transfused blood
• Concurrent illness
• Onset of bleeding while hospitalized
• Coagulopathy

Prognostic Factors: Endoscopic
Barkun et al. (Aliment Pharmacol Ther 1999;13:1565-84)

High Risk Bleeds

Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study
Francisco Juez de Astarloa, Luis Alberto Garcia Rodriguez, Dennis H Montesinos

<table>
<thead>
<tr>
<th></th>
<th>NSAID (N=1651)</th>
<th>Controls (N=1000)</th>
<th>Adjusted relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>1515 (73.5)</td>
<td>983 (98.3)</td>
<td>1</td>
</tr>
<tr>
<td>Current use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>265 (17.0)</td>
<td>632 (63.2)</td>
<td>0.37 (0.22 to 0.62)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>30 (2.3)</td>
<td>90 (9.0)</td>
<td>0.36 (0.17 to 0.76)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs and selective serotonin reuptake inhibitors</td>
<td>18 (1.1)</td>
<td>9 (0.9)</td>
<td>1.58 (0.49 to 5.41)</td>
</tr>
</tbody>
</table>
**Goals of Therapy**

- Hemodynamic Stabilization and Resuscitation (ABC)
- Determine Cause
- Stop Bleeding
- Prevent Recurrence

**Management**

- Oxygen
- Fluid
- Blood Transfusion
- Endoscopic Therapy
- Surgery
- Pharmacotherapy

**Endoscopic Therapy: Meta-Analysis**

Cook et al. Gastroenterol 1992;102:139-48

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>0.38 (0.32-0.45)</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.36 (0.28-0.45)</td>
</tr>
<tr>
<td>Death</td>
<td>0.55 (0.40-0.76)</td>
</tr>
</tbody>
</table>

**Pharmacological Therapy**

- Splanchnic blood pressure modifiers
  - vasopressin, octreotide, somatostatin
- Antifibrinolytic Agents
  - tranexamic acid
- **Antisecretory Agents**
  - H2-receptor antagonists (H2RA)
  - proton-pump inhibitors (PPI)

**Role of Gastric Acid on Hemostasis**

- Impairs clot formation
- Impairs platelet aggregation and causes disaggregation
- Accelerates clot lysis
- Acid-stimulated pepsin
- Impairs mucous/bicarbonate barrier

Cook et al. Gastroenterol 1992;102:139-48

Aliment Pharmacol Ther 1999;106:1565-84
H2RA in Acute GI Bleeding: Meta-Analysis
Collins et al. (NEJM 1985;313:660-6)

- 27 trials, N=2500
- randomized, placebo-controlled trials
- H2RA vs. Placebo

ENDPOINTS
- rebleeding
- surgery
- mortality

Famotidine in Acute GI Bleeding
Walt et al. (Lancet 1992;340:1058-62)

Acute Endoscopically-proven GI Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=1005

Famotidine 10 mg IV bolus followed by 3.2 mg/h x 72h

ENDPOINTS:
Primary: Death during hospitalization
Secondary: Rebleeding

Tolerance: Intragastric pH>4
Merki and Wilder-Smith (Gastroenterol 1994;106:60-4)

Day 1 Day 3
Omeprazole Ranitidine

Proton-Pump Inhibitors
Mechanism of Action
PPI is Acute GI Bleeding Peptic Ulcers

- 12 randomized, controlled trials since 1990
- omeprazole only PPI evaluated in these trials
- 5 placebo-controlled, 7 H2RA-controlled

Issues
- Efficacy? Safety? Cost?
- PPI Alone vs. Adjuvant to Endoscopy?
- PPI Alone vs. Endoscopy Alone?
- Intermittent Dosing vs. Continuous Infusion?
- IV vs. PO?

Omeprazole: Intermittent Bolus

Daneshmend et al. (BMJ 1992;304:143-7)

Clinically-Diagnosed Acute GI Bleeding
P, MC, R, DB, PC
n=1147

Omeprazole 80 mg IV bolus followed by 40 mg IV Q8h x 24h followed by 40 mg PO BID x 3 days

Placebo

ENDPOINTS:
Primary: Death, Rebleeding, Surgery, Transfusion

Omeprazole: Intermittent Bolus

Daneshmend et al. (BMJ 1992;304:143-7)

Omeprazole 80 mg IV bolus then 40 mg IV Q8h x 24h then 40 mg PO BID x 3 days

Proven Gastric/Duodenal Ulcer

Daneshmend et al. (BMJ 1992;304:143-7)

Placebo

Omeprazole 80 mg IV bolus then 40 mg IV Q8h x 24h then 40 mg PO BID x 3 days

p=ns

Omeprazole: Intermittent Bolus/Endoscopy

Villanueva et al. (Endoscopy 1995;27:308-12)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, R, OL
n=86

