OPTIMIZING CLINICAL OUTCOMES

MANAGING GI RISK IN THE ARTHRITIS PATIENT ON CHRONIC NSAID THERAPY

pmiCME Updates
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David A. Peura, MD

Educational Partner:
Innovations Consulting Group, LLC
Session 2: Optimizing Clinical Outcomes:
Managing GI Risk in the Arthritis Patient on Chronic NSAID Therapy

Learning Objectives
1. Discuss the importance of gastroprotection for at-risk patients who require nonsteroidal anti-inflammatory drug (NSAID) treatment for the relief of signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis (OA).
3. Describe the risks and benefits of different gastroprotective strategies.
4. Summarize the latest clinical trial results supporting the effectiveness of the combination therapies naproxen plus esomeprazole and ibuprofen plus famotidine.
5. Review case studies addressing important challenges in the management of patients who require NSAIDs and gastroprotection.

Faculty

Allan Gibofsky, MD, JD
Professor of Medicine and Public Health
Weill Medical College of Cornell University
New York

Dr Allan Gibofsky is professor of medicine and public health at the Weill Medical College of Cornell University, professor of law at Fordham University. He is an attending physician and rheumatologist at the Hospital for Special Surgery. Dr Gibofsky has authored or co-authored numerous papers and text chapters, primarily on rheumatic diseases and legal aspects of medical practice. Currently secretary-treasurer of the New York Rheumatism Association, Dr Gibofsky is past chair of the Medical and Scientific Committee of the New York Chapter of the Arthritis Foundation and is a recipient of their Physicians’ Leadership Award. He also served as a member of the local and national Arthritis Foundation Board of Trustees, and was chair for professional education. In 2002, Dr Gibofsky served as president of the American College of Rheumatology. He is a member of the Health and Public Policy Committee of the American College of Physicians, past president of the American College of Legal Medicine, past chair of the American Board of Legal Medicine, and past chair of the Arthritis Advisory Committee of the Food and Drug Administration.

David A. Peura, MD
Emeritus Professor
Department of Medicine, Division of Gastroenterology and Hepatology
University of Virginia School of Medicine
Charlottesville

Dr David A. Peura is emeritus professor of medicine in the division of gastroenterology and hepatology at the University of Virginia School of Medicine in Charlottesville, Virginia. Throughout his career he has been actively involved in clinical investigation relating to acid peptic disorders, particularly peptic ulcer disease. He serves as a reviewer for most of the major medicine and gastroenterology subspecialty journals and has authored or co-authored more than 100 original articles, book chapters, and reviews. Over the years, Dr Peura has held leadership positions in the major national gastroenterology organizations and received numerous commendations and awards for his contributions, including being selected as a master of the American College of Gastroenterology in 2004, and fellow of the American Gastroenterologic Association (AGA) in 2006. Dr Peura served as the 100th president of the AGA from 2005 to 2006. He is an internationally recognized clinician and educator and a popular speaker in the area of upper gastrointestinal disease.
Faculty Financial Disclosure Statement

The presenting faculty report the following:

Allan Gibofsky, MD, JD, has received honoraria as an advisor from Horizon Pharma and AstraZeneca. He has received honoraria as an advisor and a speaker from Abbott, Amgen, UCB, and Genentech.

David A. Peura, MD, has received consulting fees from Horizon Pharma and AstraZeneca. He has received consulting and speaker fees from Takeda.

Education Partner Financial Disclosure Statement

The content collaborators at Innovations Consulting Group, LLC report the following:

Robert Rhoades, PhD, Medical Director, has no financial relationships to disclose.

Valorie J. Thompson, President, has no financial relationships to disclose.

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
<td>OTC</td>
<td>over the counter</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
<td>UGI</td>
<td>upper gastrointestinal</td>
</tr>
<tr>
<td>coxib</td>
<td>selective cyclo-oxygenase-2 inhibitor</td>
<td>ASA</td>
<td>aspirin</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
<td>H2RA</td>
<td>histamine-2 receptor</td>
</tr>
<tr>
<td>ns</td>
<td>non-specific</td>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>PUB</td>
<td>perforation, obstruction, bleeding</td>
<td>BID</td>
<td>twice a day</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
<td>TID</td>
<td>three times a day</td>
</tr>
<tr>
<td>MTX</td>
<td>methotrexate</td>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
<td>Hgb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


**Objectives**

1. Discuss the importance of gastroprotection for at-risk patients who require nonsteroidal anti-inflammatory drug (NSAID) treatment for the relief of signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis (OA).


