# Safe Pharmacologic Treatment Strategies for Osteoarthritis Pain in African Americans with Hypertension, and Renal and Cardiac Disease

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Arthritis is the leading cause of disability in the United States. Osteoarthritis, the most common form of arthritis, is a degenerative joint disease affecting both whites and African Americans similarly. African Americans have a high incidence rate of comorbidities, including hypertension, cardiovascular disease (CVD) risk factors and diabetes. Treatment of osteoarthritic pain in patients with comorbidities is often complicated by potential safety concerns. Traditional nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) specific NSAIDs have been shown to increase blood pressure in hypertensive patients taking antihypertensive medications. Patients with CVD risk factors taking low-dose aspirin for secondary prevention may be at increased risk for gastrointestinal bleeding with NSAIDs. Diabetics face an increased risk of renal complications. Because NSAIDs are associated with adverse renal effects, they should be used cautiously in patients with advanced renal disease. Acetaminophen is the most appropriate initial analgesic for African Americans with chronic osteoarthritic pain and concurrent hypertension, CVD risk factors or diabetes, and is recommended by the American College of Rheumatology as first-line treatment. Many of the adverse effects commonly associated with NSAIDs are not associated with acetaminophen. Safety concerns surrounding pharmacologic treatment of osteoarthritis in African Americans are reviewed.

**Key words:** African Americans ■ acetaminophen ■ osteoarthritis ■ hypertension ■ diabetes mellitus ■ cardiovascular disease

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## INTRODUCTION

Arthritis is one of the most prevalent chronic diseases in the United States. Nearly 70 million Americans, or about one in every three adults, are affected by arthritis and chronic joint symptoms.[1] Although arthritic diseases affect both men and women, they are more common in women, and the prevalence increases with age.[2] Arthritis is the leading cause of disability in the United States and carries an economic as well as physical toll, costing the United States more than $82 billion in 1995.[1] Prevalence rates are similar for whites (35.3%) and African Americans (31.5%); compared with other minority groups, African Americans are among the most frequently affected.[1,3] African Americans report the highest rate of arthritis-related activity limitation compared with other ethnic populations with arthritis. Of the 3.6 million African Americans with arthritis, one-fourth (24.5%) report having limited their activity because of their disease.[3]

Included in the category "arthritis" are multiple entities that affect the joints. Osteoarthritis is a degenerative joint disease characterized by the breakdown of cartilage in the joints. It is extremely common, affecting over 20 million Americans.[4] Osteoarthritis is a major cause of back, knee and hip pain in older Americans. Pain and decreased range of motion are characteristic of the disease. Decreased muscle bulk and unstable joints are common features of the progression. Decreasing pain and improving joint movement are the goals of treatment in osteoarthritis. Approaches include both nonpharmacologic and pharmacologic methods. Medications that have been used to try to control osteoarthritic pain include acetaminophen, nonacetylated salicylates, nonsteroidal antiinflammatory drugs (NSAIDs), corticosteroids and glucocorticoids.[4] The NSAID group includes traditional nonselective agents binding to both cyclooxygenase (COX) 1 and 2, and newer agents having the ability to bind specifically to COX-2. Additionally, glucosamine and chondroitin sulfate are being

studied as possible disease-modifying agents.[5,6]

Treatment of osteoarthritis in African Americans is often complicated by the presence of comorbidities. This paper will review considerations in prescribing analgesic therapy for African-American patients with osteoarthritis and concomitant hypertension, cardiovascular disease (CVD) risk factors or diabetes.

## Frequent Comorbidities in African Americans

Hypertension is a leading cause of morbidity and mortality in the United States.[7] The prevalence of hypertension in African Americans is among the highest in the world, affecting 36.8% of non-Hispanic African-American men and 39.4% of non-Hispanic African-American women (Figure 1).[7] Generally, compared with Caucasian Americans, African Americans have higher blood pressure on average; develop hypertension earlier in life; and have a 1.3-times greater risk of nonfatal stroke, 1.8-times greater risk of fatal stroke, 1.5-times greater risk of heart disease death and 4.2-times greater risk of end-stage renal disease (ESRD).

Approximately 300 variables have been associated with coronary heart disease (CHD). Intervention studies that have correlated a diminishing risk factor with a lowering of risk have substantiated only a small number of variables as clinically important.[8] Several major modifiable and nonmodifiable risk factors account for the majority of CVD risk. Among the most important of these are hypertension and diabetes (Table 1).