Omeprazole 80 mg IV bolus followed by 40 mg IV Q8h x 4 days followed by 20 mg PO daily

Ranitidine 50 mg IV Q6h x 24h followed by 150 mg PO BID

All patients received endoscopic therapy within 4h

ENDPOINTS:
Primary: Death, Rebleeding, Surgery

Omeprazole: Intermittent Bolus/Endoscopy

Villanueva et al. (Endoscopy 1995;27:308-12)

p=ns for all endpoints

Omeprazole 80 mg IV bolus then 40 mg IV Q8h x 4 days then 20 mg PO/day

Ranitidine 50 mg IV Q6h x 24h then 150 mg PO BID
Summary: Intermittent Bolus

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI Control</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunner (1990)</td>
<td>Omeprazole (n=19)</td>
<td>Ranitidine (n=20)</td>
</tr>
<tr>
<td>Daneshmend (1992)</td>
<td>Omeprazole (n=578)</td>
<td>Placebo (n=569)</td>
</tr>
<tr>
<td>Lanas (1995)</td>
<td>Omeprazole (n=23)</td>
<td>Ranitidine (n=23)</td>
</tr>
<tr>
<td>Villanueva (1995)</td>
<td>Omeprazole (n=45)</td>
<td>Ranitidine (n=41)</td>
</tr>
<tr>
<td>Grosso (1995)</td>
<td>Omeprazole (n=21)</td>
<td>Endo/Ran (n=21)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Omeprazole N=686</td>
<td>Control N=674</td>
</tr>
</tbody>
</table>

Omeprazole: Continuous Infusion/Endoscopy

Schaffalitzky et al. (Scand J Gastroenterol 1997;32:320-7)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=265

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days
Placebo

All patients received endoscopic therapy within 12h

ENDPOINTS: Overall Outcome (ordinal scale)

Primary Variables:
- Death (5)
- Surgery (4)
- Endoscopic Treatment (3)
- Transfusion > 3 units (2)
- Transfusion 1-3 units (1)

Overall Outcome of Treatment after 72 hours

<table>
<thead>
<tr>
<th>Category</th>
<th>Outcome</th>
<th>Omeprazole* (n=130)</th>
<th>Placebo (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.0%</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.4%</td>
<td>2.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.1%</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91%</td>
<td>89.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>31.4%</td>
<td>30.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.2%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

*p=0.0004

Omeprazole: Continuous Infusion

Hasselgren et al. (Scand J Gastroenterol 1997;32:328-33)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, MC, R, DB, PC
n=322

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days
Placebo

ENDPOINTS:

Primary Variables:
- Degree of bleeding
- Duration of bleeding
- Surgery
- Endoscopic Treatment
- Mortality
- Treatment Failure

Secondary Variables:
- Rebleeding
- Surgery
- Death
- Treatment Failure

Omeprazole 80 mg IV bolus then 8 mg/h x 72 hours
Placebo

Rebleeding: 8.2% vs 9.8%, p=0.004
Surgery: 2.5% vs 2.5%, p=0.003
Death: 0.6% vs 0.6%, p=0.0009
Treatment Failure: 6.2% vs 7.3%, p=0.0009
Omeprazole: Continuous Infusion/Endoscopy
Lau et al. (NEJM 2000;343:310-6)

Acute Endoscopically-proven Actively Bleeding Peptic Ulcer
P, R, DB, PC n=240

Omeprazole 80 mg IV bolus followed by 8 mg/h x 3 days followed by 20 mg PO daily x 8 wks
Placebo x 3 days followed by omeprazole 20 mg PO daily x 8 wks

All patients received endoscopic therapy within 24h

ENDPOINTS:
Primary: Rebleeding at 30 days
Secondary: Surgery at 30 days
Death at 30 days

**Summary: Continuous Infusion**

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI</th>
<th>Control</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hasselgren</td>
<td>Omeprazole (n=159)</td>
<td>Placebo (n=163)</td>
<td>↑ Overall Outcome ↓ Rebleeding ↓ Surgery</td>
</tr>
<tr>
<td>Schaffalitzky</td>
<td>Omeprazole (n=120)</td>
<td>Placebo (n=135)</td>
<td>↑ Overall Outcome ↓ Rebleeding ↓ Surgery</td>
</tr>
<tr>
<td>Lin (1998)</td>
<td>Omeprazole (n=50)</td>
<td>Ranitidine (n=50)</td>
<td>↓ Rebleeding</td>
</tr>
<tr>
<td>Lau (2000)</td>
<td>Omeprazole (n=120)</td>
<td>Placebo (n=120)</td>
<td>↓ Rebleeding</td>
</tr>
</tbody>
</table>