3. Describe the risks and benefits of different gastroprotective strategies.

4. Summarize the latest clinical trial results supporting the effectiveness of the combination therapies, naproxen plus esomeprazole and ibuprofen plus famotidine.

5. Review case studies addressing important challenges in the management of patients who require NSAIDs and gastroprotection.
Question

Which of the following is/are effective ways to reduce risk of NSAID associated ulcers?
1. Buffer the NSAID or give with an antacid
2. Give NSAID with a high-dose H2RA
3. Give NSAID with a PPI
4. 2 and 3 are effective
5. All are effective
6. Unsure

Question

A number of factors have been identified as increasing the risk for NSAID-associated ulcer complications. Which of the following has NOT been confirmed as a risk factor:
1. Age > 70 y
2. Past history of uncomplicated ulcer
3. H pylori infection
4. SSRI use
5. Clostridium difficile infection
6. None of the above – they are all risk factors
7. Unsure

Question

In a patient who takes aspirin for cardiovascular (CV) prophylaxis, which strategy is best to reduce the risk for an NSAID related upper gastrointestinal (UGI) complication?
1. Use celecoxib with a buffered aspirin
2. Use an NSAID and a high-dose H2RA
3. Use an NSAID and a PPI
4. Both 2 and 3
5. All are appropriate
6. Unsure

Question

The benefit of proton pump inhibitors (PPIs) in the prevention of NSAID induced gastric ulcers has been confirmed; however, PPIs have also been associated with the following risks:
1. Hip fracture
2. Community acquired pneumonia
3. Community acquired clostridium difficile infection
4. 1 and 2
5. All of the above
6. Unsure

The Size of the Problem

Prevalence of Selected Musculoskeletal Conditions in the United States

Arthritis and other musculoskeletal conditions affect more than 29,000,000 people in the United States
Baseline CV-GI risk factors in patients with osteoarthritis and rheumatoid arthritis in the United States

Prevalence (%)

GI and CV Risk Factors Are Common in Patients With Arthritis

- CV disease
- Coronary heart disease
- Stroke
- Heart failure
- High blood pressure
- Hypercholesterolemia
- Diabetes
- Smoking
- Peptic ulcer


Use of Nonsteroidal Anti-inflammatory Drugs in the US

- In 2004, individuals in the United States spent >$2.5 billion on over-the-counter (OTC) NSAIDs and filled >100 million NSAID prescriptions
- Most commonly used OTC analgesics:
  - Aspirin
  - Acetaminophen
  - Ibuprofen

The Severity of the Problem

Ulcers in Patients Taking NSAIDs

- Endoscopically-demonstrable ulcers develop in 15-30% of regular NSAID users and the annual rate of upper GI (UGI) clinical events is approximately 2.5-4.5%.
  - Only a minority of patients who have serious gastrointestinal complications report any antecedent dyspepsia
  - In a study of patients with serious gastrointestinal complications, the proportion of patients with prior symptoms was 2.7% versus 2.0% for those with no symptoms

GI Bleeding in NSAID Users

Estimated Mortality Attributable to NSAID/aspirin-associated GI Complications

- Estimated mortality rate per million people


Gaziano JM. Am J Cardiol. 2006;97:10-16.


Entire Country Population NSAID/aspirin Users

Spain

United Kingdom

United States

Spain

United Kingdom

United States

Lack of Symptoms Does Not Mean Patients Are Safe

- Results for 235 consecutive patients with a life threatening complication of peptic ulceration, who either died or required emergency surgery:
  - 78 patients died (25 at home, 19 in hospital without surgery, and 34 postoperatively)
  - 98 had bleeding ulcers
  - 132 had perforated ulcers
  - 5 had both bleeding and perforated ulcers
  - 140 of the 235 patients (60%) were taking an NSAID:
    - Nearly 80% of all ulcer related deaths occurred in patients using an anti-inflammatory agent

- The first sign of an ulcer was a life threatening complication in 56.2% of patients taking a NSAID


What Are the Risk Factors for NSAID-Associated Ulcer Complications?