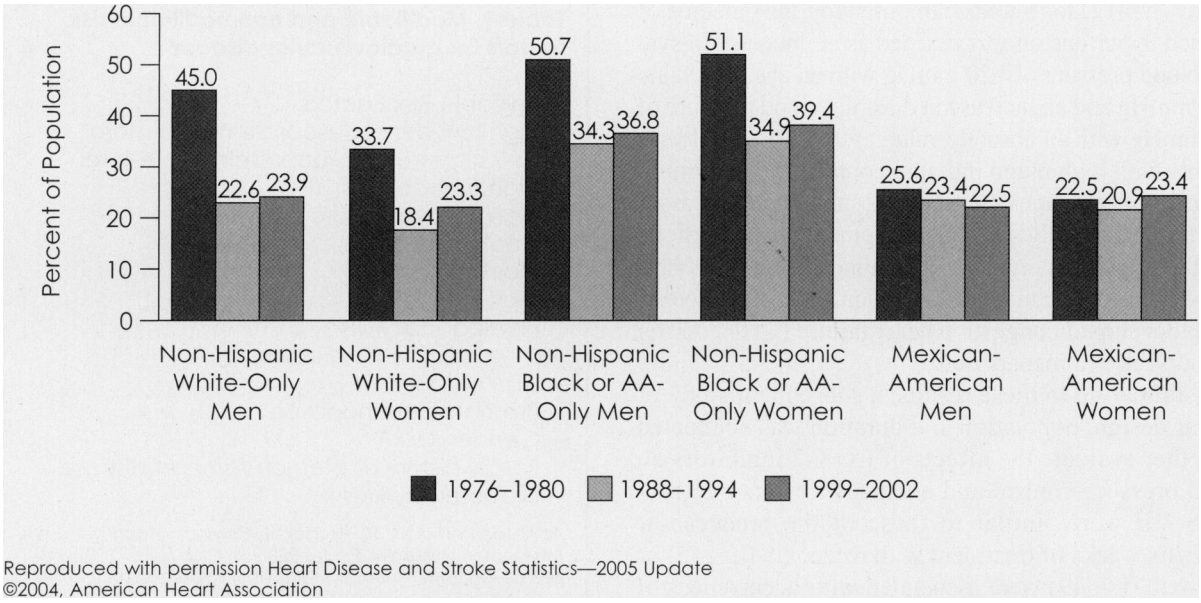
Exemplified by a dramatic 61% increase since 1990 in the prevalence of people diagnosed with diabetes, diabetes is on the rise in the United States.[7] This increase was observed across the spectrum of gender, age, ethnicity and level of education. About 13% of African Americans have diabetes, comprising about 2.8 million people.[9] African Americans are twice as likely to have diabetes as Caucasian Americans by age group; of those with diabetes, African Americans develop ESRD at about quadruple the rate of Caucasian Americans.[9]

## Treatment of Osteoarthritic Pain in the Setting of Concurrent Hypertension

Hypertension affects 1 in 3 American adults.[7] Diligent treatment of hypertension is important in reducing the risks of cardiovascular complications, as even high-normal blood pressures (130–139 mmHg systolic or 85–89 mmHg diastolic) are associated with increased cardiovascular risk.[10,11] The importance of maintaining good blood pressure control in avoiding serious sequelae is becoming increasingly clear.[12] It has been reported that 30% of patients with arthritis also have hypertension.[13] Because both of these diseases increase with advancing age, it is likely that hypertension and osteoarthritis will occur simultaneously in many patients. It is also likely that patients may be taking medications to treat both of these conditions at the same time.[2,11]

The ability of NSAIDs, both traditional and specific COX-2 inhibitors, to increase blood pressure and possibly inhibit the antihypertensive efficacy of hypertensive medications has been extensively evaluated and may have important clinical and public health implications.[12,14-21]

**Figure 1. Age-adjusted prevalence trends for high blood pressure in Americans, ages 20–74 by race/ethnicity, sex and survey**

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**Traditional NSAIDs.** A meta-analysis of published NSAID intervention studies was conducted a decade ago to assess the effect of NSAID therapy on blood pressure.[15] The results of this analysis demonstrated an increase in mean arterial pressure (MAP) of 3.32 mmHg in hypertensive patients and an increase of 1.12 mmHg in normotensive persons. After adjusting for salt intake in the hypertensive population, the most significant increases in MAP were observed with indomethacin (3.59 mmHg) and naproxen (3.74 mmHg). Sulindac, aspirin, ibuprofen and placebo showed modest reductions in MAP. Nevertheless, the high use of salt by many persons with hypertension suggest the need for caution in prescribing NSAID therapy to persons with high blood pressure.

A year later, another meta-analysis of randomized trials involving NSAIDs was conducted to study the effect on blood pressure.[16] Results of this analysis demonstrated an increase in mean blood pressure of about 5.0 mmHg with NSAID use over a period of several weeks. Elevations in blood pressure observed with NSAIDs in this analysis were more marked in normotensive volunteers given antihypertensive drugs. Piroxicam was associated with statistically significant elevations in supine mean blood pressure of 6.2 mmHg; aspirin and sulindac minimally affected supine mean blood pressure. Tiaprofenic acid, diclofenac, naproxen, and flurobiprofen were shown to have intermediate effects on blood pressure.

**COX-2 Inhibitors.** The cardiorenal effects of two COX-2 inhibitors, rofecoxib and celecoxib, were evaluated in the SUCCESS VI study, a multicenter, parallel-group, double-blind, double-dummy, randomized, controlled trial.[22] Patients aged ≥65 years with controlled hypertension and osteoarthritis were randomized to receive rofecoxib 25 mg/day (n=399) or celecoxib 200 mg/day (n=412) for 6 weeks. In this study, the outcome of elevated hypertension was defined as an increase in systolic blood pressure of >20 mmHg with an absolute value >140 mmHg and an increase in diastolic blood pressure of >15 mmHg with an absolute value >90 mmHg. In elderly patients with high blood pressure controlled with antihypertensive medications, both COX-2 inhibitors were associated with clinically significant edema, elevated systolic and diastolic blood pressures, and abnormal renal laboratory values. Additionally, four patients in the rofecoxib group developed congestive heart failure (CHF) during the six-week treatment period.

