Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Nissen SE, Yeomans ND, et al
Title	Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis
PMID	Pending
Citation	N Engl J Med 2016;
Other information if relevant	

Methods	
Aim of study	To compare the cardiovascular safety of three drugs for arthritis: celecoxib, naproxen , and ibuprofen
Design	Randomized noninferiority trial

Participants	
Population from which participants are drawn	Patients who require daily treatment with NSAIDS for either rheumatoid or osteoarthritis and are at increased risk of the development of cardiovascular disease (CVD)
Setting (location and type of facility)	926 centers in 13 countries
Age	63
Sex	15,445 women, 8636 men
Total number of participants for whom outcome data were reported	24,081

Inclusion criteria	1. High risk of coronary artery disease as defined by (a) history of stable angina, (b) history of MI, unstable angina, or coronary revascularization at least three months prior to randomization (c) angiographic stenosis >50% at catheterization 2. Occlusive disease of non-coronary arteries (TIA, ischemic stroke, carotid artery stenosis >50%, peripheral arterial disease, etc) 3. Diabetes mellitus 4. High risk of atherosclerosis as defined by at least three of these (a) age over 55, (b) history of hypertension, (c) history of dyslipidemia with LDL>150 mg/dL or HDL <40 mg/dL, (d) family history of CVD or stroke, (e) current smoking >15 cigarettes per day, (f) history of microalbuminuria or urine/protein creatinine ratio >2, (g) left ventricular hypertrophy, (h) documented ankle brachial index <0.9, (i) waist hip ratio >0.90
Exclusion criteria	Unstable angina, MI, CVA, CABG < 3 months from randomization Planned coronary, cerebrovascular, or peripheral revascularization Uncontrolled hypertension (SBP >140 mm Hg, DBP >90 mm Hg) Uncontrolled arrhythmia within 3 months of randomization NYHA class III-IV heart failure or ejection fraction ≤35% Acute joint trauma Aspirin >325 mg daily Oral corticosteroid, prednisone (or equivalent corticosteroid) >20 mg daily Warfarin GI ulceration within 60 days of randomization GI perforation, obstruction, or bleed within 6 months of randomization Inflammatory bowel disease, diverticulitis within 6 months of randomization AST, ALT, or BUN over twice the upper limit of normal Creatinine level over 1.7 mg/dL in men, 1.5 mg/dL in women Lithium therapy Malignancy within 5 years before randomization Other known, active, significant GI, hepatic, renal, or coagulation disorders Allergy to study medications Adequate symptom control with acetaminophen (not needing NSAIDs)

Other information if relevant	The study had a noninferiority design, with naproxen as the comparator for the other drugs The outcomes were calculated as hazard ratios (HR) for the time to occurrence of an undesirable event In the original design, a HR not exceeding 1.12 with an upper limit on the 97.5% confidence interval of no more than 1.33 were *both* required This means that if the HR of celecoxib was 1.10 times that of naproxen, and if the upper end of the confidence interval was 1.30, celecoxib was non-inferior to naproxen, and was considered equally safe However, if the HR was 1.10 but the upper limit of the confidence interval was 1.50, the non-inferiority criterion failed, and celecoxib was less safe than naproxen If the HR was 1.15 and the upper limit of the confidence interval was 1.30, the non-inferiority criterion also failed, and celecoxib was less safe than naproxen

Intervention Groups

Group 1	
Group name	Celecoxib
Number in group	8072
Description of intervention	Celecoxib 100 mg twice per day with placebo naproxen and placebo ibuprofen Starting dose of 100 mg bid could be increased to 200 mg bid in patients with rheumatoid arthritis, but not in patients with OA due to regulatory dosing restrictions
Duration of treatment period	Up to 10 years; mean treatment time was 20.8 months and mean followup time was 34.2 months
Co-interventions if reported	Esomeprazole 20 to 40 mg for gastric protection Low dose aspirin was permitted in patients already taking it
Additional information if relevant	Study was designed as double-blind, triple dummy, meaning that each patient received both the study drug and placebo drugs with the same appearance as the two other drugs to which it was being compared