- NSAID Dose
  - Low
  - Medium
  - High
- Other Patient/Treatment Characteristics
  - Previous Ulcer w/ Complication
  - Previous Ulcer w/ Complication
  - Anticoagulants
- Relative Risk for Upper GI Bleeding

Risk Stratification for NSAID-related GI Toxicity

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Moderate risk (1-2 risk factors)</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of a previously complicated ulcer, especially a recent flare-up</td>
<td>Age &gt;65 years</td>
<td>No risk factors</td>
</tr>
<tr>
<td>More than 2 risk factors</td>
<td>High-dose NSAID therapy</td>
<td>Helicobacter pylori is an independent risk factor and needs to be addressed separately</td>
</tr>
<tr>
<td>History of uncomplicated ulcer</td>
<td>Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants</td>
<td></td>
</tr>
</tbody>
</table>
| Risk of ulcer complications
  - Naproxen > Aspirin > Ibuprofen > Acetaminophen (a non-NSAID)* |
  - Dose related |

Substitute Acetaminophen

Approaches to the Problem: Risk Reduction
Risk for Upper GI Complications With Acetaminophen


Relative Risk for Upper GI Complication

Risk for Upper GI Complications With Acetaminophen

Acetaminophen Versus NSAIDs: Efficacy and Patient Preferences

- Meta-analysis: randomized, controlled trials in osteoarthritis
  - Acetaminophen less effective overall vs. NSAIDs for
    - Pain reduction
    - Stiffness
    - Function
    - Patient and investigator global assessments


Adding a Gastroprotective Agent

Prevention of NSAID Gastric and Duodenal Ulcers: Addition of PPI


PPI Outcomes Prevention: Recurrent Ulcer Bleeding in High-risk Patients

Adding an H2RA to a Conventional NSAID


Fracture Risk with PPIs and H2RAs

Adjusted Odds Ratio for Hip Fracture

PPI
H2 RA

1.44 (95% CI: 1.30-1.59)
1.23 (95% CI: 1.14-1.33)


Pneumonia Risk with PPI and H2RA

Relative Risk for Community-acquired Pneumonia

95% CI:

PPI
H2 RA

1.16 (95% CI: 0.80-1.20)
0.98


Clostridium difficile Infection with PPI and H2RA

Rate Ratio for Cases Versus Controls

95% CI:

NSAID H2RA PPI

1.3 (95% CI: 1.2-1.5)
2
2.9


Substituting a Coxib for a Conventional NSAID

Cumulative Incidence, % (95% CI)

Patients at risk

Etoricoxib 17,412 13,704 10,972 8,400 6,509 4,063 821
Diclofenac 17,289 13,190 10,396 8,027 6,306 3,867 820

64 2 24
12 18 30 36

Months

Etoricoxib 60 and 90 mg pooled (176 events)
Diclofenac 150 mg (246 events)

Etoricoxib vs diclofenac
HR=0.69 (95% CI: 0.57, 0.83)
P<0.001


CLASS Trial: Upper GI Complications Alone and With Symptomatic Ulcers (6-month results)

Annualized Incidence, %

NSAIDs (ibuprofen + diclofenac)

Celecoxib

All Patients

P=0.03

0.76 1.44

0.88 1.27

0.86 1.4

P=0.02

2.55 3.54

0.45 1.27

1.4 3.91

P=0.49

4.7 5.9

Patients Taking Aspirin

Patients Not Taking Aspirin

Ulcer Complications

Symptomatic Ulcers and Ulcer Complications

Update on GI Safety of Coxibs

Cochrane Systematic Review

<table>
<thead>
<tr>
<th>Relative Risk (95% CI)</th>
<th>COX-2 inhibitors vs nsNSAIDs</th>
<th>Endoscopically detected ulcers (26 studies)</th>
<th>0.26 (0.23, 0.30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinically important PUBs (8 studies)</td>
<td>0.39 (0.31, 0.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COX-2 inhibitors + concomitant aspirin vs nsNSAIDs (4 studies)</td>
<td>Clinically important PUBs</td>
<td>0.89 (0.52, 1.53)</td>
</tr>
</tbody>
</table>

ns = nonselective, PUBs = perforation, obstruction, bleeding, or the presence of symptomatic ulcers.