In follow-up to these results, a subsequent study of similar design, population and duration was conducted to further evaluate the effects of COX-2 inhibitors on blood pressure control and edema.[23] Results of SUCCESS VII were similar to those of the predecessor study: six weeks of treatment with rofecoxib (n=543) or celecoxib (n=549) were associated with occurrences of edema and elevations in systolic and diastolic blood pressures. Significantly more patients in the rofecoxib group compared with the celecoxib group developed an increase in systolic blood pressure (14.9% vs. 6.9%, P<0.001) and edema (7.7% vs. 4.7%, P<0.05). New-onset or worsening CHF was observed in three patients treated with rofecoxib and in two patients treated with celecoxib. Based upon the results of SUCCESS VI and VII, careful monitoring of blood pressure is advisable upon initiation of COX-2 therapy in patients with controlled hypertension.

**Potential mechanism of increased blood pressure.** The inhibition of COX blocks the formation of prostacyclin ($PGI_2$) and prostaglandin $E_2$ ($PGE_2$) and results in alteration of blood pressure homeostasis.[24] These prostaglandins have essential vasodilatory functions, inhibit renal absorption of salt and reabsorption of water, and promote release of renin (Figure 2).[25] Renin stimulates production angiotensin II, a potent vasoconstrictor; and aldosterone, a hormone promoting salt and water retention. Therefore, COX inhibitors augment the renal vasoconstriction and retention of salt and water that would have normally been countered by $PGI_2$ and $PGE_2$. On the contrary, the blockade of renin secretion could potentially offset the hypertensive effects of NSAIDs. However, African Americans with hypertension typically have low plasma renin activity, NSAIDs have little effect on plasma renin levels in this population, making them more susceptible to increases in blood pressure due to COX inhibition.

**Acetaminophen.** Controlled prospective trials have shown that acetaminophen does not share the blood pressure effects observed with NSAIDs in hypertensive patients receiving antihypertensive medications. Four placebo-controlled, randomized, crossover studies in patients whose blood pressure was controlled with anti-

**Table 1. Modifiable and nonmodifiable risk factors for cardiovascular disease**

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| Modifiable Risk Factors |
| High low-density lipoprotein cholesterol |
| Low high-density lipoprotein cholesterol |
| High triglycerides |
| High blood pressure |
| Smoking |
| Obesity |
| High-fat diet |
| Physical inactivity |
| Nonmodifiable Risk Factors |
| Age |
| Premature menopause |
| Gender |
| Family history of premature heart disease |
| Diabetes mellitus |

Adapted from AJH, 12, Poulter, N, Coronary Heart Disease is a Multifactorial Disease, Pages 92S-95S, Copyright 1999, with permission from *American Journal of Hypertension*, Ltd.

hypertensive agents demonstrated that indomethacin was associated with increased blood pressure but that aspirin, sulindac, naproxen and acetaminophen (paracetamol) were not.[17] Additionally, plasma renin activity was not affected by low-dose aspirin or acetaminophen but was reduced by 50–60% with indomethacin, sulindac, naproxen and full-dose aspirin.

