NSAIDs: Clinical Use

Lee S. Simon, MD
Principal, SDG LLC
Consulting

- Anthera
- Affinergy
- Astrazeneca
- Abraxxis
- Alpha Rx
- NuvoResearch
- Pfizer
- Novartis
- PLx Pharma
- Hisamatsu
- Dr Reddys
- Biosense
- Avanir
- Cerimon
- Leerink Swann
- Alimera
- Nomura
- Luxor
- Paraexel
- Horizon Pharma
- Bayer
- Combinatoryx/Zalicus
- Rigel
- Chelsea
- Regeneron
- Genelabs
- Asahi
- Solace
- White Mountain Pharma
- Takeda
- Abbott
- Omeros
- Jazz
- Teva
- Zydus
- Proprius
- Savient
- Alder
- ProStrakan
- Chemocentryx
- Purdue
- EMD Serono
- Altea
- Calosyn
- Transpharma
- Phosphagenics
- Bone Medical
- Shire
- Lux
- Nicox
- Horizon
- Neos
- Logical Therapeutics
- Baxter
- Phosphagenics
Topics:
- Review status of NSAIDs
- Review efficacy
- Review safety
  - GI
  - Renal and hypertension
  - CV risk
- Review use of topical NSAIDs
Interesting Times

- Pre 1990’s Generally Available NSAIDs
- 1990s broad evidence of the GI, HBP, and renal risks of NSAIDs
  - Leads to increased use of opioids
- 1999/2000 culmination of the development of COX-2 selective drugs with regulatory approvals
  - Leads to decreased use of opioids
  - Increased use of NSAIDs particularly the new COX-2 selective drugs
- Under treatment of pain leading to pain as the 5th vital sign
- 2003-2008 CV risk issues are better defined targeting COX-2 selective inhibitors; noting the risk to all NSAIDs to a greater or lesser degree
  - Decrease use of NSAIDs, increase use of opioids
- Now: the Opioid crisis
  - And?
NSAID Use

Total US dispensed NSAID scripts

Dispensed scripts (millions)

- NS NSAIDs
- Coxibs

1999: 70.6, 22.4
2000: 61.4, 45.5
2001: 58.7, 52.5
2002: 58.0, 53.3
2003: 57.6, 53.9
2004: 60.8, 50.6
2005: 73.8, 16.0
2006*: 70.0, 13.0

IMS Health, IMS National Sales Perspectives™, 2/2006
*Wolters Kluwer Source® Pharmaceutical Audit Suite PHAST Prescription Monthly
Nearly 1 in 4 arthritis patients have heart disease

Research indicates that long-term use of high doses\(^*\) of ibuprofen may increase cardiovascular risk.\(^2\)

\(^*\)2400 mg/day for 4 weeks

TYLENOL\(^\text{®}\) is safe when used as directed and is as effective as Rx or OTC ibuprofen for OA of the knee.\(^3\)

REFERENCES:
ACTA Cross-over Clinical Trial
WOMAC Joint Pain

ACTA Cross-over Clinical Trial
Improvement in SF-36 Bodily Pain Score

PACES: WOMAC and Preference of Celecoxib vs Acetaminophen

**WOMAC Score**

<table>
<thead>
<tr>
<th>Period I</th>
<th>Period II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Celecoxib 200 mg QD</td>
</tr>
<tr>
<td>N = 182</td>
<td>N = 189</td>
</tr>
</tbody>
</table>

**Patient Preference**

- *P=0.002
- Prefer celecoxib
- Prefer acetaminophen
- No preference

**Change from Baseline (SE)**

- Placebo
- Celecoxib 200 mg QD
- Acetaminophen 1000 mg QID

- *Celecoxib vs acetaminophen: P<0.01
- †Celecoxib vs acetaminophen: P<0.001
- ‡Celecoxib vs placebo: P<0.001
- $Acetaminophen vs placebo: P<0.05

PACES = Patient Preference for Placebo, Acetaminophen or Celecoxib Efficacy Studies

WOMAC = Western Ontario McMaster Osteoarthritis Index

Demonstrated Pain Relief At Low Doses\textsuperscript{1}

Secondary Efficacy Endpoint: Average Pain Intensity Over 48 Hours

Percentage Mean Change From Baseline at Week 12 for WOMAC Subscales

Reference: Data on file, Iroko Pharmaceuticals
Benefits vs Risks of NSAIDs

Dilemma of balancing need for pain relief and gastrointestinal (GI) and CV risk benefit vs harm with varying patient characteristics and comorbidities

- Real patients need treatment, real patients are complex
- Data driven decisions

Need to balance patient characteristics and comorbidities for treatment of pain and inflammation

- Hypercholesterolemia
- GI ulcer/bleed
- Hypertension
- Elderly
- Cerebrovascular disease (CVD)
- Coronary heart disease (CHD)
- Diabetes
- Smokers
- Renal dysfunction
Current NSAID Label

**Cardiovascular Risk**
- NSAIDs 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. (See WARNINGS and CLINICAL TRIALS).