**TOTAL**
Omeprazole N=459
Control N=468

**Meta-Analysis**
Zed PJ et al. (Ann Pharmacother 2001;35:1528-34)

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI Better</th>
<th>H2RA/Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daneshmend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grosso</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasselgren</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL**
PPI Better 1 H2RA/Placebo Better

**ODDS RATIO**

OR 0.50, (95% CI 0.33-0.77) p=0.002; NNT = 9

**Meta-Analysis**
Zed PJ et al. (Ann Pharmacother 2001;35:1528-34)

<table>
<thead>
<tr>
<th>Study</th>
<th>PPI Better</th>
<th>H2RA/Placebo Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daneshmend</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grosso</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hasselgren</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lau</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL**
PPI Better 1 H2RA/Placebo Better

**ODDS RATIO**

OR 0.47, (95% CI 0.29-0.77) p=0.003; NNT = 17

---

**Table 2: Outcomes with Endoscopic Therapy**

<table>
<thead>
<tr>
<th>Event</th>
<th>Omeprazole Group</th>
<th>Placebo Group</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>26</td>
<td>39</td>
<td>0.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>6</td>
<td>2</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>Procedure-related mortality</td>
<td>2</td>
<td>8</td>
<td>0.25</td>
<td>0.03</td>
</tr>
<tr>
<td>Surgery</td>
<td>22</td>
<td>26</td>
<td>0.85</td>
<td>0.25</td>
</tr>
<tr>
<td>Other endoscopic therapy</td>
<td>6</td>
<td>10</td>
<td>0.60</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
1. ORs indicate the relative risk of an outcome in the placebo group as compared with the omeprazole group. CI denotes confidence interval.
2. The number of the total number of patients in each group who had successful bleeding within 30 days of intervention.
3. PPI = proton pump inhibitors, H2RA = histamine-2 receptor antagonists.
### Acute Endoscopically-proven High Risk Peptic Ulcer

**Omeprazole vs. Omeprazole/Endoscopy**

Sung et al. (Ann Intern Med 2003;139:237-43)

- **Endoscopy**
- **Sham Endoscopy**

All patients omeprazole 80 IV bolus then 8 mg/h x 72h

**ENDPOINTS:**
- **Primary:** Rebleeding at 30 days
- **Secondary:** Surgery at 30 days
- **Death at 30 days**

### Acute Endoscopically-proven GI Bleeding Peptic Ulcer

**Omeprazole: Oral Dosing**

Khuroo et al. (NEJM 1997;336:1054-8)

- **Omeprazole**
  - 40 mg PO BID x 5 days
- **Placebo**

**ENDPOINTS:**
- **Primary:** Death
- **Rebleeding**
- **Surgery**
- **Transfusion**

### Acute Endoscopically-proven GI Bleeding Peptic Ulcer

**Omeprazole: Oral Dosing**

Javid et al. (Am J Med 2001;111:280-4)

- **Omeprazole**
  - 40 mg PO BID x 5 days
- **Placebo**

**ENDPOINTS:**
- **Primary:** Rebleeding
- **Surgery**
- **Transfusion**

---

**Primary:** Rebleeding at 30 days

**Secondary:** Surgery at 30 days

**Death at 30 days**
Conclusions

• H2RA have no role in the management of AGIB
  • cannot provide necessary pH increase
  • tolerance develops quickly
  • no benefit in clinical trials
• PPI beneficial in select patient populations
  • maintains desired intragastric pH
  • tolerance has not been reported

Helicobacter pylori

Prevention of Recurrence: H. pylori Eradication

<table>
<thead>
<tr>
<th>Study</th>
<th>Cure Rate</th>
<th>Control</th>
<th>H. pylori Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham (1993)</td>
<td>76%</td>
<td>29%</td>
<td>0%</td>
</tr>
<tr>
<td>Labenz (1994)</td>
<td>100%</td>
<td>38%</td>
<td>0%</td>
</tr>
<tr>
<td>Rokkas (1995)</td>
<td>81%</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>Jaspersen (1995)</td>
<td>83%</td>
<td>27%</td>
<td>0%</td>
</tr>
<tr>
<td>Santander (1995)</td>
<td>79%</td>
<td>12%</td>
<td>2%</td>
</tr>
<tr>
<td>Maier (1995)</td>
<td>90%</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>


Endoscopic recurrence at 6 months (%)
H. pylori Eradication

Can J Gastroenterol 1998;12:31-41

**FIRST LINE**

<table>
<thead>
<tr>
<th>PPI PO BID*</th>
<th>Metronidazole 500 mg PO BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 250 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>PPI-MC 250</td>
<td></td>
</tr>
</tbody>
</table>