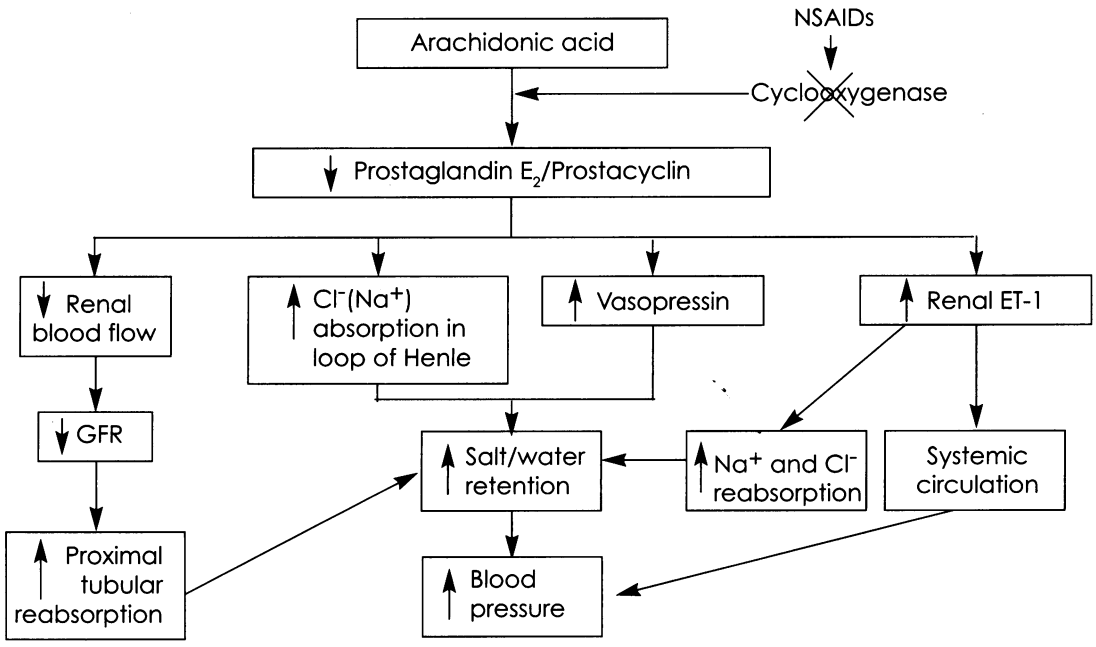
A randomized, blinded, placebo-controlled, parallel trial evaluated the effects of ibuprofen versus acetaminophen on blood pressure in patients with hypertension treated with ≥2 antihypertensive drugs.[14] Following a single-blind run-in period, patients were randomized to three weeks of treatment with ibuprofen, 400 mg every eight hours (n=12), acetaminophen, 1,000 mg every eight hours (n=15) or placebo (n=14). No statistically significant differences in supine or sitting diastolic, systolic or MAP were observed for acetaminophen or placebo over baseline. However, ibuprofen was associated with increases in all blood pressure measurements compared with placebo, with statistically significant increases observed in supine diastolic blood pressure, supine MAP and sitting MAP ($P \leq 0.0169$). The majority of patients enrolled in the study were overweight and African-American, and no evidence was found to suggest that demographic characteristics influenced the observed blood pressure effects of NSAIDs.

## Treatment of Osteoarthritic Pain in the Setting of Concurrent Cardiovascular Disease or Cardiovascular Risk

**Concomitant therapy with aspirin.** The administration of low-dose aspirin (75–150 mg/day) for its antiplatelet effect has been demonstrated to protect patients at risk for vascular events, such as acute myocardial infarction, ischemic stroke, angina, peripheral arterial disease or atrial fibrillation.[26] Patients receiving low-dose aspirin therapy for CVD risk reduction may also have osteoarthritis. Appropriate additional drug therapy for osteoarthritis pain in this population should be carefully considered. Selection of analgesic treatment for these patients should be individualized, taking into account possible safety issues in the setting of background low-dose aspirin therapy.

Clinical evidence has suggested a drug interaction between ibuprofen and low-dose aspirin therapy involving ibuprofen interfering with aspirin's inhibitory effects on platelet aggregation.[27,28] Potential interactions between low-dose aspirin (81 mg) and osteoarthritis therapies (ibuprofen, rofecoxib, acetaminophen or diclofenac) were investigated in two six-day studies—one a randomized crossover study and the other a parallel-group, randomized, open-label study.[27] Results demonstrated that low-dose aspirin inactivates COX in the anucleate platelet; pretreatment with ibuprofen blocks this inhibition and the subsequent impairment of platelet aggregation. Acetaminophen, rofecoxib and

**Figure 2. Potential mechanism of systemic hypertension induced by nonsteroidal antiinflammatory drugs**




Cl-: chlorine; ET: endothelin; GFR: glomerular filtration rate; Na+: sodium; NSAIDs: nonsteroidal antiinflammatory drugs; Adapted from *Drugs & Aging*, Volume 12, Number 1, Johnson AG, NSAIDs and Blood Pressure: Clinical Importance for Older Patients, Pages 17–27, Copyright 1998, with permission from Adis International-Wolters Kluwer Health Pharma Solutions

diclofenac did not antagonize the irreversible platelet inhibition induced by aspirin, allowing the clinically desirable inhibition of platelet aggregation. In another study, patients with known CVD (myocardial infarction, angina, stroke or transient ischemic attack, and peripheral vascular disease) on low-dose aspirin (<325 mg/day) who received ibuprofen had a significantly higher risk of all-cause mortality (P=0.0011) and cardiovascular mortality (P=0.0305) than patients taking aspirin alone.[28] No statistically significant differences in either mortality end point were observed in patients treated with aspirin monotherapy or combination therapy with diclofenac or any other NSAID.

**Myocardial infarction.** The risk of myocardial infarction, a secondary outcome, was assessed in a prospective, randomized, double-blind study (the VIGOR Study), designed to compare rofecoxib and naproxen in >8,000 patients with rheumatoid arthritis.[29] Patients received rofecoxib, a specific COX-2 inhibitor, 50 mg/day (n=4,047) or naproxen 500 mg twice daily (n=4,029). The median follow-up time was nine months in both treatment groups. Myocardial infarctions occurred in 0.1% of the naproxen group and in 0.4% of the rofecoxib group. Of the entire study population, 4% had a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty or coronary bypass; therefore, they should have been receiving low-dose aspirin for secondary cardiovascular prophylaxis but were not. Thirty-eight percent of the patients who experienced a myocardial infarction in this study were part of this group—a finding that prompted the immediate notification of all investigators in ongoing rofecoxib studies to allow the concomitant use of low-dose aspirin in study participants.

