

The Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs: Putting the Evidence in Perspective



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Learning Objectives

- Summarize the evidence and events that led the US Food and Drug Administration to require labeling changes regarding the safety of nonsteroidal anti-inflammatory drugs
- Compare the effects of nonsteroidal anti-inflammatory drugs and aspirin on platelets
- Summarize the evidence from clinical trials and registry studies regarding the cardiovascular risks associated with nonsteroidal anti-inflammatory drugs
- Describe the real-world implications of the results of the PRECISION trial

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INTRODUCTION

Pain and inflammation are common complaints experienced by all humans at some time during their lifetime. Among the wide variety of available analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for relief of acute and chronic pain. Data from the 2010 National Health Interview Survey suggest that approximately 43 million adults in the United States took aspirin at least 3 times per week for more than 3 months, while more than 29 million adults used an NSAID regularly.¹ Traditional NSAIDs (tNSAIDs), such as aspirin, ibuprofen, naproxen, and diclofenac, represent an effective, long-lasting option that may offer advantages over cyclooxygenase-2 (COX-2) selective NSAIDs, such as celecoxib. The use of NSAIDs is not without controversy, however.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) trial, published in 2000, was the first to raise concerns that NSAIDs (specifically, the COX-2 selective inhibitor rofecoxib) might be associated with a higher risk for cardiovascular (CV) events.² As discussed below, subsequent trials and meta-analyses have demonstrated a higher CV risk with use of not only COX-2 inhibitors (coxibs) but also certain tNSAIDs. These investigations have contributed to actions by the US Food and Drug Administration (FDA), most recently in July 2015, requiring strengthening of CV risk warnings on labels for all prescription and over-the-counter NSAIDs, despite evidence suggesting that differences in CV risk may exist among the NSAIDs.

To address unanswered questions regarding CV risk of coxibs versus tNSAIDs, the FDA mandated a comparison of celecoxib with 2 tNSAIDs, ibuprofen and naproxen.³ [Nissen 2016] As a result, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial was launched in 2006. PRECISION was a non-inferiority trial to assess CV outcomes with long-term use, with secondary endpoints such as gastrointestinal (GI), renal, and other outcomes. The results of the PRECISION trial, which were published in November 2016, are difficult to interpret due to its limitations and may have added further confusion regarding the CV safety of NSAIDs. Before discussing the PRECISION trial in detail and its implications for primary care providers, it is important to put the PRECISION trial in perspective by first highlighting the pharmacologic differences among the NSAIDs and their implications for CV safety followed by an historical review of key CV safety trials involving NSAIDs.

CLINICAL PHARMACOLOGY OF NSAIDs

NSAIDs reduce pain and inflammation through inhibition of the cyclooxygenase enzyme resulting in downstream inhibition of the production of thromboxane A₂ (TxA₂), prostacyclin, and other prostanoids.⁴ [Brune 2015] The analgesic and anti-inflammatory effects of NSAIDs largely result from inhibition of the COX-2 isoform at sites of inflammation, while gastrointestinal and other adverse events stem from inhibition of COX-1 isoforms, which are constitutive, present in most organs, and serve primarily a homeostatic function. For example, in the stomach, COX-1 mediates a cytoprotective effect, helping maintain mucosal integrity by increasing mucosal blood flow and increasing GI mucus and bicarbonate secretion^{4,5} [Whittle 2000] [Brune 2015/108/1] Inhibition of COX-1 is the mechanism primarily responsible for the gastric and duodenal ulceration and bleeding long associated with tNSAID use. In vascular endothelium, COX-2 is involved in the production of prostacyclin (PGI₂), which antagonizes platelet activation and produces vasodilation, whereas in platelets, COX-1 is responsible for the production of TxA₂, which causes platelet activation and vasoconstriction. It is thought that the selective inhibition of COX-2 by coxibs results in a relative reduction in endothelial PGI₂ synthesis, leaving platelet production of TxA₂ intact. As a result, it has been theorized that coxibs shift the balance of prostaglandin production to TxA₂ at the platelet-vascular endothelial interface, thereby favoring thrombogenic stimulation and arterial vasoconstriction and a greater risk for an atherothrombotic cardiovascular event.⁶ [Yu 2012]

Although COX-2 selectivity is a likely contributor to the higher CV risk seen with NSAID use, it is not the only factor since a higher CV risk has been seen with both coxibs as well as tNSAIDs. Other important variables implicated in NSAID risk include dosage, half-life, impact on blood pressure, and interaction with aspirin.⁷ [Farkouh 2009]