- TRADENAME is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

**Gastrointestinal Risk**
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See WARNINGS).
What Do We Know?

- There is clear evidence of improved GI safety in all patients who use COX-2 selective inhibitors as compared to non selective NSAIDs.
- This improved safety profile becomes important in patients who are at increased risk for a GI complication or who are frail and could not sustain an important GI insult.
- Otherwise healthy people who take daily NSAIDs at anti-inflammatory doses risk for a major GI complication requiring hospitalization is 1/1000 per year but in patients with 4 risk factors that rate rises to 18/100 per year.
Peptic Ulcer Complications
Effect of Individual NSAIDs
Relative Risk Current Use vs Nonuse

Risk of UGI Bleeding With Duration of NSAID Use

Increased risk appears at start of therapy and is maintained during use.

## OR of Subjects Taking Analgesics Who Develop UGI Bleeding*

<table>
<thead>
<tr>
<th>Analgesic (Prescription and OTC)</th>
<th>% Cases (n=627)</th>
<th>% Controls (n=590)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>27</td>
<td>12</td>
<td>2.7</td>
<td>1.9-3.8</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>10.1</td>
<td>5.8</td>
<td>2.4</td>
<td>1.5-3.9</td>
</tr>
<tr>
<td>APAP</td>
<td>4.5</td>
<td>6.3</td>
<td>0.9</td>
<td>0.5-1.6</td>
</tr>
<tr>
<td>Total OTC NSAIDs</td>
<td>36.2</td>
<td>17.5</td>
<td>3</td>
<td>2.2-4.1</td>
</tr>
<tr>
<td>Rx NS-NSAIDs</td>
<td>9.3</td>
<td>5.9</td>
<td>2.1</td>
<td>1.2-3.4</td>
</tr>
<tr>
<td>Total NSAIDs</td>
<td>42.9</td>
<td>22</td>
<td>3.1</td>
<td>2.3-4.1</td>
</tr>
</tbody>
</table>

*Analysis involved subjects with upper and lower GI bleeding.

GI Risks of Nonselective (ns)-NSAIDs

- Quantitative assessment of safety data from randomized, controlled clinical trials, observational studies, case-control studies, and case series

- With at least 2 months of NSAID or ASA treatment:
  - 1 in 5 patients will have endoscopic ulcer
  - 1 in 70 patients will have a symptomatic ulcer
  - 1 in 150 patients will have a bleeding ulcer
  - 1 in 1200 patients will die of a bleeding ulcer

Risk Factors for Adverse GI Events Induced by NSAIDs

- Factors that are associated with a high risk of developing GI complications following NSAID therapy:
  - Age >65 y
  - Previous history of gastroduodenal ulcer, GI bleed, or gastroduodenal perforation with or without previous use of NSAIDs
  - Concomitant use of medications that increase the likelihood of GI adverse events (eg, steroids and anticoagulants)
  - Presence of serious comorbidity, such as CVD, renal or hepatic impairment, diabetes, and hypertension
  - Requirement for the prolonged use of maximum recommended doses of standard NSAIDs
EVIDENCE OF IMPROVED GI OUTCOMES WITH COX 2 SELECTIVE INHIBITORS
Time to Gastroduodenal Ulcer, Bleeding, Perforation, or Obstruction (ITT cohort)

- Celecoxib 400 mg bid
- Ibuprofen 800 mgs TID
- Diclofenac 75 mg BID

Log rank P-values:
- Celecoxib vs NSAIDs 0.040
- Celecoxib vs Diclofenac 0.296
- Celecoxib vs Ibuprofen 0.017

GI Bleeding Data: RCT Cox 2 Selective Inhibitor vs nsNSAID plus PPI

GI Bleeding PROBE Trial: Cox 2 Selective Inhibitor vs. Any nsNSAID

Cryer et al GI-REASONS: A Novel 6-Month, Prospective, Randomized, Open-Label, Blinded Endpoint (PROBE) Trial Am Jour Gastro  2013
DRUGS WHICH PREVENT OR TREAT NSAID-INDUCED GI DAMAGE
PPI Prevention of NSAID Ulcers:
High Risk Population: Hx of GU and HP negative
Lansoprazole 15 or 30mg qd vs. Misoprostol 200µg qid in DB-RCT

