

Blood Pressure Destabilization and Related Healthcare Utilization Among Hypertensive Patients Using Nonspecific NSAIDs and COX-2-Specific Inhibitors

Sean Z. Zhao, MD, PhD; Thomas A. Burke, PharmD, MPH;
Andrew Whelton, MD, PhD; Heather von Allmen;
and Scott C. Henderson, MS

Abstract

Objective: To determine the incremental cost of blood pressure (BP) destabilization among patients with stable hypertension who newly initiate therapy with celecoxib, rofecoxib, or 3 commonly used nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen, diclofenac, or naproxen, based on incidence rates of BP destabilization and costs of BP destabilization events obtained from a single observational data source.

Methods: Historical group observational analysis was performed based on real-life practice data that are contained in the LifeLink™ Integrated Claims Solutions employer claims databases. Patients with stable hypertension who had newly initiated therapy with rofecoxib, celecoxib, ibuprofen, diclofenac, or naproxen between January 1, 1999, and September 30, 2000, were identified from the database. The study consists of 3 components. First, the incidence rate of BP destabilization, based on patients' time of exposure to studied drugs, was estimated. Then, the cost of a BP destabilization event was determined by matching all BP destabilization cases with non-BP destabilization cases and following them for 90 days. The differences in the total costs between cases and controls were considered an estimate of the costs associated with managing the BP destabilization event. Last, the drug-specific incremental costs of BP destabilization of using each treatment were estimated in comparison with celecoxib. Incremental costs of BP destabilization were determined by multiplying the specific excess incidence rate of BP destabilization for each of the specific drugs, relative to celecoxib, by the cost of a BP destabilization event.

Results: The adjusted incidence rate of outpatient BP destabilization for celecoxib was 2.27 per 1000 patient-days vs 2.66 for rofecoxib ($P < .001$)

or 2.65 for nonspecific NSAIDs ($P < .001$). The incremental cost of BP destabilization per patient per day of drug utilization for the study drugs compared with celecoxib were \$0.18 for rofecoxib and \$0.17 for nonspecific NSAIDs. The higher costs of BP destabilization relative to celecoxib were due to the higher incidence of outpatient BP destabilization associated with the other study drugs. The average incremental healthcare cost for an outpatient BP destabilization event within the first 90 days of the event was \$458.99. The incidence of inpatient BP destabilization among rofecoxib users was significantly higher than among celecoxib users (risk rate = 4.17; 95% CI, 1.86-9.26; $P < .001$). Incremental cost was not estimated for inpatient BP destabilization because the sample size was too small to provide a stable result.

Conclusion: The costs of managing BP destabilization were significantly lower for celecoxib compared with rofecoxib and nonspecific NSAIDs. The observed differences among these anti-inflammatory drugs in the costs of BP destabilization will have a significant impact on the total cost of therapy in patients with stable hypertension. In addition to the monetary cost of BP destabilization, the physical cost to the patient regarding development or exacerbation of this serious medical condition should be considered when choosing between cyclooxygenase-2-specific inhibitor therapies.

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Arthritis and hypertension are the 2 most prevalent chronic conditions affecting people aged 65 years and older; for many patients, they exist as

comorbid disorders.¹ In the United States, approximately 20 million people are receiving concurrent therapy for arthritis and hypertension.² In many cases, nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, or diclofenac, are used for symptomatic relief of arthritis in conjunction with antihypertensive medications needed for blood pressure (BP) control. Historically, nonspecific NSAIDs could complicate the management of hypertension.³ Nonspecific NSAIDs are well known to cause increases in BP and to disrupt the antihypertensive effects of some medications, particularly angiotensin-converting enzyme inhibitors and β -blockers. Meta-analyses indicate that nonspecific NSAIDs increase mean arterial BP by up to 5 mm Hg, with effects particularly evident in patients whose BP had been well controlled.^{4,5}