ASPIRIN INTERACTION

In contrast to inhibition of arachidonic acid observed with other NSAIDs, aspirin causes an irreversible inactivation of COX-1 and COX-2. Inhibition of COX-1 is responsible for the antiplatelet effects of aspirin and its cardioprotective effect.⁴ [Brune 2015]

The co-administration of some tNSAIDs, eg, ibuprofen and naproxen (but not COX-2 selective

inhibitors) with low-dose aspirin (LD-ASA) causes transient and modest inhibition of COX-1, and has been shown to interfere with the antiplatelet effect of aspirin.^{7,8} [Schmidt 2016] [Farkouh 2009] The effect of naproxen on the antiplatelet effect of LD-ASA may be lower than with ibuprofen.⁹ [Farkouh 2004/682] Concerns such an interaction might reduce the cardioprotective effect of LD-ASA resulted in an advisory from the FDA in 2007 recommending ibuprofen be taken at least 30 minutes after aspirin to avoid any potential interaction.¹⁰ [Antman 2007] Taking naproxen 2 hours after aspirin appears to lessen the interference.¹¹ [Anzelotti 2011] In addition, there is evidence that suggests that high-dose naproxen at a prescription dose of 500 mg twice daily may actually produce its own aspirin-like antiplatelet effect.¹² [Patrono 2014]

The variable effect of NSAIDs to interfere with the ability of aspirin to inhibit platelet activation may be due to differences in their ability to form hydrogen bonds with specific amino acids within the COX-1 hydrophobic channel.¹³ [Saxena 2013] The possibility of differences among NSAIDs with respect to an interaction with aspirin is of clinical importance since many patients who use NSAIDs for anti-inflammatory and analgesic effects often use low-dose aspirin for prevention of CV events. This becomes a particularly important consideration in older adults with osteoarthritic pain since they are likely to be at increased CV risk.¹⁴ [Mamdani 2004]

CARDIOVASCULAR SAFETY

The CV safety of NSAIDs has been assessed in hundreds of clinical trials over the past nearly 2 decades. Details regarding several key clinical trials are provided in the **Table**.^{2,15-21} These trials show that NSAIDs variably alter the rate of thromboembolic events and suggest that NSAIDs with a greater affinity for COX-2, particularly at higher doses, impart a higher CV risk.

KEY PROSPECTIVE CLINICAL TRIALS

The VIGOR trial was the first trial to suggest a higher incidence of adverse CV outcomes with COX-2 selective inhibitors compared with tNSAIDs.² [Bombardier 2000] After a median follow-up of 9 months, the incidence of myocardial infarction (MI) was found to be 4-fold higher with rofecoxib than naproxen (0.4% vs 0.1%, respectively). [Bombardier 2000] A post hoc analysis was also concerning, showing that the relative risk of developing a confirmed adjudicated thrombotic CV event with rofecoxib compared with naproxen was 2.38 (95% confidence interval (CI) 1.39-4.00).¹⁵ [Mukherjee 2001]

The Adenoma Prevention with Celecoxib (APC) trial compared 2 doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal adenomas.¹⁶ After approximately 3 years of follow-up, the study was terminated early due to a dose-related increase in a composite of CV events with celecoxib. [Solomon 2005]

The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial determined the effect of rofecoxib vs placebo on the risk of recurrent neoplastic polyps of the large bowel in patients with a history of colorectal adenomas.¹⁷ [Bresalier 2005] The rate of a confirmed thrombotic event was significantly higher with rofecoxib, becoming apparent after 18 months of treatment. The results primarily reflect a greater number of MIs and ischemic cerebrovascular events in

the rofecoxib group. The results of APPROVe contributed to the withdrawal of rofecoxib from the market in 2004.

The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) assessed the CV outcomes in high-risk patients with osteoarthritis. TARGET comprised 2 parallel substudies comparing the COX-2 selective inhibitor lumiracoxib (not available in the United States) 400 mg daily with either ibuprofen 800 mg three times daily or naproxen 500 mg two times daily.¹⁸ [Farkouh 2007] In aspirin users, ibuprofen was associated with a significantly higher rate of CV events at 1 year compared with lumiracoxib, whereas naproxen was not. In non-aspirin users, naproxen was associated with significantly fewer CV events compared with lumiracoxib, whereas ibuprofen was not. In addition, ibuprofen was associated with a higher rate of congestive heart failure. Shortcomings of this trial included the post hoc design; not being appropriately powered for CV safety, resulting in imprecision due to the small number of events in the subgroups; the use of aspirin in some but not all patients for unspecified reasons; aspirin use during the study was not collected; and a lack of a placebo arm, making it difficult to understand absolute CV risk.

The Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT) evaluated naproxen 220 mg twice daily and celecoxib 200 mg twice daily with placebo for the primary prevention of Alzheimer's dementia.¹⁹ [ADAPT 2006] After the results of the APC trial were released, the ADAPT study was terminated, with a median of approximately 15 months of treatment. ADAPT suggested the cardiovascular and cerebrovascular risks with celecoxib to be similar to placebo. The CV risk with naproxen was significantly greater with naproxen compared with placebo, due to a higher incidence of heart failure and transient ischemic attack. Besides early termination, the study had several limitations, including that it was not designed to detect differences in CV or cerebrovascular risk and was not appropriately powered for CV safety, resulting in imprecision due to the small number of events; the patient population had unknown CV risk at baseline, complicating extrapolation to the general population; and there was no a priori procedure for adjudication of CV or cerebrovascular events.

Finally, the Standard Care versus Celecoxib Outcome Trial (SCOT) was a prospective, open, blinded endpoint trial which compared the CV and GI safety of celecoxib with a variety of tNSAIDs (eg, diclofenac, ibuprofen, naproxen, meloxicam) in patients ages >60 years with osteoarthritis (OA) or rheumatoid arthritis (RA) but free of CV disease.²⁰ [MacDonald 2013] Over a median of 3 years, fewer patients than expected developed an on-treatment CV event with a rate similar for celecoxib and tNSAIDs.²¹ [MacDonald 2016]. Although conducted in the United Kingdom, Denmark, and the Netherlands, full data regarding mean NSAID daily doses were available only in Scotland: celecoxib 169.8 mg (SD 80.6), diclofenac 79.4 mg (SD 38.3), ibuprofen 675.9 mg (SD 345.9), and naproxen 581.9 mg (SD 263.4). Significantly more patients withdrew from celecoxib than tNSAIDs with the dominant reason for withdrawal being lack of efficacy. The rate of NSAID-associated GI complications was low (attributed by the authors to the co-administration of concomitant anti-ulcer agents as well as the relatively low doses of the NSAIDs used) and, as expected, was higher with tNSAIDs than celecoxib.

DANISH REGISTRY STUDY

A nationwide registry of Danish patients ages ≥ 30 years admitted with first-time MI was analyzed to assess NSAID use and CV risk.²² [Olsen 2011] Overall, NSAID treatment was significantly associated with an increased risk of death/recurrent MI commencing within 7 days of treatment initiation (HR 1.45, 1.29-1.62). [Olsen 2011] The risks persisted over more than 5 years of follow-up, with an increased risk of death (HR 1.60, 1.49-1.71) and coronary death or nonfatal recurrent MI (HR 1.41, 1.29-1.56).²³ [Olsen 2012/Suppl table 1a] The risk of coronary death or nonfatal recurrent MI was greater with rofecoxib (HR 2.19, 1.27-3.77) than celecoxib (HR 1.17, 0.63-2.17). Among the most commonly used tNSAIDs, the risk was greatest with diclofenac (HR 1.58, 1.31-1.91) and lowest with naproxen (HR 1.15, 0.71-1.85).

The bleeding rates were also significantly greater in patients treated with NSAID therapy. The risk of a CV event or bleeding were independent of concomitant antithrombotic treatment.²⁴ [Olsen 2015] These results suggest that NSAIDs should be used cautiously, if at all, in patients with a history of MI.