12-wk ulcer cumulative incidence

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>133</td>
<td>60</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>134</td>
<td>40</td>
</tr>
<tr>
<td>Lanso 30</td>
<td>132</td>
<td>20</td>
</tr>
<tr>
<td>Lanso 15</td>
<td>136</td>
<td>10</td>
</tr>
</tbody>
</table>

*p < 0.001 vs. placebo  Graham et al. Arch Int Med 2002;162:169
PPI Outcomes Prevention: Recurrent Ulcer Bleeding in High-Risk Patients
Outcome Studies Correlate with Endoscopic Studies

<table>
<thead>
<tr>
<th></th>
<th>Non-ASA NSAIDs</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>18.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>4.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recurrent Ulcer Clinical Events:
6-Month Double-Blind Trial of Coxib vs. NSAID + PPI

Recurrent ulcer events

RR = 0.58 (0.17 - 1.93)

Events = 8 overt bleeding, 2 Hgb ↓ ≥ 2 g/dl, 1 severe pain
Celecoxib 200mg qd vs. Naproxen 250mg tid + Lansoprazole 30mg qd in
patients with NSAID-associated ulcer bleeding
Combination Drugs: Ibu + H2 Blocker

Combination Drugs: Nap + PPI

Figure Clinical efficacy 1: Incidence of gastric ulcers in pivotal studies (pooled data, ITT population)

Public Assessment Report of the Medicines Evaluation Board in the Netherlands;
EU Procedure Number: NL/H/1848/001/DC Registration Number in the Netherlands: RVG 106235 17 January 2011
UGI Bleeding Risk Related to ASA Prophylaxis*

<table>
<thead>
<tr>
<th>ASA (daily dose)</th>
<th>Odds Ratio</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg</td>
<td>2.3</td>
<td>(1.2-4.4)</td>
</tr>
<tr>
<td>150 mg</td>
<td>3.2</td>
<td>(1.7-6.5)</td>
</tr>
<tr>
<td>300 mg</td>
<td>3.9</td>
<td>(2.5-6.3)</td>
</tr>
</tbody>
</table>

*Case-controlled study of 1121 patients with GU/DU bleeds ≥5 days a week for ≥1 month. Weil et al. BMJ. 1995;310:827-830.
Incidence of Gastroduodenal Ulcers in Healthy Elderly Subjects: Concomitant ASA Use—1 Week Study

- **Celecoxib 200 mg qd + ASA 325 mg qd (n=182):**
  - Patients With Gastroduodenal Ulcers (%): 18.7
  - RR = 0.63
  - 95% CI (0.44-0.92)
  - P = 0.016

- **Naproxen 500 bid + ASA 325 mg qd (n=176):**
  - Patients With Gastroduodenal Ulcers (%): 27.3
  - RR = 3.68
  - 95% CI (1.79-7.60)
  - P < 0.001

- **Placebo + ASA 325 mg qd (n=92):**
  - Patients With Gastroduodenal Ulcers (%): 7.6
  - RR = 2.62
  - 95% CI (1.19-5.78)
  - P = 0.008

464 patients, aged 50 to 75 years.
Hospitalization for UGI Bleeding or Perforation—Use of NSAIDs, COX-2 Selective Inhibitors, and ASA

Retrospective cohort study in Quebec, Canada, government health insurance databases
April 1999 to December 2002
Elderly users of COX-2 inhibitors or NSAIDs
Total of 791,696 prescriptions
Cox proportional regression analysis

<table>
<thead>
<tr>
<th></th>
<th>NSAIDs Only</th>
<th>NSAIDs + ASA</th>
<th>COX-2 Only</th>
<th>COX-2 + ASA</th>
<th>COX-2 + ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference</td>
<td>151,553</td>
<td>151,553</td>
<td>515,773</td>
<td>515,773</td>
</tr>
<tr>
<td>NSAIDs Only</td>
<td>1</td>
<td>1</td>
<td>0.62</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>NSAIDs + ASA</td>
<td>1.61</td>
<td>1</td>
<td>1.61</td>
<td>1.61</td>
<td>1.61</td>
</tr>
<tr>
<td>COX-2 Only</td>
<td>0.53</td>
<td>0.53</td>
<td>0.53</td>
<td>0.53</td>
<td>0.53</td>
</tr>
<tr>
<td>COX-2 + ASA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Recommendations Regarding NSAID Induced GI Damage in Those Patients at Risk

Determine risk factors for the patient and if at risk consider

- Concomitant treatment with a PPI or H2 Blocker; unlikely that Misoprostol will be tolerated
- Choice of a combination product
  - Naproxen plus PPI
  - Ibuprofen plus Famotidine
  - Diclofenac plus Misoprostol
- Cox 2 Selective inhibitor
- Don’t use a NSAID
What Do We Know?