Group 2	
Group name	Naproxen
Number in group	7969

Description of intervention	Naproxen at a starting dose of 375 mg bid Dose could be increased to 500 mg bid
Duration of treatment period	Up to 10 years; mean treatment time was 20.5 months and mean followup time was 34.2 months
Co-interventions if reported	Esomeprazole 20 to 40 mg for gastric protection Low dose aspirin was permitted in patients already taking it
Additional information if relevant	The study was designed as a non-inferiority study for cardiovascular safety, and naproxen was the primary comparator for celecoxib and ibuprofen Study was designed as double-blind, triple dummy, meaning that each patient received both the study drug and placebo drugs with the same appearance as the two other drugs to which it was being compared

Group 3	
Group name	Ibuprofen
Number in group	8040
Description of intervention	Ibuprofen at a starting dose of 600 mg tid Starting dose could be increased to 800 mg tid
Duration of treatment period	Up to 10 years; mean treatment time was 19.6 months and mean followup time was 33.8 months
Co-interventions if reported	Esomeprazole 20 to 40 mg for gastric protection Low dose aspirin was permitted in patients already taking it
Additional information if relevant	Study was designed as double-blind, triple dummy, meaning that each patient received both the study drug and placebo drugs with the same appearance as the two other drugs to which it was being compared

Primary outcome	
Outcome name and criteria for definition	The first occurrence of an adverse event that met the criteria of the Antiplatelet Trialists Collaboration (APTC): death from cardiovascular causes (myocardial infarction or stroke), nonfatal MI, or nonfatal stroke
Time points measured and/or reported	Analysis was event-driven; each time an event occurred, the time to that event was recorded for that patient for the main analysis

Differences between groups	The primary event occurred in2.3% of the celecoxib group, 2.5% of the naproxen group, and in 2.7% of the ibuprofen group The HR for celecoxib compared to naproxen was 0.93, and the upper end of the confidence interval was 1.13 The HR for celecoxib compared to ibuprofen was 0.85, and the upper end of the confidence interval was 1.04 The HR for ibuprofen compared with naproxen was 1.08 with the upper end of the confidence interval being 1.31 Celecoxib was thus noninferior to both naproxen and ibuprofen, and ibuprofen was also noninferior to naproxen
Additional information if relevant	During the ten years of followup, 68.8% of patients stopped taking the study drug and 27.4% discontinued followup 70.6% of ibuprofen patients discontinued study treatment, compared to 68.3% of naproxen and 67.5% of celecoxib patients

Secondary outcomes	
Outcome name and criteria for definition	Major adverse cardiovascular events, encompassing the APTC outcomes plus coronary revascularization or hospitalization for unstable angina plus transient ischemic attack
Time points measured	Same as for primary outcome
Differences between groups	The HR for celecoxib compared to naproxen was 0.97, and the upper end of the confidence interval was 1.12 The HR for celecoxib compared to ibuprofen was 0.87, and the upper end of the confidence interval was 1.01
Additional information if relevant	For death from any cause, the HR for celecoxib compared to naproxen was 0.80, and the upper end of the confidence interval was 1.00; the HR for celecoxib compared to ibuprofen was 0.92, and the upper end of the confidence interval was 1.17

Tertiary outcomes	
Outcome name and criteria for definition	GI and renal adverse outcomes
Time points measured and/or reported	Same as for primary outcome

Differences between groups	For serious GI events, the HR was significantly lower for celecoxib versus naproxen (HR 0.71, upper confidence interval 0.93) and for celecoxib versus ibuprofen (HR 0.65, upper confidence interval 0.85) For renal events, the HR was significantly lower for celecoxib versus ibuprofen (HR 0.61, upper confidence interval 0.85), but there was no significant difference between celecoxib versus naproxen
Additional information if relevant	Hospitalizations for hypertension were also measured, and celecoxib was noninferior to the other two drugs