META-ANALYSES

Meta-analyses have been conducted to assess the CV risk of NSAIDs. The McGettigan-Henry meta-analysis examined population-based controlled observational studies of individual NSAIDs used at typical doses in community settings.²⁵ [McGettigan 2011] Trelle et al conducted a network meta-analysis of 31 large-scale randomized, controlled trials comparing any NSAID with another NSAID or placebo.²⁶ [Trelle 2011] The Coxib and Traditional NSAID Trialists' (CNT) Collaboration identified 639 randomized trials of an NSAID versus placebo or 1 NSAID regimen versus another for analysis and included 297 trials which compared a COX-2 selective NSAID versus placebo or a COX-2 selective NSAID versus tNSAID.²⁷ [Bhala 2013]

The 3 meta-analyses yielded generally similar results suggesting that all NSAIDs are associated with an increased CV risk, with naproxen conferring the lowest risk. The CNT analysis showed the estimated relative risk for major CV events among the tNSAIDs versus placebo was highest with diclofenac (HR 1.41, 1.12-1.78) and ibuprofen (HR 1.44, 0.89-2.33) and lowest with naproxen (HR 0.93, 0.69-1.27).²⁷ Although the CNT analysis showed a similar risk of major CV events with rofecoxib and celecoxib, the McGettigan-Henry analysis showed a higher risk with rofecoxib (HR 1.45, 1.33-1.59) vs celecoxib (HR 1.17, 1.08-1.27).^{25,27} [Bhala 2013] [McGettigan 2011]. All 3 meta-analyses provided support to the premise that the CV risk associated with celecoxib was dose-dependent, with the CNT and the McGettigan-Henry analyses suggesting no increased risk with doses of 200 mg daily. In addition to looking at CV risk, the CNT analysis also looked at upper GI complications (ie, upper GI bleeding and/or perforation, or peptic ulcer) and found the risk to be nearly twice as high for ibuprofen and naproxen compared to diclofenac or a coxib.²⁷

US FOOD AND DRUG ADMINISTRATION ACTIONS

Following publication of the CNT meta-analysis, the FDA convened 2 advisory panels to review this and other related information.²⁸ Results of this meeting, as well as its own analysis, led the

FDA to issue a drug safety communication in July 2015 which revised prescription NSAID labels to communicate the following:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any particular NSAID is definitely higher or lower than that of any other particular NSAID.
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without these risk factors because they have a higher risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

PRECISION TRIAL

This CV safety trial mandated by the FDA in 2014 was actually initiated in 2006 following a 2004 FDA review. The PRECISION trial enrolled patients who required NSAID therapy for OA or RA and deemed at high CV risk of CV disease based on having established CV disease or risk factors for CV disease (approximately 35% of patients had a history of diabetes, 78% a history of hypertension, and 62% a history of dyslipidemia). Patients were randomized to celecoxib 100–200 mg twice daily, ibuprofen 600–800 mg three times daily, or naproxen 375–500 mg twice daily.³ [Nissen 2016] The primary endpoint was non-inferiority on the composite of CV death (including hemorrhagic death), nonfatal MI, or nonfatal stroke. A total of 24,081 patients were randomized with a mean treatment duration of 20.3 months and a mean follow-up period of 34.1 months. During the trial, 68.8% of patients stopped taking the treatment drug and 27.4% discontinued follow-up.

Celecoxib was found to be non-inferior to ibuprofen and naproxen with regards to CV safety with the primary endpoint occurring in 2.3% of celecoxib patients compared with 2.7% and 2.5% of ibuprofen and naproxen patients, respectively. [Nissen 2016] Hazard ratios for celecoxib were 0.85 (0.70-1.04) vs ibuprofen and 0.93 (0.76-1.13) versus naproxen ($P<.001$ for both). In contrast, pairwise comparisons for each of the components of the primary endpoint showed no significant differences between celecoxib and ibuprofen as well as celecoxib and naproxen. As expected based on their mechanistic differences, the risk of GI events was

significantly lower with celecoxib than with ibuprofen ($P=.002$) or naproxen ($P=.01$). The risk of renal events was significantly lower with celecoxib compared with ibuprofen ($P=.004$), but not compared with naproxen ($P=.19$).

The design and results of PRECISION have been questioned and its findings should be interpreted with caution.²⁹ [FitzGerald 2016] In addition to high rates of patients discontinuing the study drug as well as discontinuing follow-up, the rate of primary outcome events occurring during the study period was considerably lower than expected and appeared more indicative of a study group at relatively low risk for CV events. Because of this lower rate and problems with subject recruitment, the statistical power for noninferiority, which was originally planned to be 90% was relaxed to 80%, thereby lessening the reliability of any judgement of noninferiority. Moreover, based on prior studies, the CV risk associated with celecoxib use appears dose-related. In the PRECISION trial, the mean daily celecoxib dose of 209 mg may be considered low-dose³⁰ [Felson 2016] and lower than that associated with increased CV risk. For comparison, the mean daily doses of ibuprofen and naproxen were 2045 mg and 852 mg. Finally, since interference with the antiplatelet activity of LD-ASA and potential negation of its cardioprotective effect is not a class effect (ie, both naproxen and ibuprofen have been shown to interfere with the antiplatelet activity of aspirin whereas celecoxib has not), the failure to control for use of LD-ASA use introduces a potential source of bias favoring celecoxib and calls into question any conclusions in this regard.