- All NSAIDs seem to have a small risk for cardiovascular thromboembolic events
  - The drugs that inhibit COX-2 activity all have different PK/PD, and have different physicochemical properties, half life

- The effects of the NSAIDs on the cyclooxygenase enzymes, hypertension, renal function, inflammation (such as CRP) as well as a possible effect on NO and may effect thromboembolic risk
What Do We Know?

- The risk for renal adverse events is similar across all NSAIDs including the selective COX-2 inhibitors with some having more of a dose response than others.
  - The risk for inducing an abnormal creatinine clearance is similar among all of these drugs with patients who are dehydrated due to any cause at increased risk.
  - No patient should be exposed to a NSAID of any type (except perhaps non acetylated salicylates if their CR CL is < 30 cc/min).
The COX-2 Hypothesis

Arachidonic acid

COX-1 constitutive
- GI cytoprotection
- Platelet aggregation
- Renal function (blood flow)

COX-2 inducible
- Inflammation
  - Fever
  - Pain
  - Headache
- Carcinogenesis
Hypertension Risk, CHF and COX-2 Selective Inhibition
Hypertension Incidence With Celecoxib

CRESCENT Trial—Study Design

Day -10 to -7

Celecoxib 200 mg qd

Week 1

Rofecoxib 25 mg qd

Week 2

Naproxen 500 mg bid

Week 6

D/C NSAID/Analgesics

Week 12

Begin APAP 1000 mg tid

Stop APAP 1000 mg tid

Cuff BP

Ambulatory BP Monitoring

Arthritis Assessments

Adverse Events

Physical exam

Medical History

24-hr Systolic BP at Baseline and Week 6

00:00=Midnight.
ABPM initiated at 09:00 ± 2 hr; morning dose administered within 5 min of initiating ABPM.
CRESCEENT: 24-Hour Mean BP Change, 6 and 12 Weeks

Least Mean Square Change (mm Hg)

<table>
<thead>
<tr>
<th>Drug</th>
<th>6 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 mg qd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg bid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRESCENT: Ambulatory SBP Changes From Baseline after 6 Weeks of COX-2 Inhibitor Treatment

Imbalance may lead to prothrombotic state and, thus, to an increase in cardiovascular (CV) events.

Post-marketing Controlled Trials
Year Long GI Safety Outcome Studies With CV Outcomes as Secondary Assessments

Three separate year long comparative DB, RCT’s demonstrate:

- rofecoxib at 50 mgs q day has an increased incidence of acute MI as compared to naproxen 500 mgs BID
  - (VIGOR: Bombardier, NEJM 2000)

- celecoxib at 400 mgs BID was not different than diclofenac 75 mgs BID or Ibuprofen 800mgs TID
  - (Silverstein, CLASS, JAMA 2000)

- lumericoxib 400 mgs q day was no different than naproxen 500 mgs BID or ibuprofen 800 mgs TID
  - (Farkou, TARGET, Lancet, 2004)
Three Year Long Trials
Summary of Three-Year Long Studies

Four three year long studies evaluated CV and GI risk, three as secondary outcomes and one as primary design:

- **APPROVe**: rofecoxib 25 mgs vs placebo demonstrated statistical decrease in recurrent colonic polyps but more than two fold increased risk for CV outcome.

- **APC**: 200 mgs BID, 400 mgs BID celecoxib vs placebo and **preSAP**: 400 mgs q day vs placebo demonstrated statistical decrease in recurrent colonic polyps with only the 400 mgs BID with statistically important increase CV risk.

- **MEDAL**: etoricoxib 60, 90 mgs q day compared with diclofenac 75 mgs BID no difference in MI but increased rate of withdrawal due to CHF and uncontrolled elevated BP.