Conclusions	
Key conclusions of study authors	- The PRECISION trial was designed in the aftermath of the withdrawal of rofecoxib for adverse cardiovascular events due to concerns that celecoxib might present a similar adverse cardiovascular risk profile - The primary outcome analysis provides statistically strong evidence that celecoxib does not present a greater cardiovascular risk profile than naproxen or ibuprofen - The data do not support the widely held belief that naproxen has better cardiovascular outcomes than other NSAIDs - All-cause mortality was lower with celecoxib than the other drugs, but this must be considered an exploratory result, since it was of borderline statistical significance and was not adjusted for multiple endpoint comparisons - The gastrointestinal safety profile of celecoxib was better than that of naproxen or ibuprofen, despite the fact that all patients were given a proton pump inhibitor (esomeprazole) - The large percentage of patients who discontinued treatment or dropped out of the trial may complicate the interpretation of the results, even though attrition was evenly distributed across treatment groups - The dose of celecoxib was limited to 200 mg daily for most patients due to regulatory requirements, but mean doses for the nonselective NSAIDs were also submaximal

Risk of bias assessment		
Domain	Risk of bias Low High Unclear	Comments

Random sequence generation *(selection bias)*	Low	
Allocation concealment *(selection bias)*	Low	
Blinding of participants and personnel *(performance bias)*	Low	
Blinding of outcome assessment *(detection bias)*	Low	
Incomplete outcome data *(attrition bias)*	Unclear	The high dropout rates were about even between groups, and are not excessively surprising for a ten year study, but the reasons for dropout (ineffectiveness in pain relief versus emergence of side effects) is undefined
Selective outcome reporting? *(reporting bias)*	Low	
Other bias		

Sponsorship if reported		
Study funding sources if reported	Pfizer	
Possible conflicts of interest for study authors	The disclosure documents show several authors have received personal fees from several pharmaceutical manufacturers	
Notes:		

Comments by DOWC staff

- Because of the size and scope of the study, some of the pertinent information is not in the text of the article itself
- For example, the list of exclusion criteria was published early in the study (Becker 2009)
- The main study protocol is in a separate document, but it does not have the definition of "renal events" which are referred to in the text
- The protocol tells the reader that the definition of renal events is in "Appendix 4", but the protocol does not have an Appendix 4; the final appendix is Appendix 2.2
- Interpretation of the study probably requires some familiarity with dosing of celecoxib and other drugs, especially since about 90% of the patients had osteoarthritis, for which there is a regulatory cap of 100 mg bid; only 10% of the patients had rheumatoid arthritis, for which the dose of celecoxib can be increased to 200 mg bid
- This may mean that the noninferiority of celecoxib for safety outcomes applies to a fairly low dose of 200 mg daily
- The events of interest were slow to accrue, and some of the details of the analysis of the protocol outcomes were adjusted during the study; this may be due to the population being at an elevated but not very high risk of a cardiovascular event (Table 1 shows more than 75% of patients designated "primary prevention" and therefore not having had a previous MI or other endpoint event
- The very large size of the study is clearly an important strength
- Adherence to the protocol would be tedious and cumbersome for the patients, since it is a "triple dummy" study, meaning that each patient had to take three different "medications" every day
- Because ibuprofen was to be taken three times per day and the other drugs twice per day, each patient would need to follow a fairly complicated schedule of drug-taking; the naproxen and the celecoxib patients would be taking a placebo ibuprofen three times per day for years, in addition to their assigned study drug and a placebo of the other NSAID twice per day

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	There is good evidence that celecoxib in a dose of 200 mg per day, administered over a long period, does not have a worse cardiovascular risk profile than naproxen at a dose of up to 1000 mg per day or ibuprofen at a dose of up to 2400 mg per day. There is good evidence that celecoxib has a more favorable safety profile than ibuprofen or naproxen with respect to serious gastrointestinal adverse events, and has a more favorable safety profile than ibuprofen with respect to renal adverse events. There is an absence of evidence concerning the relative safety of celecoxib at doses greater than 200 mg per day.
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Becker MC, Wang TH, et al. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. Am Heart J 2009; 157: 606-12.