SUMMARY

At the present time, the totality of evidence suggests all NSAIDs are associated with an increased risk for adverse CV events. Several factors are involved, including COX-2 selectivity, dosage, half-life, impact on blood pressure, and interaction with aspirin. Although the evidentiary standard needed by FDA to rank order NSAID compounds with regards to CV risk has not been met, the balance of evidence continues to favor naproxen as being the safest NSAID from a CV perspective, with the caveat that it may also pose a higher risk for an upper GI bleed than other tNSAIDs. Although recent data from the SCOT trial and the PRECISION trial support the improved CV safety of low-dose celecoxib (200 mg daily) seen in earlier studies, the shortcomings of these two trials serves only to raise doubt regarding any conclusions drawn pertaining to the comparative safety of the NSAID agents studied and leaves unanswered the question of differential CV risk.

Although widely used and clinically valuable, NSAID use is not without risk. When considering the use of a NSAID, careful consideration of risk factors associated with NSAID toxicity should be given, including the patient's age as well as risk for developing renal, GI, and CV complications. NSAIDs should be used only with due caution in patients with known CV disease and are best avoided in patients following a myocardial infarction. Until definitive evidence becomes available, it remains prudent to follow the basic rule to prescribe the lowest effective dose of an NSAID for the shortest duration possible.

TABLE Evidence concerning the cardiovascular risks associated with COX-2 inhibitors

Trial; year(s) conducted	Design; patients	Treatment	Results ^a	Limitations
VIGOR, 1999 ^{2,15}	R, DB, MC Patients with RA (N=8076)	Rofecoxib 50 mg/d vs Naproxen 500 mg bid (median follow-up 9 mos)	GI events (per 100 PY): 2.1 vs 4.5 (HR, 0.5; 95% CI, 0.3-0.6) MI: 0.4% vs 0.1% MACE ^b : HR, 2.38; 95% CI, 1.39-4.00	Withdrawal from treatment: 29.3% vs 28.5%; not placebo-controlled
APC, 1999-2002 ¹⁶	R, DB, MC Patients at risk for colorectal adenoma (N=2035)	Celecoxib 200 mg bid vs Celecoxib 400 mg bid vs Placebo (2.8-3.1 y follow-up)	MACE ^c : HR vs PBO: HR, 2.3; 95% CI, 0.9-5.5; HR, 3.4; 95% CI, 1.4-7.8	
APPROVe, 2000-2001 ¹⁷	R, DB, MC Patients with colorectal adenoma (N=2586)	Rofecoxib 25 mg/d vs Placebo X 3 y	Thrombotic event ^d (per 100 PY): 1.50 vs 0.78 (HR, 1.92; 95% CI, 1.19-3.11) Cardiac events (per 100 PY): 1.01 vs 0.36 (HR, 2.80; 95% CI, 1.44-5.45) Cerebrovascular events (per 100 PY): 0.49 vs 0.21 (HR, 2.32; 95% CI, 0.89-6.74)	Withdrawal from treatment: 31.9% vs 24.6%
TARGET, 2001-2002 ¹⁸	R, DB, MC Patients with OA ages ≥50 y (N=18,325)	Lumiracoxib 400 mg/d vs Ibuprofen 800 mg tid X 52 wks	High-risk using aspirin (75-100 mg/d): MACE ^e : 0.25% vs 2.14% (HR, 9.08; 95% CI, 1.13-72.8) High-risk not using aspirin: MACE ^e : 0.80% vs 0.92% (HR, 0.91; 95% CI, 0.15-5.47)	Post hoc analysis; not placebo-controlled; few events; withdrawal from treatment: 43%
		Lumiracoxib 400 mg/d vs Naproxen 500 mg bid X 52 wks	High-risk using aspirin (75-100 mg/d): MACE ^e : 1.48% vs 1.58% (HR, 1.07; 95% CI, 0.40-2.84) High-risk not using aspirin: MACE ^e : 1.57% vs 0% (HR, N/A)	
ADAPT, 2001-2004 ¹⁹	R, DB, MC Patients ages ≥70 y with family history of AD (N=2528)	Celecoxib 200 mg bid vs Naproxen 220 mg bid vs Placebo X 3 y	MACE ^f : 5.54% vs 8.25% vs 5.68% [HR vs PBO: HR, 1.10; 95% CI, 0.67-1.79; HR, 1.63; 95% CI, 1.04-2.55]	