Because of the difference in the incidence of myocardial infarctions in patients taking naproxen and rofecoxib in the VIGOR study, a further analysis of cardiovascular thrombotic events associated with rofecoxib in clinical studies was conducted.[30] The safety analysis included >28,000 rofecoxib-treated patients, the majority of whom were receiving the medication for the treatment of osteoarthritis. A similar rate of cardiovascular events for rofecoxib and diclofenac, ibuprofen or nabumetone was observed. Naproxen was associated with a lower risk of cardiovascular events than rofecoxib, possibly related to coronary protective effects due to antiplatelet activity.

**Congestive heart failure.** The kidneys of patients with CHF may depend on prostaglandins to preserve renal blood flow and glomerular filtration rate,[31] so inhibition of COX—enzymes that regulate prostaglandin synthesis—with NSAIDs in these patients often has detrimental renal effects. Because of adverse renal events associated with traditional NSAIDs and the selective COX-2 inhibitors, these agents should be used cautiously or not at all in patients with CHF, chronic renal failure, severe cardiac disease or hepatic failure.

The use of NSAIDs has been associated with a doubling of the risk of new-onset CHF and a nearly 10-times greater risk of recurrent CHF.[32,33] A matched-case control study involving elderly patients hospitalized with CHF was conducted to evaluate the possibility of a relationship between recent NSAID use and CHF.[32] Use of NSAIDs, not including low-dose aspirin (100–300 mg/day), during the week before the onset of CHF was associated with a 2.8-times greater risk of new-onset heart failure and a 10.5-times greater risk of recurrent heart failure. The cause of this increased risk has not been fully elucidated but may have been due to exacerbation of an originally undetected risk factor for the development of CHF, such as left ventricular impairment. Another investigation of a cohort of participants in the Rotterdam Study—a population-based, prospective study on the prevalence of various diseases in the elderly—demonstrated a dramatic 9.9-times greater risk of recurrent CHF associated with NSAID use.[33]

**Concurrent diabetes.** Diabetes mellitus has been proven to be a risk factor for CVD. Osteoarthritic patients with diabetes share similar chronic pain treatment needs as other CVD-risk patients. In addition to the increased risk of CVD observed in diabetics, these patients are also at an increased risk of renal disease. In both whites and African Americans, diabetes is the leading cause of ESRD in the United States (Figu re 3).[43]

**Gastrointestinal bleeding.**

*NSAIDs.* The association between gastrointestinal bleeding and aspirin administration is well established[34] and is also observed with low-dose aspirin (100–150 mg/day).[35] When low-dose aspirin and NSAIDs are used concurrently, the risk of gastrointestinal bleeding increases.

**Table 2. Renal syndromes related to conventional nonsteroidal antiinflammatory agents**

| |
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| Fluid and Electrolyte Abnormalities |
| Sodium chloride and water retention |
| Hyperkalemia |
| Acute Renal Failure |
| Hemodynamic compromise |
| Nephrotic Syndrome |
| Minimal-change glomerulopathy with interstitial nephritis |
| Membranous glomerulopathy |
| Papillary Necrosis |
| Acute (typically single-drug pathogenesis) |
| Chronic (typically multidrug pathogenesis) |
| Other Systemic Interactions |
| Hypertension (treated) |
| Chronic heart failure |

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A double-blind, randomized, controlled trial (the CLASS study) involving >8,000 patients with osteoarthritis or rheumatoid arthritis was conducted to evaluate the safety of celecoxib compared with ibuprofen or diclofenac.[36] In patients who were receiving concurrent low-dose aspirin (≤325 mg/day), a significantly increased risk (relative risk 4.5) for upper gastrointestinal ulcer complications was observed in the celecoxib group. This effect was not observed in patients taking low-dose aspirin combined with ibuprofen or diclofenac.

A meta-analysis of osteoarthritis and rheumatoid arthritis studies was conducted to evaluate the gastrointestinal safety and arthritis efficacy of the COX-2 inhibitor celecoxib.[37] Four of these studies included safety data specifically categorized by concomitant aspirin use (≤325 mg/day). Fewer ulcers were observed in the celecoxib group compared with other NSAIDs, regardless of aspirin use. Compared with other NSAIDs, the beneficial effects of celecoxib were greater in patients not taking aspirin (73% reduction in ulcers) than in those who were taking aspirin (51% reduction in ulcers).

