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JOURNAL CLUB

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BRINGING CLINICIANS TOGETHER TO DISCUSS CURRENT DRUG THERAPY

July 2018 • Vol. 15, No. 7

Checklist

BEFORE THE MEETING

- ☐ Print your copy of *PL Journal Club* LEADER NOTES, which will be emailed to you from *Pharmacist's Letter*
- ☐ Provide the LEADER NOTES to the *PL Journal Club* discussion leader
- ☐ Instruct your *PL Journal Club* participants to go to PharmacistsLetter.com to print their PARTICIPANT NOTES. Instruct them to search for the keyword "Journal Club" and tell them which month *PL Journal Club* you intend to use
- ☐ Provide instructions to your PARTICIPANTS and LEADERS about how to obtain PDFs of original articles from your local medical library (Adhere to institution's copyright policy)

DURING THE MEETING

- ☐ Pass out any needed *PL Journal Club* PARTICIPANT NOTES
- ☐ Discuss any recommendations that you have made, or new information that you have learned or observed based on the discussion at the last *PL Journal Club* meeting
- ☐ Proceed to use your *PL Journal Club* LEADER NOTES to facilitate the PL Journal Club discussion

AFTER THE MEETING

- ☐ Note the next *PL Journal Club* meeting date and time
- ☐ Determine who will serve as the next *PL Journal Club* discussion leader
- ☐ Go to PharmacistsLetter.com to learn about other topics in this month's issue, including charts, algorithms, toolboxes, etc, and listen to panelists and experts discuss our recommendations in *PL Voices*

LEADER NOTES

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The following succinct analysis appeared in *Pharmacist's Letter*. Based on vol. 34. No. 7

ASPIRIN

New data and talk of OTC label changes will reignite debate about whether NSAIDs reduce the CV protective effect of aspirin.

Many of us remember when FDA warned that ibuprofen may interact with aspirin. This is because aspirin binds to COX-1 to inhibit platelet aggregation...and nonselective NSAIDs can compete for the same receptor.

OTC ibuprofen labels even say it may decrease aspirin's CV benefit.

Now FDA will likely require a similar warning for OTC naproxen labels...due to a recent study suggesting naproxen may interfere with the antiplatelet effects of aspirin 81 mg/day.

Continue to recommend limiting NSAIDs in patients at high CV risk

But put this interaction in perspective.

Using a chronic NSAID with aspirin only leads to a small decrease in platelet inhibition. It doesn't seem to reduce aspirin's CV benefit.

If patients on low-dose aspirin need a chronic NSAID, don't be too concerned about the interaction. Emphasize adherence to aspirin instead.

But tell worried patients that taking nonenteric-coated aspirin about 30 minutes before the NSAID may let aspirin reach platelets first.

Don't suggest going to a higher aspirin dose or a different antiplatelet med (clopidogrel, etc). There's no evidence either approach leads to better CV outcomes...but may cause more bleeding.

Reassure patients that aspirin does not interact with PRN or topical NSAIDs...or with celecoxib, since it's COX-2 selective.

Suggest a PPI for patients who need aspirin and any chronic NSAID... since the combo increases GI bleeding risk, even with celecoxib.

Listen to *PL Voices* to hear us discuss this issue with a CV expert. And see our chart, *Managing NSAID Risks*, for more advice on safe use.

(For more on this topic, see Clinical Resource #340702 at PharmacistsLetter.com.)

Primary Reference – Reed GW, Abdallah MS, Shao M, et al. Effect of aspirin coadministration on the safety of celecoxib, naproxen, or ibuprofen. J Am Coll Cardiol 2018;71:1741-51.

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DISCUSSION QUESTIONS

OVERVIEW OF CURRENT THERAPY

1. **What is known about using a chronic NSAID in patients who need low-dose aspirin for cardiovascular prevention?**