- Dose trend of ASA for increasing CV events (Baron et al)

- OTC naproxen worse than placebo for APTC and CHF combined outcome (ADAPT)
Meta-analyses of NDA Studies and Post-marketing Studies
## Meta-analysis of the “Means” of Randomized Trials

### Events/Person Years

<table>
<thead>
<tr>
<th>COX-2 Inhibitor</th>
<th>No. of Trials</th>
<th>Allocated COX-2 Inhibitor</th>
<th>Allocated Placebo</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>37</td>
<td>98/6638</td>
<td>72/6415</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>41</td>
<td>84/8976</td>
<td>29/4953</td>
<td></td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>17</td>
<td>7/753</td>
<td>2/414</td>
<td></td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>12</td>
<td>14/1375</td>
<td>6/584</td>
<td></td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>14</td>
<td>13/748</td>
<td>3/273</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>121</td>
<td>216/18,490</td>
<td>112/12,639</td>
<td>1.42 (1.13 to 1.78)</td>
</tr>
</tbody>
</table>

(1.2%/year) (0.9%/year)

Heterogeneity between 5 drugs: \( \chi^2 = 0.5, df = 4, P = 1.0 \)

### Meta-analysis of Randomized Trials (cont’d)

<table>
<thead>
<tr>
<th>COX-2 Inhibitor</th>
<th>No. of Trials</th>
<th>Allocated COX-2 Inhibitor</th>
<th>Allocated Placebo</th>
<th>Rate Ratio COX-2 Inhibitor: Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>37</td>
<td>54/6638</td>
<td>30/6415</td>
<td>1.86 (1.33 to 2.59) P=.0003</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>41</td>
<td>44/8976</td>
<td>9/4953</td>
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<tr>
<td>Etoricoxib</td>
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<td>2/753</td>
<td>0/414</td>
<td></td>
</tr>
<tr>
<td>Lumiracoxib</td>
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<td>5/1375</td>
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<td>1/273</td>
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<td>121</td>
<td>113/18,490</td>
<td>42/12,639</td>
<td>1.86 (1.33 to 2.59) P=.0003</td>
</tr>
</tbody>
</table>

(0.6%/year) (0.3%/year)

Heterogeneity between 5 drugs: $\chi^2=1.0$, $df=4$, $P=.9$
CV vs GI risk with Coxibs, Diclofenac, Ibuprofen, Naproxen

Coxib and traditional NSAID Trialists' (CNT) Collaboration: Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials The Lancet, Early Online Publication, 30 May 2013
doi:10.1016/S0140-6736(13)60900-9
Cohort Studies and Epidemiologic Evaluations
## Adjusted Relative Risk of AMI With Rofecoxib Compared With Celecoxib

<table>
<thead>
<tr>
<th>Time</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-30</td>
<td>1.43</td>
<td>1.12-1.83</td>
<td>.005</td>
</tr>
<tr>
<td>Days 31-90</td>
<td>1.46</td>
<td>1.14-1.861</td>
<td>.003</td>
</tr>
<tr>
<td>Days &gt;90</td>
<td>1.04</td>
<td>0.223-1.38</td>
<td>.8</td>
</tr>
</tbody>
</table>

Risk of AMI and SCD With Current Use of COX-2 Selective and NS-NSAIDs vs Remote NSAID Use

AMI=acute myocardial infarction; SCD=sudden cardiac death.
†Adjusted for age, gender, health plan region, medical history, smoking, and medication use.
Adapted from Graham et al. Published online January 25, 2005.
Medi-Cal: NSAIDs and Risk for AMI

Medi-Cal Population (>18 years) with Physician-diagnosed Arthritis (1999-2004)*

OR for AMI (95% CI)

<table>
<thead>
<tr>
<th>NSAID</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remote use</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.71 (1.35-2.17); P&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>1.41 (1.01-1.96); P&lt;0.04</td>
<td></td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1.37 (1.05-1.78); P&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.32 (1.22-1.42); P&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.11 (1.01-1.22); P&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.09 (1.02-1.15); P&lt;0.008</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.08 (0.95-1.22); P=0.22</td>
<td></td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>0.99 (0.72-1.37); P=0.97</td>
<td></td>
</tr>
<tr>
<td>Nabumetone</td>
<td>0.83 (0.60-1.14); P=0.26</td>
<td></td>
</tr>
</tbody>
</table>

*2,356,885 person-y of follow-up; 15,343 cases of AMI

## Risk for Cardiovascular Events With Various COX-2 Inhibitors and NSAIDs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Summary Relative Risk for Cardiovascular Event (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib, ≤25 mg</td>
<td>1.33 (1.00-1.79)</td>
</tr>
<tr>
<td>Rofecoxib, &gt;25 mg</td>
<td>2.19 (1.64-2.91)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.06 (0.91-1.23)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.40 (1.16-1.70)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.97 (0.87-1.07)</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>1.06 (0.70-1.59)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.07 (0.97-1.18)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>1.25 (1.00-1.55)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.30 (1.07-1.60)</td>
</tr>
</tbody>
</table>