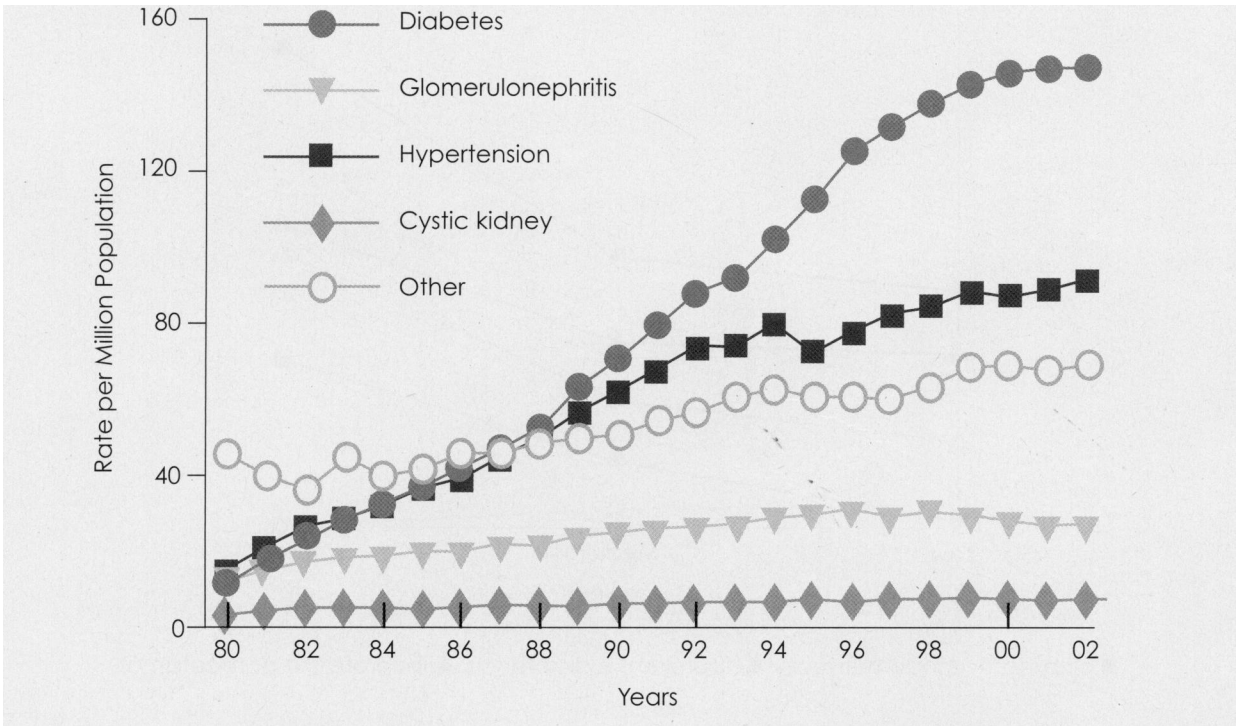
*Acetaminophen.* The lack of association between the development of gastrointestinal bleeding and acetaminophen use was established over 20 years ago[38] and subsequent investigations have supported this finding.[34,39-42]

A hospital-based, case-control study in patients without a known predisposition to upper gastrointestinal tract bleeding was conducted to assess the relationship between nonnarcotic analgesics and major upper gastrointestinal bleeding.[34] The use of aspirin at least every other day was associated with a 15-fold increased risk of major upper gastrointestinal tract bleeding. No evidence was found to support increased bleeding risk with acetaminophen.

Laporte et al. conducted a multicenter, case-control study in 875 patients hospitalized with acute upper gastrointestinal bleeding matched with 2,682 control patients to quantify the risk of upper gastrointestinal bleeding associated with NSAID therapy during the seven days before onset of the event.[39] Acetaminophen (paracetamol) use did not increase the risk of upper gastrointestinal bleeding. Aspirin, diclofenac, indomethacin, naproxen and piroxicam were associated with 4.9–19.1-times greater bleeding risk. The results were similar among patients with no history of upper gastrointestinal bleeding.

The American College of Gastroenterology (ACG) conducted a case-control study to assess the risk of gastrointestinal bleeding associated with the use of analgesics at over-the-counter doses.[40] Approximately 66% of the 627 cases and 590 controls were non-Hispanic whites. The risk of gastrointestinal bleeding was more than double in patients who were using aspirin or ibuprofen at over-the-

**Figure 3. Incidence of end-stage renal disease by primary diagnosis**




The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

counter dosages. Similar increases in risk were observed when users of aspirin, ibuprofen and naproxen were combined and users of prescription NSAIDs were analyzed. No excess risk for gastrointestinal bleeding was found among users of acetaminophen.