Cochrane Systematic Review


High-risk Patients with Recent NSAID Ulcer Bleed: Comparison of Coxib vs nsNSAID Plus PPI

<table>
<thead>
<tr>
<th>RR (95% CI)</th>
<th>Bleeding ulcers</th>
<th>Endoscopic ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.77 (0.30-2.02)</td>
<td>4.9</td>
<td>19.0</td>
</tr>
<tr>
<td>0.70 (0.42-1.18)</td>
<td>6.4</td>
<td>26.0</td>
</tr>
</tbody>
</table>


Recurrent Ulcer Bleeding with Coxib plus PPI vs Coxib Alone

Results of a single center RCT comparing esomeprazole 20 mg BID vs placebo added to celecoxib 200 mg BID in 441 high-risk patients

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Celecoxib</th>
<th>Celecoxib + PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8.9</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P=0.0004


Current Guidelines: What the Experts Suggest

American College of Rheumatology 2010

- Exercise, weight-loss, self-management programs, aids
- Acetaminophen
- NSAIDs: oral (age <75 years) or topical (age ≥75 years)
  - If GI risk, selective COX-2 inhibitor or nonselective NSAID+PPI or selective COX-2 inhibitor + PPI
  - If low dose aspirin, nonselective NSAID+PPI
- Suggest not to use oral NSAIDs if patient ≥75 years of age
- Tramadol
- Intra-articular steroid or hyaluronate

Osteoarthritis Society International 2008

- Acetaminophen (up to 4 g/d)
- NSAIDs should be used at the lowest effective dose but their long-term use should be avoided if possible
  - In patients with increased GI risk, either a COX-2 selective agent or a non-selective NSAID with co-prescription of a PPI or misoprostol for gastroprotection may be considered
  - NSAIDs, including both nonselective and COX-2 selective agents, should be used with caution in patients with CV risk factors
- Weak opioids and narcotic analgesics can be considered
  - Stronger opioids should only be used for the management of severe pain in exceptional circumstances
- Nonpharmacologic therapies should be continued in such patients and surgical treatments should be considered

Management Algorithm for OA Patients with Comorbidities (American College of Gastroenterology)

Assessment
Education Information
Nonpharmacologic Core Therapies
Acetaminophen
Consider Topical NSAID
Assess for CV Risk
Low CV Risk
Assess for GI risk†
Low
Moderate
High

Low CV Risk
Low
Moderate
High

Low CV Risk
Low
Moderate
High


Question 1

What is the next step?
1. Switch OTC NSAID to Rx dose
2. Switch to opiate until her dyspepsia improves
3. Test her for H. pylori
4. Add an H2RA and stop her NSAIDs
5. Add a PPI and continue her NSAIDs
6. Refer her for endoscopy

Case Study

- 64-year-old white woman with OA of both knees and chronic pain (6 on a 10-point visual analog scale) that is not effectively managed with up to 4 g/day acetaminophen.
- The patient has no history of cardiovascular disease, but is taking a bisphosphonate for osteoporosis.
- She self-manages her pain with over-the-counter ibuprofen or naproxen but continues to have joint pain. She presents to her primary care physician with abdominal pain and dyspepsia.

Question 2

What are your treatment options for her?
1. Heal the ulcer with a PPI and avoid future NSAIDs
2. Heal ulcer with a PPI and restart NSAID with gastroprotective therapy (H2RA, PPI or misoprostol) to prevent ulcer recurrence
3. Switch to coxib since ulcer will heal by itself on this safer class of NSAIDs
4. Switch to opiate since ulcer will heal when NSAID is discontinued

Case Study (cont’d)

- The patient is referred to a gastroenterologist for endoscopy. This evaluation reveals several gastric ulcers ranging from 5-15 mm in diameter. Biopsies for H pylori are negative.