*CI=confidence interval.
McGettigan et al. JAMA. 2006;296.
The WHI and Analgesics

- Women, aged 44 to 69 years, medication data biennially from 1990-2002, over 70,000 people enrolled
- 2041 major CV events were noted.
- Adjusting for risk factors: women who frequently used NSAIDs had a relative risk for a CV event of 1.44 (95% CI 1.27-1.65) compared with nonusers
- Frequent users of acetaminophen had a relative risk for a CV event of 1.35 (95% CI 1.14-1.59).
- Compared with nonusers, the relative risk for a CV event among women who used 15 or more tablets per week was 1.86 (95% CI 1.27-2.73) for NSAIDs and 1.68 (95% CI, 1.10-2.58) for acetaminophen.
- Elevated risk associated with frequent NSAID use was particularly evident among current smokers (relative risk 1.82, 95% CI 1.38-2.42) and was absent among never smokers.
- The investigators found that women taking NSAIDs or acetaminophen only occasionally—roughly 1 to 21 days per month—did not experience a significant increase in the risk of CV events

Use of Nonsteroidal Antiinflammatory Drugs. An Update for Clinicians. A Scientific Statement From the American Heart Association
Elliott M. Antman, Joel S. Bennett, Alan Daugherty, Curt Furberg, Harold Roberts and Kathryn A. Taubert
Circulation published online Feb 26, 2007;
DOI: 10.1161/CIRCULATIONAHA.106.181424
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org
Death and NSAIDs

Gislason et al Circulation 2006; 113: 2906-2913
Reinfarction and NSAIDs

Figure 2. Hazard ratios for the risk of readmission for MI associated with the use of selective COX-2 inhibitors and nonselective NSAIDs after acute myocardial infarction. Adjusted for age, sex, year of MI, concomitant medical treatment, socioeconomic status, and comorbidity. Reference group: no use of COX-2 inhibitors or NSAIDs. Error bars indicate 95% CIs.

Gislason et al Circulation 2006; 113: 2906-2913
Time to MI/coronary death in cohort with recent hospitalization for serious CVD

Conclusions Regarding NSAIDs and Heart Risk

- Aspirin is the only “NSAID” that conclusively conveys primary and secondary prevention (risk reduction ~25%)
- There is no evidence that nonselective NSAIDs are cardioprotective; naproxen has been shown to have less risk than others while diclofenac and ibuprofen high dose have risk approaching that with rofecoxib
- Ibuprofen and naproxen have been shown to interfere with the anti-platelet effects of aspirin and could lead to potential harm
- The role of rise in mean blood pressure, effects on NO, prostacyclin are all likely to play a role
- Mechanistic, RCT, and epidemiological data support that the CV risk of the COX-2 selective inhibitors and ns NSAIDs appear to be similar
Mean Inhibition of Platelet Aggregation on Ibuprofen Plus ASA

- Ibuprofen before ASA
- ASA before ibuprofen

Inhibition of Clinical Benefits of ASA on First MI by NS-NSAIDs

Adjusted RR of MI (95% CI) by Time-Varying NSAID Use Separately for Each Cohort

ASA Cohort

ASA
325 mg qod + no NSAIDs (reference)

ASA + NSAIDs
1-59 d/y

ASA + NSAIDs
≥60 d/y

Adjusted for baseline information on age (5-year increments), body mass index, exercise, history of arthritis, smoking status, and randomized β-carotene status.

TOPICAL NSAIDS
Topical NSAID Administration: Pharmacokinetics

- Peak plasma levels <10% vs oral (range 0.1%-8.0%)
  - Below therapeutic oral NSAID drug levels
  - Total systemic absorption 3%-5% oral route
  - Time until \( C_{\text{max}} \) 2.2-23 hrs, 10x longer than oral

- Formulation can enhance systemic absorption as much as 5-fold

- Steady state within 2-5 days of repeated application

Meta-Analysis: Topical NSAIDs in Acute Pain

- 26 double-blind, placebo-controlled trials (2,853 pts)
  - Topical NSAIDs significantly more effective (50% ↓ pain) vs placebo at wk 1 in 19/26 trials
    - Relative benefit: 1.6
    - NNT: 3.8
    - Mean placebo response rate: 39% (8%-75%)
    - Mean topical NSAID response rate: 65% (41%-100%)
  - 3 trials: topical vs oral NSAID (433 pts)
    - No difference in efficacy (57% vs 62%)
  - Local AEs (4%), systemic AEs (2.5%), withdrawals (0.8%)
    - No difference between topical NSAID & placebo
  - Different application schedules, concentration, & formulations