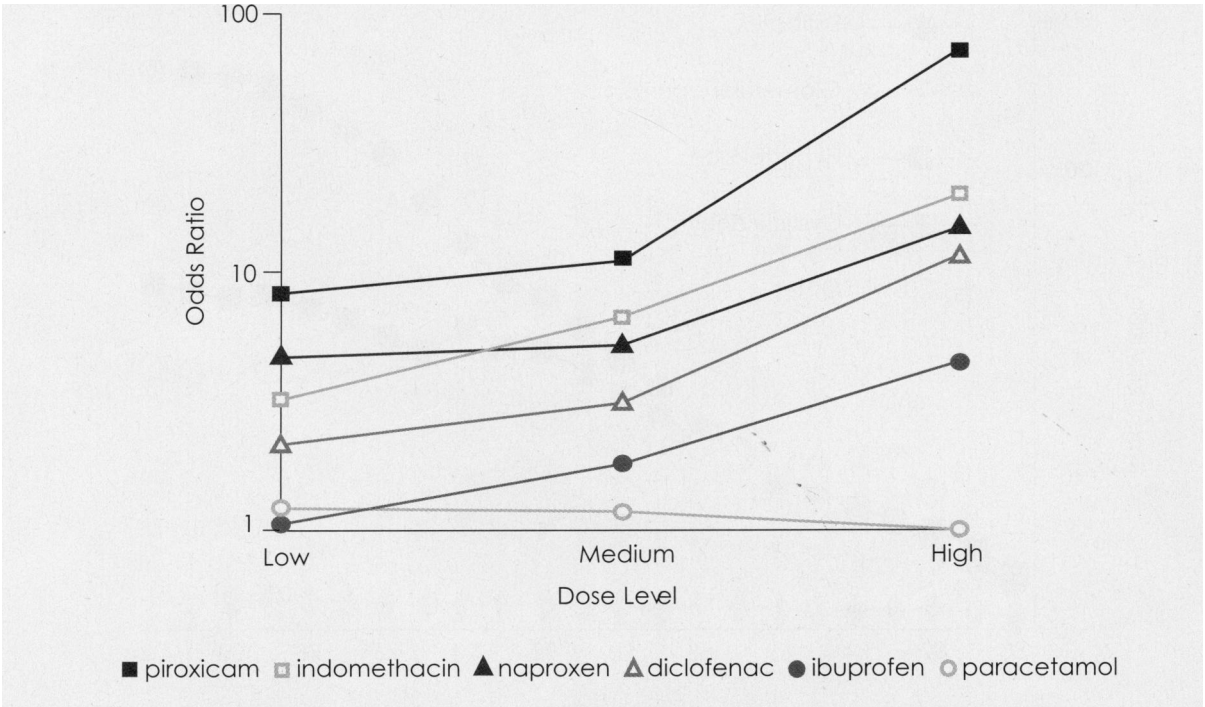
Results published by Laporte et al. were combined with two other studies to create a meta-analysis of three large clinical studies evaluating the incidence of serious upper gastrointestinal bleeding with nonaspirin NSAID therapy.[41] In total, 2,472 cases and 5,877 controls were included in the analysis. The risk of developing serious upper gastrointestinal bleeding with individual nonaspirin NSAIDs was greatest for ketoprofen [odds ratio (OR)=34.9] followed by piroxicam (13.1), naproxen (9.1), indomethacin (6.0), diclofenac (4.9) and ibuprofen (1.7), with marked dose-response relationships observed for each of these agents except ketoprofen (because of the small number of patients with >1 dose) (Figure 4). Acetaminophen was not associated with an increased risk of serious upper gastrointestinal bleeding (OR=1.2), and no dose-response relationship was observed.

A more recent case-control study evaluating the risk of upper gastrointestinal bleeding with cardiovascular drugs provided further data regarding analgesics and bleeding risk.[42] Patients hospitalized with bleeding from peptic lesions (n=1,122) comprised the patient group, and the control group included patients treated for other reasons (n=2,231). Acetaminophen (paracetamol) use was associated with a 40% reduction in the risk of upper gastrointestinal bleeding. Use of diclofenac, naproxen, aspirin, piroxicam and ketorolac was associated with a 5.1–56.7-times greater bleeding risk.

## Renal Safety and Acetaminophen

To date, little evidence exists suggestive of an association between renal toxicity and acetaminophen use. Perneger et al. conducted a case-control study in 716 patients with ESRD and 361 healthy controls to determine if the use of analgesics was associated with an increased risk of ESRD.[44] This study was conducted in the United States and participants were asked to recall their lifetime exposure to the following analgesics: acetaminophen, aspirin, phenacetin and NSAIDS (namely, ibuprofen, naproxen and indomethacin). The investigators concluded that the use of acetaminophen or NSAIDs, but not aspirin, was associated with an increased risk of ESRD. However, caution is advised in interpreting the results of this study, as several flaws in its design have been described.[45-47] The control population was not similar to the case patients regarding race, gender and presence of a chronic disease. No time relationship between the initiation of acetaminophen therapy and the onset of renal dysfunction was estab-

**Figure 4. Dose-response relationships for the risks (odds ratios) of upper gastrointestinal bleeding with individual nonaspirin, nonsteroidal antiinflammatory drugs**




Reprinted from *British Journal of Pharmacology*,[54] Lewis SC, Langman MJS, Laporte JR, et al, Dose-Response Relationships Between Individual Nonaspirin Nonsteroidal Anti-Inflammatory Drugs (NANSAIDs) and Serious Upper Gastrointestinal Bleeding: a Meta-Analysis Based on Individual Patient Data, pages 320-326, Copyright 2002, with permission from Blackwell Publishing Ltd.

lished. Such a correlation is imperative for interpreting a potential link between analgesic use and ESRD because patients who have developed renal disease are instructed to use acetaminophen for analgesia rather than NSAIDs or aspirin. Lastly, flaws associated with the validity of patient recollection of analgesic use and the lack of quantification of the actual dose of analgesics taken by study participants have put the results in a questionable light.