Addressing Adherence with Risk Reduction
At least 1 risk factor (n = 303,787)
At least 2 risk factors (n = 30,133)
3 or more risk factors (n = 1,503)

Risk factors:
• Age ≥ 65 years
• Concomitant corticosteroid use
• Concomitant anticoagulant use
• History of upper GI events
• High average daily dose

Adherence to Guidelines for Prescribing NSAIDs According to GI Risk

Number of Medications Negatively Affects Adherence

Combination Naproxen-Esomeprazole

Overview of Two Pivotal Trials
• Approximately 400 subjects entered into each trial and randomized to receive either combination naproxen-esomeprazole or enteric-coated naproxen 500 mg BID
• Subjects underwent upper endoscopies at baseline and at 1, 3, and 6 months
• Primary endpoint: cumulative incidence of gastric ulcers* through 6 months
• Results showed that significantly fewer subjects taking the combination naproxen-esomeprazole experienced endoscopically confirmed gastric ulcers compared to subjects receiving naproxen alone

Combination Ibuprofen-Famotidine vs Ibuprofen Alone: REDUCE-1 and REDUCE-2

• Objective: to determine if a single-tablet combination of ibuprofen (800 mg) and famotidine (26.6 mg) will significantly decrease ulcers compared to ibuprofen alone
• REDUCE-1 and REDUCE-2 randomized 812 and 570 patients, respectively, in a 2:1 ratio to single tablet combination of ibuprofen-famotidine or identical-appearing ibuprofen 800 mg tablets TID
• Endoscopies were done at 8, 16, and 24 weeks
• Primary endpoint: incidence of gastric and duodenal ulcers* at 24 weeks

* ≥ 3 mm in diameter with significant depth

Adherence to Gastroprotective Therapy in Patients Prescribed NSAIDs

Nonadherence was defined as lack of co-therapy for gastroprotection on <75% of days on which NSAIDs were prescribed

Combination Naproxen-Esomeprazole: Study Results

Percent with Gastric Ulcers

* ≥ 3 mm in diameter with depth

Combination Ibuprofen-Famotidine vs Ibuprofen Alone: REDUCE-1 and REDUCE-2

* ≥ 3 mm in diameter with significant depth
Combination Ibuprofen-Famotidine vs Ibuprofen Alone: Results of REDUCE-1 and REDUCE-2

<table>
<thead>
<tr>
<th>Ulcers</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Ulcers</td>
<td>10</td>
</tr>
<tr>
<td>Duodenal Ulcers</td>
<td>1.5</td>
</tr>
<tr>
<td>REDUCE-1 (N = 812)</td>
<td></td>
</tr>
<tr>
<td>HZT-501 (n=812)</td>
<td>19.8*</td>
</tr>
<tr>
<td>Ibuprofen TID (n=570)</td>
<td>9.7</td>
</tr>
<tr>
<td>Gastric Ulcers</td>
<td>4.7*</td>
</tr>
<tr>
<td>Duodenal Ulcers</td>
<td>9.7</td>
</tr>
<tr>
<td>REDUCE-2 (N = 570)</td>
<td></td>
</tr>
</tbody>
</table>

Ulcers were defined as being ≥3 mm in diameter with significant depth

Laine LA, et al. Oral presentation at: Digestive Disease Week; May 30-June 4, 2009; Chicago, Illinois. P<0.05

Case Study

- 57-year-old black man with RA being treated with methotrexate (MTX) and etanercept. The patient has a history of MI with PCI and stenting and is taking aspirin (162 mg/day) plus clopidogrel (75 mg/day).
- The patient is currently taking naproxen (500 mg bid) for management of pain associated with RA. He has been prescribed lansoprazole for protection against UGI events, but often forgets to take it if he does not have any GI symptoms. He also has intermittent diarrhea believed to be related to treatment with MTX and etanercept.
- He presents to his rheumatologist for routine follow up and is noted to have a Hgb of 7.2 g/dL.

Question 1

What is the next step?
1. Check 3 stools for occult blood
2. Start iron and see how his Hgb responds
3. Barium small bowel x-rays to exclude Crohn’s disease in view of his diarrhea
4. Refer for colonoscopy to evaluate anemia
5. Refer for both endoscopy and colonoscopy
6. Refer for upper endoscopy only

Safety Information:
Combination Naproxen-Esomeprazole and Combination Ibuprofen-Famotidine

- Warning: Cardiovascular and Gastrointestinal Risks
  - Cardiovascular Risk
  - Naproxen, a component of the combination tablet of naproxen-esomeprazole, and, ibuprofen, a component of the combination tablet of ibuprofen-famotidine, may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
  - The combination products of naproxen-esomeprazole and ibuprofen-famotidine are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

Safety Information:
Combination Ibuprofen-Famotidine vs Ibuprofen Alone: Results of REDUCE-1 and REDUCE-2

- The use of aspirin and the combination of ibuprofen-famotidine may increase the risk of adverse events.
- With concomitant use of LDA and ibuprofen, it is recommended that aspirin be taken at least 30 minutes before ibuprofen.