**SECOND LINE**

<table>
<thead>
<tr>
<th>PPI PO BID*</th>
<th>Metronidazole 500 mg PO BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 500 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>PPI-MC 500</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PPI PO BID*</th>
<th>Amoxicillin 1000 mg PO BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 500 mg PO BID</td>
<td></td>
</tr>
<tr>
<td>PPI-AC</td>
<td></td>
</tr>
</tbody>
</table>

*Omeprazole 20 mg or Lansoprazole 30 mg or Pantoprazole 40 mg

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**Prevention: Misoprostol (MUCOSA)**

Silvestrini et al. (Ann Intern Med 1995;123:241-5)

- P, MC, R, DB, P C N=8843
- RA, >52 yrs, NSAID-users

Misoprostol 200 mcg PO QID vs. Placebo

**ENDPOINT**

Serious GI Complications at 6 months

- ARR=0.38% 0.95%
- p=0.049 0.57%

---

**Prevention: H2RA**

NSAID-Induced Peptic Ulcer Disease

Taha, NEJM 1996;334:1435-9

- Famotidine 40 mg/d
- Famotidine 80 mg/d
- Placebo

**ENDPOINTS**

- Healing at 8 weeks
- Maintenance at 6 months

---

**Treatment and Prevention of Recurrence**

NSAID-Induced Peptic Ulcer Disease


- P, MC, R, DB, N=915
- NSAID-induced PUD
  - Misoprostol vs. Omeprazole

**ENDPOINTS**

- Healing at 8 weeks
- Maintenance at 6 months

---

**Treatment and Prevention of Recurrence**

NSAID-Induced Peptic Ulcer Disease


- P, MC, R, DB, N=541
- NSAID-induced PUD
  - Ranitidine vs. Omeprazole

**ENDPOINTS**

- Healing at 8 weeks
- Maintenance at 6 months

---

**Treatment and Prevention of Recurrence**

NSAID-Induced Peptic Ulcer Disease


- P, MC, R, DB, N=915
- NSAID-induced PUD
  - Misoprostol vs. Omeprazole

**ENDPOINTS**

- Healing at 8 weeks
- Maintenance at 6 months

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**Treatment and Prevention of Recurrence**

NSAID-Induced Peptic Ulcer Disease


- P, MC, R, DB, N=915
- NSAID-induced PUD
  - Misoprostol vs. Omeprazole

**ENDPOINTS**

- Healing at 8 weeks
- Maintenance at 6 months

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- RA, >52 yrs, NSAID-users

Misoprostol 200 mcg PO QID vs. Placebo

**ENDPOINT**

Serious GI Complications at 6 months

- ARR=0.38% 0.95%
- p=0.049 0.57%

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**Prevention: Misoprostol (MUCOSA)**

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Celecoxib vs. Diclofenac/Omeprazole
Chan et al. (NEJM 2002;347:2104-10)

OA/RA, H. pylori-negative endoscopically-proven healed peptic ulcer
P, R, DB, PC
n=287

Celecoxib 200 mg PO BID Placebo po daily x 6 months

Diclofenac 75 mg PO BID Omeprazole 20 mg PO daily x 6 months

All patients received endoscopic evaluation every 2 months x 3

PRIMARY ENDPOINT: Rebleeding within 6 months
• clinical features/Hg drop + endoscopic confirmation

Celecoxib vs. Diclofenac/Omeprazole
Chan et al. (NEJM 2002;347:2104-10)

16 recurrent ulcers at 6 months
Difference: -1.5% (95% CI –6.8% to 3.8%, p=ns)

Probability of Recurrent Ulcer Bleeding

Celecoxib vs. Diclofenac/Omeprazole
Chan et al. (NEJM 2002;347:2104-10)

Table 1: Incidence of Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Celecoxib</th>
<th>Diclofenac/Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>12 (4.3%)</td>
<td>12 (4.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (4.3%)</td>
<td>12 (4.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (3.5%)</td>
<td>10 (3.5%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (2.8%)</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (2.1%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (1.8%)</td>
<td>5 (1.8%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (1.8%)</td>
<td>5 (1.8%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>4 (1.4%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (1.4%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (1.4%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Perforation</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>49 (17.1%)</td>
<td>49 (17.1%)</td>
</tr>
</tbody>
</table>

*Total adverse events were defined by a programme doctor on the basis of being 2.2 mg per day aspirin (20 mg per day for 4 weeks). There were no significant differences between the groups.

Celecoxib vs. Diclofenac/Omeprazole
Chan et al. (NEJM 2002;347:2104-10)

Post Acute Therapy for AGIB

Is patient H.p.+?

YES

Treat with H. Pylori eradication therapy

NO

Is patient taking NSAIDS?

NO

PPI X 4-8 weeks

YES

Can NSAID be discontinued?

Reduce to lowest dose possible + PPI

NO