- Aspirin inhibits platelet function by inhibiting platelet COX-1. Nonselective NSAIDs such as ibuprofen or naproxen compete with aspirin for this receptor. However, unlike aspirin, NSAIDs do not completely and persistently inhibit COX-1 irreversibly.
- Platelet function studies demonstrate that taking a nonselective NSAID regularly may interfere with aspirin's antiplatelet effect. However, some data suggest taking non-enteric coated aspirin about 30 minutes before the NSAID may allow aspirin to bind to platelet COX-1 before the NSAID. In addition, occasional NSAID use is not expected to interfere with chronic aspirin therapy.
- Most evidence for this interaction comes from studies with ibuprofen and naproxen, but the interaction is also likely with other nonselective NSAIDs. Celecoxib is COX-2 selective and is not expected to interfere with aspirin.
- Of note, studies of this interaction have been with non-enteric coated aspirin. Therefore, little is known about using NSAIDs chronically in patients taking enteric-coated aspirin for CV prevention.
- No randomized studies have prospectively tested the clinical impact of this interaction. However, data from observational studies seem to suggest this interaction doesn't reduce aspirin's CV benefit.
- Using chronic low-dose aspirin or an NSAID regularly increases the risk of GI bleeding via direct irritation of GI mucosa and inhibition of COX-1. Celecoxib may cause less GI bleeding due to its COX-2 selectivity. However, celecoxib may not be safer than nonselective NSAIDs past six months of use, or in patients taking low-dose aspirin.

ANALYSIS OF NEW STUDY

2. **What type of study was this? How were the patients selected for inclusion?**

- This was a *post hoc* analysis of the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen) trial, aiming to study the safety impact of aspirin use in patients on celecoxib, naproxen, or ibuprofen.
- PRECISION was a randomized, multicenter, double-blind trial that primarily aimed to test whether the CV safety of celecoxib is noninferior to ibuprofen or naproxen.
- Patients were included in PRECISION if they were 18 years or older, required daily treatment with an NSAID for osteoarthritis (OA) or rheumatoid arthritis (RA) pain, and were at increased CV risk. Patients were considered at high CV risk if any three of the following criteria were present: age > 55 years, hypertension, dyslipidemia, family history of premature CV disease, current smoker, left ventricular hypertrophy, documented ankle brachial index less than 0.9, microalbuminuria, or waist hip ratio of 0.9 or above.
- Patients were excluded from PRECISION if they had BP above 140/90 mmHg; severe heart failure, atrial fibrillation or other serious arrhythmia; were being treated with more

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than 325 mg/day of aspirin or warfarin; had moderate or severe liver or kidney disease; or were at high risk of bleeding.

3. How were the study groups defined?

- Patients were randomized on a 1:1:1 basis to receive celecoxib 100 mg BID, ibuprofen 600 mg TID, or naproxen 375 mg BID. Patients in each group received matching placebo.
- The dose of ibuprofen or naproxen could be increased to 800 mg TID or 500 mg BID, respectively, if needed. However, the dose of celecoxib could only be increased to 200 mg BID in patients with RA.
- All patients were given esomeprazole 20 to 40 mg daily for GI prophylaxis. Randomization was stratified based on the use of aspirin at baseline.

4. How were the outcomes evaluated?

- The primary endpoint of this *post hoc* analysis was the composite of any safety event, defined as the first occurrence of any major adverse cardiovascular event (MACE), noncardiovascular death, clinically significant GI event, iron-deficiency anemia of GI origin, or serious renal event.
- Secondary endpoints were individual components of the composite outcome.
- Patients were followed for a minimum of 18 months and a maximum of 43 months.
- Four different analyses were performed: aspirin use versus no aspirin use with either of the NSAIDs; aspirin use versus no aspirin use with celecoxib, naproxen, or ibuprofen each analyzed separately; each NSAID analyzed separately in patients not taking aspirin; and each NSAID analyzed separately in patients taking aspirin.
- Outcomes were analyzed via the modified intention-to-treat method that included all patients confirmed to be taking the study drug at follow-up. Only patients with confirmed data on aspirin use or non-use were included in the analysis.
- Missing data were imputed with the use of statistical software.
- Student's *t*-tests or chi-square tests were used to compare differences between aspirin and non-aspirin groups at baseline.
- Outcome data were analyzed via the Cox proportional-hazards model to provide hazard ratios (HR) and confidence intervals (CI). A p-value of < 0.05 was considered significant.
- Kaplan-Meier curves were also created to compare outcomes among the NSAIDs in the aspirin and non-aspirin groups.
- Adjustment for differences between aspirin users and non-users was performed with propensity scores.
- Sensitivity analysis was performed that evaluated outcomes based on the presence or absence of coronary artery disease (CAD).

5. What were the outcomes of this trial?

- PRECISION included 24,081 patients. However, the current *post hoc* analysis included 23,953 patients since data on aspirin use/non-use was missing for 128 patients.
- Of these patients, 8,030 were randomized to celecoxib, 7,933 to naproxen, and 7,990 to ibuprofen.