TABLE Evidence concerning the cardiovascular risks associated with COX-2 inhibitors (*Continued*)

Trial; year(s) conducted	Design; patients	Treatment	Results ^a	Limitations
Danish Registry, 1997-2006 ²²	Retrospective review of national registry Patients ages ≥30 y with first-time MI (N=83,675)	Any NSAID	Risk for death or recurrent MI (>90 days treatment) All NSAIDs: HR, 1.55; 95% CI, 1.46-1.64 Rofecoxib: HR, 1.72; 95% CI, 1.45-2.04 Celecoxib: HR, 1.65; 95% CI, 1.42-1.92 Ibuprofen: HR, 1.53; 95% CI, 1.40-1.69 Diclofenac: HR, 1.92; 95% CI, 1.66-2.22 Naproxen: HR, 1.50; 95% CI, 0.10-2.05 Other NSAIDs: HR, 1.44; 95% CI, 1.28-1.62	Observational design; informational bias
SCOT, 2008-2013 ^{20,21}	PROBE, MC Patients ages ≥60 y with OA or RA (N=7297)	Celecoxib ≤200 mg bid vs tNSAID ^f (median follow-up 3 y)	MACE (per 100 PY) ^h : 1.14 vs 1.10 (HR, 1.04; 95% CI, 0.81-1.33) Hospitalization or death for upper GI ulcer (per 100 PY): 0.09 vs 0.04 (HR, 2.08; 95% CI, 0.65-7.74)	Withdrawal from treatment: 48.2% vs 31.5%

Abbreviations: AD, Alzheimer's disease; ADAPT, Alzheimer's Disease Anti-inflammatory Prevention Trial; APC, Adenoma Prevention with Celecoxib; APPROVe, Adenomatous Polyp Prevention on Vioxx; bid, twice daily; CHF, congestive heart failure; CV, cardiovascular; d, day; DB, double-blind; GI, gastrointestinal; HR, hazard ratio; MACE, major adverse cardiovascular events; MC, multicenter; MI, myocardial infarction; N/A, not applicable; N, number; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PBO, placebo; PROBE, prospective, randomized, open-label, blinded endpoint evaluation; PY, person-years; R, randomized; RA, rheumatoid arthritis; SCOT, Standard care versus Celecoxib Outcome Trial; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; tid, 3 times daily; tNSAID, traditional, ie, non-COX-2 selective NSAID; VIGOR, Vioxx Gastrointestinal Outcomes Research; wks, weeks; y, year(s).

^a95% confidence interval.

^bComposite of MI, unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischemic stroke, transient ischemic attack

^cComposite of CV death, MI, stroke, heart failure.

^dComposite of fatal and nonfatal MI, unstable angina, sudden cardiac death, fatal and nonfatal ischemic stroke, transient ischemic attack, peripheral arterial thrombosis, peripheral venous thrombosis, pulmonary embolism.

^eComposite of CV death, nonfatal MI, stroke.

^fComposite of CV death, MI, stroke, congestive heart failure, transient ischemic attack.

^gIbuprofen, aceclofenac, acemetacin, dexibuprofen, dexketoprofen, diclofenac sodium, diflunisal, etodolac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid, diclofenac/misoprostol.

^hComposite of hospitalization for nonfatal MI or other biomarker for positive acute coronary syndrome, nonfatal stroke, or CV death.

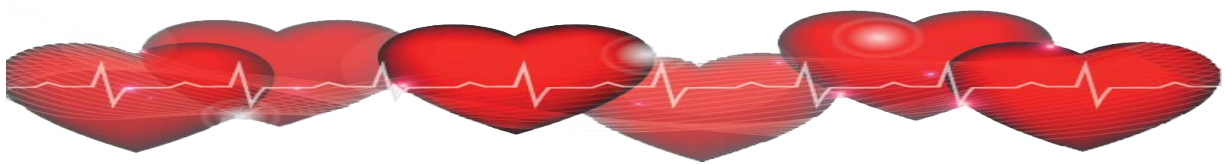
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