Product labeling: www.fda.gov

Question 1

What is the next step?
1. Check 3 stools for occult blood
2. Start iron and see how his Hgb responds
3. Barium small bowel x-rays to exclude Crohn’s disease in view of his diarrhea
4. Refer for colonoscopy to evaluate anemia
5. Refer for both endoscopy and colonoscopy
6. Refer for upper endoscopy only
Case Study (cont’d)

- The patient is referred for both endoscopy and colonoscopy. The colonoscopy is normal but the endoscopy shows a large deep pre-pyloric ulcer (15 mm in diameter). Biopsies for *H pylori* are negative.

**Question 2**

How do you manage him now?
1. Heal the ulcer and avoid future NSAIDs
2. Heal the ulcer and start a coxib
3. Heal the ulcer and restart therapy with either individual tablets of PPI and NSAID or a single tablet combination product of PPI-NSAID product to reduce ulcer recurrence
4. Heal the ulcer and restart therapy with either individual tablets of H2RA and NSAID or a single tablet combination H2RA- NSAID product to reduce ulcer recurrence
5. Heal the ulcer and restart NSAID with a combination misoprostol NSAID product to reduce ulcer recurrence

**Risk Reduction: Cardiovascular Implications**

**Risk of AMI and SCD With Current Use of COX-2 Selective and Nonselective NSAIDs**

- AMI = acute myocardial infarction, SCD = sudden cardiac death
- Adjusted for age, sex, health plan region, medical history, smoking, and medication use

**Cardiovascular Risk with Higher Dose Celecoxib (200 mg bid)**

- CV Death, Nonfatal MI, Stroke, HF, TE, angina, CV Procedure
- CV Death, Nonfatal MI, Stroke, HF, TE, angina
- CV Death, Nonfatal MI, Stroke, HF, TE
- CV Death, Nonfatal MI, Stroke
- CV Death, Nonfatal MI
- CV Death

- Hazard Ratio

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CV Event</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, HF, TE, angina, CV Procedure</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, HF, TE, angina</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke, HF, TE</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>CV Death, nonfatal MI, stroke</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>CV Death, Nonfatal MI, Stroke</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>CV Death, Nonfatal MI</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

- *P<0.05 based on 95% CI*

**Factors Associated with Increased Risk for CV Events during Treatment with NSAIDs/coxibs**

- ≥80 years of age
- Hypertension
- Prior myocardial infarction
- Prior cardiovascular disease
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease
- Chronic renal disease

Ibuprofen: Cardiovascular Data Interaction with Aspirin

• January 2001
  – Ibuprofen reported to block aspirin from binding to platelets in vitro – potentially reducing cardioprotective effects

• February 2003
  – Retrospective analysis of 7107 patients showed patients taking ibuprofen + ASA had higher mortality than those taking ASA alone or aspirin plus other NSAIDs (adjusted hazard ratio 1.93, 95% CI 1.30-2.87, P=0.0011)

• Recommend separating dosing of aspirin and NSAID if combination must be used

Interference with Antiplatelet Effects of Aspirin

<table>
<thead>
<tr>
<th>NSAID/Coxib</th>
<th>Ibuprofen</th>
<th>Indomethacin</th>
<th>Naproxen</th>
<th>Tiaprofenic acid</th>
<th>Sulindac</th>
<th>Celecoxib</th>
</tr>
</thead>
</table>

PPI-Clopidogrel Interaction: Platelet Aggregation

<table>
<thead>
<tr>
<th>Mean Maximal Platelet Aggregation</th>
<th>Clopidogrel</th>
<th>Clopidogrel + PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>40.88</td>
<td>36.42</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>55.73</td>
<td>48.46</td>
</tr>
</tbody>
</table>

PPI-Clopidogrel Interaction: Clinical Consequences

Association between acid-reducing therapies and recurrent MI within 90 days after hospital discharge for acute MI