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- Aspirin was used by 11,108 of these patients. Of the aspirin users, 3,683 were randomized to celecoxib, 3,640 to naproxen, and 3,695 to ibuprofen.
- As expected, there were many baseline differences between aspirin users and non-users. Patients taking aspirin were older and more likely to be male than patients not taking aspirin. In addition, aspirin users were more likely to have established coronary artery disease, diabetes, hypertension, or dyslipidemia.
- Conversely, non-aspirin users were more likely to be smokers and less likely to be taking a statin than aspirin users.
- However, baseline characteristics were balanced after propensity score adjustment.
- Results of aspirin or no aspirin plus an NSAID
    - The composite safety endpoint was similar among NSAID users who were or were not taking aspirin when data were pooled for use of either celecoxib, naproxen, or ibuprofen.
    - When data were analyzed for each NSAID separately, use of ibuprofen or naproxen did not increase the risk of the composite safety endpoint for patients who were taking aspirin versus those who were not taking aspirin.
    - However, aspirin use with celecoxib resulted in a higher risk of the composite safety endpoint versus use of celecoxib alone (2.0% vs 1.0%; HR 1.44; 95% CI 1.13 to 1.82; p=0.003; number needed to harm [NNH] 100). This was due to a higher risk of MACE with celecoxib plus aspirin versus celecoxib alone (1.4% vs 0.7%; HR 1.51; 95% CI 1.14 to 2.01; p=0.004; NNH 143).
- Results of celecoxib, naproxen, or ibuprofen withOUT aspirin
    - There was a higher risk of the composite safety endpoint with naproxen or ibuprofen versus celecoxib (naproxen vs celecoxib 4.5% vs 3.0%; HR 1.52; 95% CI 1.22 to 1.90; p<0.001; NNH 67; ibuprofen vs celecoxib 5.0% vs 3.0%; HR 1.81; 95% CI 1.46 to 2.26; p<0.001; NNH 50).
    - These differences were primarily due to a higher risk of GI events with naproxen or ibuprofen versus celecoxib (naproxen vs celecoxib 1.3% vs 0.5%; HR 2.60; 95% CI 1.59 to 4.27; p<0.001; NNH 125; ibuprofen vs celecoxib 1.5% vs 0.5%; HR 3.2; 95% CI 1.97 to 5.22; p< 0.001; NNH 100).
    - In addition, MACE events were slightly more frequent with ibuprofen versus celecoxib (2.5% vs 2.1%; HR 1.35; 95% CI 1.02 to 1.78; p=0.039; NNH 250), and renal events were slightly more frequent with naproxen versus celecoxib (0.8% vs 0.4%; HR 2.09; 95% CI 1.10 to 3.96; p=0.024; NNH 250).
- Results of celecoxib, naproxen, or ibuprofen with aspirin
    - Use of ibuprofen with aspirin increased the risk of the composite safety endpoint compared to the use of celecoxib with aspirin (7.1% vs 6.0%; HR 1.27; 95% CI 1.06 to 1.51; p=0.01; NNH 91). This difference was largely due to the increased risk of GI events and renal events with ibuprofen plus aspirin versus celecoxib plus aspirin (GI events, 1.4% vs 0.9%; HR 1.71; 95% CI 1.10 to 2.67; p=0.017; NNH 200; renal events, 1.2% vs 0.6%; HR 2.01; 95% CI 1.23 to 3.30; p=0.005; NNH 167).
    - Overall, the risk of the composite safety endpoint was similar between patients who used naproxen plus aspirin or celecoxib plus aspirin. However, the risk of GI events was higher with naproxen plus aspirin versus celecoxib plus aspirin (1.6% vs 0.9%; HR 1.91; 95% CI 1.24 to 2.94; p=0.003; NNH 143).

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  - Of note, the risk of MACE did not differ among celecoxib, naproxen, or ibuprofen in patients on aspirin.
- Sensitivity analysis of patients with and without CAD revealed no significant impact of CAD on study results.
- Only 304 patients discontinued aspirin after study randomization, and 964 patients who were not on aspirin at randomization started it during the study. Study results were not impacted when data from these patients were excluded.