Meta-Analysis: Topical NSAIDs in Chronic Musculoskeletal Pain

- 14 double-blind, placebo-controlled trials (1,502 pts)
  - Topical NSAID significantly more effective (50% ↓ pain) vs placebo at wk 2
    - Relative benefit: 1.9
    - NNT: 4.6
    - Mean placebo response rate: 26% (7%-78%)
    - Mean topical NSAID response rate: 48% (2%-90%)

- 18 placebo-controlled trials (2,032 pts) provided AE information
  - No significant difference for local AEs (6%), systemic AEs (3%), or withdrawal due to AE (1%)

Meta-Analysis: Topical NSAIDs in Chronic Musculoskeletal Pain

- 3 trials compared topical vs oral NSAID (764 pts)
  - No difference in efficacy (37%)

- 8 active controlled trials (1,461 pts) provided AE information
  - Local AEs more common with topical (8%) vs oral (3%)
  - Systemic AEs & AE withdrawals did not differ between topical & oral
  - No study documented upper GI bleeding or symptomatic ulcers

Meta-analysis: Topical NSAIDs in Acute & Chronic Pain

- Both active & placebo treatments were rubbed on
  - Effect of rubbing equal in both groups
- Short duration studies do not capture long-term safety information
  - Information indicates that topical NSAIDs do not cause GI harm found with oral NSAIDs
  - Nor are they associated with increased renal failure
- Clinical trial evidence from long-terms studies necessary to fully elucidate role & safety of topical NSAIDs in management of chronic pain

Meta-Analysis: OA Pain

• However, another meta-analysis of RCTs comparing topical NSAIDs with placebo or oral NSAIDs in OA found
  – Topical NSAIDs superior to placebo only in first 2 weeks of treatment
• Effect sizes
  – Wk 1: 0.41
  – Wk 2: 0.40
  – No benefit observed over placebo in wks 3 & 4
  – Inferior to oral NSAIDs in wk 1 of treatment
  – Associated with more local side effects

Lin J, et al. BMJ. 2004;329:324; online first. Doi:10.1136/bmj.38159.639028.7c
Topical NSAIDs

• Topical diclofenac/DMSO approved 2009, 2013
  • Signs and symptoms of OA of the knee

• Methylsalicylate patch OTC, 2007
  • Minor arthritis, sprains, etc

• Diclofenac epolamine topical patch
  – Approved by US FDA in Jan 2007
    • Topical treatment of acute pain due to minor strains, sprains, & contusions

• Topical diclofenac sodium gel
  – Approved by US FDA in Oct 2007
  – Approved for pain of OA of hand and knee
  – Available in Europe
Primary endpoint: pain on movement (VAS score) during first 6 hr & at day 1, 3, & 7
  – Significant efficacy vs placebo from 4 hr until end day 7

All secondary endpoints significantly improved since day 3
  – Pain at rest
  – Pain on passive stretch
  – Pain on pressure
  – Pain on single foot leaning

Topical Diclofenac Epolamine Patch: Ankle Sprain (7-d)

Decrease in spontaneous pain

- Diclofenac patch
- Placebo patch


*P<.05
### Topical Diclofenac Epolamine Patch: Common AEs (Incidence ≥1%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N=564)</th>
<th>Diclofenac patch (N=572)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>44 (8%)</td>
<td>31 (5%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3 (&lt;1%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Burning</td>
<td>8 (1%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (3%)</td>
<td>22 (4%)</td>
</tr>
<tr>
<td><strong>GI disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (2%)</td>
<td>17 (3%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (&lt;1%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (1%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (2%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>8 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (&lt;1%)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>
Topical Diclofenac Sodium Gel: Efficacy

Efficacy in patients with knee OA: 12-wk, randomized, double-blind, vehicle controlled, trial

Mean change from baseline


*P<.05
Topical Diclofenac Sodium Gel: Safety

- **Short-term placebo-controlled trials (8-12 wks)**
  - AEs reported ≥1% patients
    - Application site reactions
      - Diclofenac gel: 7%
      - Placebo (vehicle): 2%
    - Discontinuation rate due to AEs
      - Diclofenac gel: 5%
      - Placebo (vehicle): 3%

- **Long-term open-label safety trial (up to 1 yr)**
  - Application site dermatitis: 11% patients
  - Discontinuation due to AEs: 12%
    - Most common cause discontinuation: application site dermatitis (6% patients)
### Topical Diclofenac 1.5% and 45.5% DMSO