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Cases n/N</th>
<th>Controls n/N</th>
<th>Odds Ratio for Recurrent MI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI + Clopidogrel Recurrent MI (&lt;90 days)</td>
<td>194/734</td>
<td>424/2057</td>
<td>1.27 (1.03-1.57)</td>
</tr>
<tr>
<td>Current PPI</td>
<td>397/1344</td>
<td>158/1680</td>
<td>0.86 (0.63-1.19)</td>
</tr>
<tr>
<td>Remote PPI</td>
<td>177/1344</td>
<td>63/1680</td>
<td>0.81 (0.61-1.11)</td>
</tr>
<tr>
<td>PPI without Clopidogrel</td>
<td>426/2375</td>
<td>1280/17291</td>
<td>1.02 (0.70-1.47)</td>
</tr>
<tr>
<td>HRA</td>
<td>377/1344</td>
<td>106/1680</td>
<td>0.94 (0.63-1.40)</td>
</tr>
</tbody>
</table>

Risk Reduction and Cardiovascular Implications: What the Experts Say
Balancing GI and Cardiovascular Risks of NSAID Therapy

<table>
<thead>
<tr>
<th>Cardiovascular Risk</th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (no aspirin)</td>
<td>Nonselective NSAID alone</td>
<td>Nonselective NSAID + PPI/misoprostol</td>
<td>Coxib + PPI/misoprostol</td>
</tr>
<tr>
<td>High (aspirin)</td>
<td>Naproxen + PPI/misoprostol</td>
<td>Naproxen + PPI/misoprostol</td>
<td>Avoid NSAID or Coxib if possible</td>
</tr>
</tbody>
</table>

First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents

<table>
<thead>
<tr>
<th>Average GI Risk</th>
<th>High GI Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nonselective NSAID alone</td>
<td>• Nonselective NSAID + PPI/misoprostol or Coxib + PPI/misoprostol</td>
</tr>
<tr>
<td>• Naproxen (if not on aspirin)</td>
<td>• Naproxen + PPI/misoprostol (if on aspirin)</td>
</tr>
<tr>
<td>• Avoid NSAIDs if possible</td>
<td>• Avoid NSAIDs if possible</td>
</tr>
</tbody>
</table>

High GI risk was defined as age ≥70 years, prior upper GI event, and concomitant use of concomitant aspirin, corticosteroids, or anticoagulants

High cardiovascular (CV) risk was defined as established coronary artery disease, any CV disease that required prophylactic low-dose aspirin, or an estimated 10-year CV risk >20%

Question

Which of the following is/are effective ways to reduce risk of NSAID associated ulcers?
1. Buffer the NSAID or give with an antacid
2. Give NSAID with a high-dose H2RA
3. Give NSAID with a PPI
4. 2 and 3 are effective
5. All are effective
6. Unsure

Question

A number of factors have been identified as increasing the risk for NSAID-associated ulcer complications. Which of the following has NOT been confirmed as a risk factor:
1. Age > 70 y
2. Past history of uncomplicated ulcer
3. H pylori infection
4. SSRI use
5. Clostridium difficile infection
6. None of the above – they are all risk factors
7. Unsure

Question

In a patient who takes aspirin for cardiovascular (CV) prophylaxis, which strategy is best to reduce the risk for an NSAID related upper gastrointestinal (UGI) complication?
1. Use celecoxib with a buffered aspirin
2. Use an NSAID and a high-dose H2RA
3. Use an NSAID and a PPI
4. Both 2 and 3
5. All are appropriate
6. Unsure

Question

The benefit of proton pump inhibitors (PPIs) in the prevention of NSAID induced gastric ulcers has been confirmed; however, PPIs have also been associated with the following risks:
1. Hip fracture
2. Community acquired pneumonia
3. Community acquired clostridium difficile
4. 1 and 2
5. All of the above
6. Unsure
Conclusion

- NSAIDs are used extensively for treatment of chronic pain, including that associated with OA and rheumatoid arthritis
- NSAIDs increase risk for ulcers, but this risk can be decreased by gastroprotective strategies, including H2RAs, PPIs, or misoprostol
- Research has confirmed that < 50% of patients at risk for NSAID induced ulcers are optimally managed with gastroprotective therapy. Fixed-dose combinations of NSAIDs and gastroprotective agents may theoretically improve adherence and decrease ulcer risk
- NSAID/coxib treatment may increase risk for cardiovascular events, and this risk should influence treatment decisions