6. What were the strengths and weaknesses of this study?

- This *post hoc* analysis is from a large, prospective, randomized trial and suggests celecoxib has a better safety profile than ibuprofen or naproxen in patients who don't take aspirin, but that the addition of aspirin decreases the safety benefit of celecoxib. In addition, this study indirectly suggests chronic use of ibuprofen or naproxen doesn't seem to reduce aspirin's CV benefit. However, the limitations of results from a *post hoc* analysis, or analysis of data following primary study completion, must be considered.
- *Post hoc* analyses are particularly subject to type 1 error (finding a significant difference in outcomes due to chance). As the number of statistical analyses increases, it becomes more likely that a significant result will be found. For example, if a p-value of 0.05 is considered statistically significant, one in every 20 significant findings is likely due to chance. In general, results of *post hoc* analyses should be considered exploratory or hypothesis generating.
- Authors used multivariate imputation to account for missing data, which limits bias due to missing results.
- Propensity scores were used to adjust for differences between aspirin users and non-users. This is a method to account for characteristics that make it more likely for patients to receive a certain treatment. For example, as expected, study patients who were taking aspirin were more likely to have established coronary artery disease than patients not on aspirin. However, baseline characteristics were balanced after propensity score adjustment.
- Although this study did not directly test whether using a chronic NSAID decreases the CV benefit of aspirin, it provides indirect evidence about the clinical significance of this interaction. Directly testing the clinical impact of this interaction would require a study of ibuprofen or naproxen plus aspirin versus aspirin alone, and a prospective study could take several years. In addition, such a study could be considered unethical since it would require withholding an NSAID long-term when one is indicated, or, conversely, giving a long-term NSAID when one is not indicated. Since celecoxib is COX-2 selective and isn't expected to interact with aspirin, this study provides indirect evidence that use of ibuprofen or naproxen doesn't impact the CV protective effect of aspirin (e.g., risk of MACE was similar among celecoxib, naproxen, or ibuprofen in patients on aspirin).
- Results of this study are not broadly generalizable to other NSAIDs since only celecoxib, ibuprofen, and naproxen were included in PRECISION. In addition, patients received moderate NSAID doses of ≈ celecoxib 200 mg/day, ibuprofen 2,000 mg/day, and naproxen 850 mg/day. Therefore, results could differ in patients on lower or higher NSAID doses.

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- It is also important to note that patients in PRECISION were given esomeprazole 20 to 40 mg daily for GI prophylaxis, regardless of the study arm. Therefore, study results should not be generalized to patients who aren't taking a PPI.
- When comparisons were made among NSAIDs, comparisons were made with celecoxib, but not between ibuprofen and naproxen.
- This study was funded by Pfizer, the manufacturer of branded celecoxib (*Celebrex*). Therefore, bias due to the financial interest of the study sponsor is possible.

7. Were the results expressed in terms we care about and can use?

- Yes. The outcomes were clinically relevant and what patients and caregivers are concerned about (CV safety and other treatment risks).

HOW SHOULD THE NEW FINDINGS CHANGE CURRENT THERAPY?

8. Do the results change your practice? How?

- Yes and no. In patients who aren't on low-dose aspirin, this *post hoc* analysis seems to be further evidence that moderate-dose celecoxib may have a more favorable safety profile versus naproxen or ibuprofen, mostly due to fewer GI events.
- However, when celecoxib is given with low-dose aspirin, the safety benefit of celecoxib versus naproxen or ibuprofen is reduced.
- In addition, this study provides indirect evidence that chronic use of ibuprofen or naproxen doesn't seem to reduce aspirin's CV protective benefit.
- Therefore, using celecoxib in patients who don't need low dose aspirin may lead to fewer GI events, but ibuprofen, naproxen, or celecoxib all seem to be options for patients who need low-dose aspirin. Also, a PPI should be considered in patients who need aspirin and any chronic NSAID to limit the risk of GI bleeding.

APPLY THE NEW FINDINGS TO THE FOLLOWING CASE

M.P. is a 56-year-old male in the clinic today for evaluation of low back pain. He has a past medical history of hypertension, type 2 diabetes, CAD with two cardiac stents placed four years ago, and opioid abuse for which he underwent treatment fifteen years ago. His current medications are lisinopril 20mg daily, aspirin 81mg daily, metformin 1,000mg BID, glipizide 5mg BID, atorvastatin 80mg daily, and acetaminophen 1,000 mg QID.

M.P. reports that his back pain has developed over the past two weeks, and that it is affecting his ability to do his job as a landscaper. He denies any trauma to his low back, but reports that his pain is worse with bending, twisting, and picking up heavy loads. He also denies neurologic symptoms such as bladder or bowel incontinence. He rates his pain a 7/10 when he's at work, and 4/10 when he gets up in the morning.