**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TDido&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Placebo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>DMSO&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ODido&lt;sup&gt;b&lt;/sup&gt;</th>
<th>TDido+ODido&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P value</th>
<th>TDico vs. Placebo</th>
<th>TDico vs. DMSO</th>
<th>TDico vs. ODico</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>13.2 (3.4)</td>
<td>12.9 (3.3)</td>
<td>13.0 (3.2)</td>
<td>13.2 (3.0)</td>
<td>13.2 (3.4)</td>
<td>0.015</td>
<td>0.009</td>
<td>0.429</td>
<td></td>
</tr>
<tr>
<td>Change in score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-6.0 (4.5)</td>
<td>-4.7 (4.4)</td>
<td>-4.7 (4.3)</td>
<td>-6.4 (4.1)</td>
<td>-7.0 (4.8)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>WOMAC Physical Function</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>41.7 (12.8)</td>
<td>41.6 (11.7)</td>
<td>41.4 (11.4)</td>
<td>42.1 (12.0)</td>
<td>41.0 (11.2)</td>
<td>0.034</td>
<td>0.026</td>
<td>0.319</td>
<td></td>
</tr>
<tr>
<td>Change in score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-15.8 (15.1)</td>
<td>-12.3 (14.7)</td>
<td>-12.1 (14.6)</td>
<td>-17.5 (14.3)</td>
<td>-18.7 (14.0)</td>
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<td></td>
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<tr>
<td>POHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>0.956</td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>2.34 (1.02)</td>
<td>2.22 (1.03)</td>
<td>2.30 (1.14)</td>
<td>2.23 (1.12)</td>
<td>2.19 (1.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.95 (1.30)</td>
<td>-0.37 (1.04)</td>
<td>-0.65 (1.12)</td>
<td>-0.88 (1.31)</td>
<td>-0.95 (1.21)</td>
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<tr>
<td>PGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
<td>0.018</td>
<td>0.439</td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>3.12 (0.78)</td>
<td>3.04 (0.82)</td>
<td>3.13 (0.74)</td>
<td>3.04 (0.87)</td>
<td>3.08 (0.81)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change in score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-1.36 (1.19)</td>
<td>-1.01 (1.18)</td>
<td>-1.07 (1.10)</td>
<td>-1.42 (1.29)</td>
<td>-1.53 (1.27)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WOMAC Stiffness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
<td>0.035</td>
<td>0.596</td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>5.14 (1.63)</td>
<td>5.01 (1.70)</td>
<td>5.12 (1.61)</td>
<td>5.21 (1.72)</td>
<td>5.07 (1.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-1.93 (2.01)</td>
<td>-1.52 (2.05)</td>
<td>-1.48 (2.07)</td>
<td>-2.07 (2.02)</td>
<td>-2.30 (2.00)</td>
<td>0.112</td>
<td>0.035</td>
<td>0.596</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TDico, topical diclofenac solution plus oral placebo; Placebo, topical placebo plus oral placebo; DMSO, topical dimethyl sulfoxide-containing vehicle plus oral placebo; ODico, oral diclofenac plus topical placebo; TDico+ODico, topical diclofenac solution plus oral diclofenac; WOMAC, Western Ontario McMaster Universities LK3.1 Osteoarthritis Index; POHA, patient overall health assessment; PGA, patient global assessment of the study knee.

<sup>a</sup> Data are presented as mean (SD). Maximum score for pain, 20; physical function, 68; POHA and PGA, 4; stiffness, 8.

<sup>b</sup> The number of subjects (n) varied by efficacy parameter because individual subjects did not submit a full baseline assessment.

<sup>c</sup> Final score minus baseline score.

**Simon LS et al Pain 2009**
Topical vs Oral NSAID for Chronic Knee Pain

- RCT & patient preference study (12-24 mo follow-up)
  - Patients aged ≥50 yrs with knee pain
  - Intervention: advice to use topical or oral ibuprofen
    - Equivalent effect on knee pain over 1 yr
    - No differences in major AEs in RCT or study
    - In RCT, significant difference in secondary outcomes
      - Oral group had
        » More respiratory AEs
        » Less favorable change in serum creatinine
        » More patients change treatment for AEs
      - Topical group, more patients
        » Had worse pain at 3 months
        » Changed treatment because of ineffectiveness

Underwood M, et al. BMJ. Online first. doi:10.1136/bmj.39399.656331.25
IV NSAIDs

- Predominantly for acute use
- FDA indication: For mild to moderate pain or for concomitant use with opioids for moderate to severe pain
  - IV ibuprofen (Caldolor)
  - Diclofenac (Dyloject)
Drawing by S. Harris. Reprinted with permission of The New Yorker Magazine, Inc.