Do COX-2 inhibitors worsen renal function?

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Evidence-based answer

No, COX-2 inhibitors, as a class, do not worsen renal function for those without renal disease. Celecoxib is the only COX-2 inhibitor available, and it is associated with a lower risk of renal dysfunction and hypertension when compared with controls. Available data do not allow for adjusted risk assessment for patients with preexisting renal disease on COX-2 inhibitors (strength of recommendation [SOR]: **A**, based on meta-analysis).

Clinical commentary

Use celecoxib cautiously in patients at risk of serious complications

Recent studies have raised concerns about the safety of this class of medication. For example, rofecoxib was linked with increased cardiovascular events, leading to it being pulled from the market.[1] The claim of decreased gastrointestinal bleeding with long-term use of COX-2 inhibitors has also been questioned.[2]

Although this Clinical Inquiry concludes that celecoxib does not appear to worsen renal function, it should still be used with caution for patients who are elderly, hospitalized, or at risk of developing serious complications such as acute renal failure, heart failure, and gastrointestinal bleeding.

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FAST TRACK

While celecoxib does not appear to worsen renal function, it should be used with caution in elderly and hospitalized patients

Evidence summary

A 2006 meta-analysis, including 114 trials and 116,094 patients randomized to either cyclooxygenase-2 (COX-2) inhibitor or control (placebo, nonsteroidal anti-inflammatory drug [NSAID], or mixed), indicated that the COX-2 inhibitors, as a class, had no effect on renal endpoints.[3] Trials were reviewed for data on renal endpoints, including peripheral edema, hypertension, and renal dysfunction (defined as significant worsening of serum urea or creatinine, or clinical evidence of kidney disease and renal failure).

When viewed separately, rofecoxib (Vioxx) was associated with a composite relative risk (RR) of 1.53 (95% confidence interval [CI], 1.33–1.76) for all renal endpoints compared with controls. In contrast, the composite RR for the same endpoints among patients taking celecoxib (Celebrex) was 0.97 (95% CI, 0.84–1.12), indicating no effect on renal function. In fact, for the specific outcomes of hypertension and renal dysfunction, celecoxib was associated with a decreased risk compared with controls (**TABLE**).[3]

Stratified analysis by type of control (placebo, alternate NSAID, or mixed) yielded consistent results; rofecoxib was uniquely associated with adverse renal outcomes. No effect on renal function was noted for celecoxib compared with the same controls: the RR for adverse

TABLE

Celecoxib is associated with a decreased risk of hypertension and renal dysfunction

	CELECOXIB	ROFECOXIB
Hypertension	0.83 (95% CI, 0.71–0.97)	1.55 (95% CI, 1.29–1.85)
Peripheral edema	1.09 (95% CI, 0.91–1.31)	1.43 (95% CI, 1.23–1.66)
Renal dysfunction	0.61 (95% CI, 0.40–0.94)	2.31 (95% CI, 1.05–5.07)

Source: Zhang J, Ding EL, Song Y, *JAMA* 2006.[3]

renal effects was 0.87 (95% CI, 0.55–1.38), 0.93 (95% CI, 0.70–1.23), and 1.26 (95% CI, 0.94–1.69) for celecoxib vs placebo, NSAID, and mixed controls, respectively. Statistical analysis for heterogeneity showed that the variation in effects on renal function among the COX-2 inhibitors was more likely due to actual differences than due to chance (heterogeneity [I^2]=57%; P<.001).

Data were not available to assess the effect of COX-2 agents on patients with pre-existing renal disease, primarily because trials reporting abnormal renal function at baseline were excluded from this meta-analysis.

A recent randomized controlled trial compared standard dosing of diclofenac (75 mg twice daily) and ibuprofen (800 mg 3 times daily) with high-dose celecoxib (400 mg twice daily) for patients with normal kidney function being treated for osteoarthritis and rheumatoid arthritis.[4] The mean increase in serum creatinine in the celecoxib arm was less than that noted in the diclofenac controls (0.009 mg/dL vs 0.027 mg/dL; P<.05; number needed to harm [NNH]=56). No difference in mean serum creatinine was seen among those patients using ibuprofen (800 mg 3 times daily) compared with those using high-dose celecoxib.

This evidence further supports the safety of celecoxib vs standard NSAIDs with respect to renal dysfunction.

Recommendations from others

The American Pain Society 2002 guideline recommends acetaminophen for mild pain from osteoarthritis.[5] For moderate to severe pain and inflammation, a COX-2 inhibitor was the first choice, unless there is significant risk of hypertension or kidney disorder. For active rheumatoid arthritis, the addition of a COX-2 agent to disease-modifying anti-rheumatic drugs (DMARDs) is advised unless there is uncontrolled hypertension or renal disease.[6] However, these recommendations came out before the data on the cardiovascular effects of some COX-2 inhibitors.

The American College of Rheumatology recommends the use of a COX-2 agent for osteoarthritis or pain unresponsive to acetaminophen. Their 2000 guidelines warn that due to potential renal toxicity, COX-2 inhibitors should not be used for patients with severe renal insufficiency, and used with caution in cases of mild to moderate renal insufficiency.

In 2005, these guidelines were amended to include the recommendation that patients with increased cardiovascular risk be cautioned about the risks associated with COX-2 inhibitor use.[7] ■

FAST TRACK

The American College of Rheumatology recommends a COX-2 agent for osteoarthritis or pain that is unresponsive to acetaminophen

References

1. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005; 352:1092–1102.
2. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 331:1310–1316.
3. Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events. *JAMA* 2006; 296:1619–1632.
4. Whelton A, Lefkowith JL, West CR, Verburg KM. Cardiorenal effects of celecoxib as compared with the nonsteroidal anti-inflammatory drugs diclofenac and ibuprofen. *Kidney Intl* 2006: 70:1495–1502.
5. Simon LS, Lipman AG, Jacox AK, et al. *Pain in Osteoarthritis, Rheumatoid Arthritis and Juvenile Chronic Arthritis.* 2nd ed. Glenview, Ill: American Pain Society; 2002.
6. American College of Rheumatology (ACR) Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; 43:1905–1915.
7. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002; 46:328–346.