The question of whether the use of analgesics is associated with a decline in renal function in healthy people has been addressed in two cohort studies from the Physicians' Health Study (PHS) population.[48,49] The PHS followed initially healthy men for 14 years and evaluated the use of aspirin and beta carotene in the primary prevention of CVD or cancer. In the evaluations of analgesic use and renal function, no significant associations were found between either elevated creatinine levels or reduced creatinine clearance and the use of acetaminophen, aspirin or other NSAIDS.[48] Additionally, in healthy men with baseline and follow-up creatinine levels, occasional-to-moderate use of aspirin, acetaminophen or NSAIDS was not associated with an increased risk of renal dysfunction.[49]

Use of NSAIDs can result in edema and sodium retention.[50] Because of the adverse renal effects, the use of traditional NSAIDs or COX-2 inhibitors must be approached with caution in diabetic patients with severe renal disease. Renal syndromes associated with NSAIDs are listed in Table 2. Data from published case reports suggest that COX-2 inhibitors are associated with renal events similar to those observed with traditional NSAIDs.[51] Therefore, COX-2 inhibitors should not be used in patients with advanced renal disease. Acetaminophen, which is metabolized by the liver, is not contraindicated in patients with abnormal renal function. In light of the renal safety issues surrounding NSAIDs, the National Kidney Foundation has recommended acetaminophen as the nonnarcotic analgesic of choice for episodic use in patients with underlying renal disease.[52]

## Hepatic Safety and Acetaminophen

Acetaminophen has been reported to be the most commonly used over-the-counter drug in the United States; therefore, safety is an important consideration when evaluating this analgesic.[53] Fortunately, serious adverse reactions to acetaminophen are rare, and it is striking that few cases of alleged acetaminophen hepatotoxicity with therapeutic dosages have been reported over the past 40 years.[54] The maximum daily dose of acetaminophen is 4 g/day, and overdoses, both intentional as well as unintentional, are well known to be associated with hepatotoxicity.[55] As with all medications, it is important for patients to abide by the recommended dosing guidelines for acetaminophen. Acetaminophen is among the safest of all over-the-counter analgesics, and the risk of hepatotoxicity is quite low when acetaminophen is given in recommended dosages compared with instances of repeated supratherapeutic doses (>4 g/day). A hypothesis for an alcohol–acetaminophen syndrome involving the induction of enzymes that metabolize acetaminophen has generated some controversy regarding the therapeutic use of acetaminophen in the alcoholic patient.[56] To date, data from a systematic review and a prospective study indicate that therapeutic doses of acetaminophen are not associated with liver injury in alcoholic patients.[57,58]

Four cases of liver toxicity with acetaminophen therapy of ≤4 g/day administered for two days to 13 months have been reported.[59-62] Two of these reports are confounded by a history of infectious hepatitis, presence of only one congenital kidney, and cardiopulmonary and renal insufficiency.[60,61] These four isolated cases represent a comparatively small incidence of liver toxicity associated with chronic administration of acetaminophen at the recommended dose. Therefore, acetaminophen, when taken up to 4 g/day, is a safe treatment option for the provision of analgesia.

## DISCUSSION

Osteoarthritis is a common, debilitating disease affecting men and women of all races. African Americans suffering from osteoarthritis have a high incidence rate of comorbid conditions such as hypertension, CVD risk and diabetes. Ideally, treatment of the chronic pain of osteoarthritis in African-American patients with hypertension, CVD risk or diabetes should avoid worsening hypertension, renal and cardiac disease.

Because they affect prostaglandin synthesis, traditional NSAIDs and COX-2 selective agents are associated with the blockade of the therapeutic effects of antihypertensive medications. Alternative analgesics such as acetaminophen that do not affect prostaglandin synthesis should be considered for the management of chronic pain associated with osteoarthritis in hypertensive patients. The cardioprotective benefits as well as the gastrointestinal bleeding risks of low-dose aspirin therapy are well established. The risk of gastrointestinal bleeding is increased when this therapy is used concurrently with NSAIDs. In patients with a history of CVD or CHF, NSAIDs should be used with caution because of the potential doubling of CHF risk in susceptible patients, with an even greater risk for patients with renal failure, diabetes or hypertension.[63]

Consideration of the adverse outcomes associated with NSAIDs in patients with the comorbidities described in this paper is important when selecting the best analgesic therapy for individual patients. Based on these considerations, NSAIDs and COX-2 inhibitors should be used with caution. In contrast, the bulk of the safety data suggest that acetaminophen is associated with relatively few adverse events, although isolated cases of renal or hepatic toxicity exist. Acetaminophen

is recommended in the American College of Rheumatology* (ACR) guidelines for the medical management of osteoarthritis as a first-line analgesic treatment for pain associated with osteoarthritis.[64] The National Kidney Foundation recommends acetaminophen as nonnarcotic analgesic of choice in patients with underlying renal disease.

When recommending strategies for the control of pain associated with osteoarthritis in African-American patients with hypertension, renal or cardiac disease, the clinician should take into account the safety of various analgesic agents. Acetaminophen is characterized by widespread use and an exceptional safety profile, so it should be considered as the analgesic of choice over aspirin or NSAIDs for the management of chronic osteoarthritic pain in patients with concurrent hypertension, CVD risk factors or diabetes.

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