M.P. has been icing his back nightly, as well as taking acetaminophen around-the-clock, but feels that he's getting little relief.

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9. What should you suggest for M.P.'s acute back pain?

- Acute back pain often resolves in two to four weeks. Imaging is not usually necessary within the first six weeks of pain onset unless neurological deficits are present or serious underlying conditions are suspected (e.g., cancer, vertebral fracture, infection).
- Nonpharmacologic measures such as maintenance of normal physical activity along with applying heat/cold are recommended. However, caution patients not to apply directly to skin or for longer than 15 to 20 minutes at a time.
- Physical therapy, massage, or acupuncture may also be recommended, especially if pain persists beyond four weeks.
- NSAIDs are probably a better option than acetaminophen for low back pain, as evidence suggests acetaminophen is no more effective than placebo. However, acetaminophen may be worth a try for patients who should limit NSAID use, such as patients with chronic renal disease, heart failure, or high GI or CV risk.
- Around-the-clock (e.g., "scheduled") use of NSAIDs or acetaminophen may be more effective than "as needed" use.
- Current data do not support the use of topical NSAIDs for back pain.
- There is limited evidence that muscle relaxants are helpful for acute back pain, and should be limited to short-term use (e.g., about seven days) if they're tried.
- No evidence supports the use of opioids for acute low back pain.

You discuss that acute back pain often improves in two to four weeks. You also discuss that imaging isn't needed at this time, since M.P.'s symptoms don't suggest a serious underlying cause. You advise continuing nonpharmacologic measures, along with trying an NSAID such as naproxen 375 mg twice daily for two to four weeks since his scheduled acetaminophen hasn't provided much relief.

M.P. expresses concern about naproxen, since his primary care doctor told him NSAIDs increase his CV risk and interact with his aspirin.

10. What should you tell M.P. about using NSAIDs in patients who need aspirin for CV prevention?

- All NSAIDs except aspirin increase CV risk. Therefore, NSAIDs should be used at the lowest effective dose and for the shortest possible duration, especially in patients with CV disease or high CV risk.
- Regular use of an NSAID may lead to a small decrease in platelet inhibition in patients who need aspirin for CV prevention. However, this small decrease doesn't seem to reduce aspirin's CV protective benefit.
- If patients are concerned about the interaction, taking non-enteric coated aspirin about 30 minutes before the NSAID may let aspirin reach platelets first.
- Celecoxib isn't expected to interact with aspirin since it's COX-2 selective.
- Increasing the aspirin dose in patients who need to take an NSAID hasn't been shown to improve CV outcomes and may cause more bleeding.
- A PPI should be considered for patients who need to take aspirin and any NSAID regularly.

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Additional Pharmacist's Letter Resources available at PharmacistsLetter.com

Chart, The Truth About Aspirin. Pharmacist's Letter/Prescriber's Letter. April 2018.
PL Voices, Frequently Asked Questions About Aspirin. Pharmacist's Letter/Prescriber's Letter. April 2018.
PL Voices, Celecoxib and Cardiovascular Risk. Pharmacist's Letter/Prescriber's Letter. November 2017.
Chart, Treatment of Acute Low Back Pain. Pharmacist's Letter/Prescriber's Letter. April 2017.
PL Voices, Safety of NSAIDs in Patients with CV Risks. Pharmacist's Letter/Prescriber's Letter. January 2017.
Chart, Managing NSAID Risks. Pharmacist's Letter/Prescriber's Letter. December 2016.
Chart, Safety Comparison of NSAIDs. Pharmacist's Letter/Prescriber's Letter. December 2016.
PL Voices, Aspirin to Reduce Cardiovascular Risk After a GI Bleed. Pharmacist's Letter/Prescriber's Letter. November 2016.
Chart, Aspirin for Primary Prevention. Pharmacist's Letter/Prescriber's Letter. November 2016.
PL Voices, Duration of Dual Antiplatelet Therapy. Pharmacist's Letter/Prescriber's Letter. June 2016.
Chart, Dual Antiplatelet Therapy for Coronary Artery Disease. Pharmacist's Letter/Prescriber's Letter. June 2016.
Chart, Proton Pump Inhibitors: Appropriate Use and Safety Concerns. Pharmacist's Letter/Prescriber's Letter. March 2016.

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