The cyclooxygenase (COX)-2-specific inhibitors are a new class of anti-inflammatory drugs that do not inhibit the COX-1 isozyme. Because COX-1 is mostly responsible for constitutive production of prostaglandins in the gastrointestinal (GI) tract, the COX-2-specific inhibitors offer the potential for improved GI safety relative to nonspecific NSAIDs.^{6,7} Large outcome trials have already established that COX-2-specific inhibitors provide improved upper GI safety relative to the nonspecific NSAIDs.^{8,9} However, other effects of these agents in hypertensive patients are less clear. There may be differences in BP control among COX-2-specific inhibitors that are similar to the differences observed for various nonspecific NSAIDs.³ In 2 separate head-to-head clinical trials conducted in older hypertensive osteoarthritis (OA) patients, rofecoxib patients were significantly more likely to experience clinically significant increases in systolic BP than celecoxib patients.^{10,11}

BP destabilization and its related complications may have a significant impact on healthcare utilization by increasing resource use.¹² However, the cost of BP destabilization has not been well documented in real-life practice among hypertensive patients who received nonspecific NSAIDs or COX-2-specific inhibitors.

The primary objective of this study was to determine the costs of BP destabilization associated with using rofecoxib, ibuprofen, naproxen, and diclofenac, relative to celecoxib, in a single observational database. To estimate the costs, we determined, separately, the incidence of patients with at least 1 BP destabilization event and the average cost of each event, regardless of an association with a nonspecific NSAID or COX-2-specific inhibitor, within 90 days of the occurrence of the event.

...PATIENTS AND METHODS...

Data Resources

The study was based on the LifeLink™ database (LifeLink Corp., Park City, UT) from real-life practice. LifeLink Integrated Claims Solutions is an employer claims database that captures claims from more than 40 indemnity and preferred provider organization plans. This database covers approximately 1.8 million employees, dependents, and retirees, and allows patient and prescription claims to be tracked longitudinally across multiple sites of care.

Study Design

This study includes 3 components. First, using a historical group analysis, the study determined the incidence rate of BP destabilization claims based on patients' time of exposure to study drugs and BP destabilization events associated with the exposures after adjusting for confounding factors. Then, the average incremental healthcare utilization per BP destabilization event was determined by matching all BP destabilization cases with non-BP destabilization cases and following them for 90 days. Last, drug-specific incremental costs of BP destabilization, presented as cost per patient per day of drug utilization, using rofecoxib and nonspecific NSAID (ibuprofen, naproxen, and diclofenac) treatment were estimated in comparison with celecoxib. Incremental costs were determined by multiplying the specific excess incidence rate of BP destabilization claims for each specific drug by

the average incremental cost of managing each BP destabilization event.

Study Sample Selection (Patients)

The LifeLink database was reviewed to identify users of celecoxib, rofecoxib, ibuprofen, naproxen, and diclofenac between January 1, 1999, and September 30, 2000. To qualify as a study index prescription, the patient must not have filled a prescription for any nonspecific NSAID or COX-2-specific inhibitor within the preceding 180-day period. It was possible for patients to have more than 1 study index prescription if these drug-using episodes met the definition of a study index prescription; however, each patient was observed only once on each therapy. Patients were eligible for this analysis if they had a stable hypertension condition defined as having received fixed, stable antihypertensive drug therapy for at least 3 consecutive months out of the 4 months immediately prior to this index prescription. Patients were also required to have remained continuously enrolled in the database for 12 months prior to their COX-2-specific inhibitor or nonspecific NSAID index date.

A group of 53 510 patients met inclusion criteria. They had received a total of 55 396 index prescriptions. The demographics, medical history, and drug usage of this patient population are described earlier in this supplement.¹³

Identifying the Differences in Baseline Risk of Cardiovascular Diseases and Disorders

To understand potential differences in the baseline risk factors, we evaluated the history of each patient in terms of specific risk factors for cardiovascular diseases (CVDs) and disorders during the 12 months prior to their index date. A detailed description of cardiovascular channeling bias (found in Zhao et al 2002, in this supplement¹³) showed that patients prescribed COX-2-specific inhibitors had a higher incidence of cardiovascular risk factors at baseline than those prescribed nonspecific NSAIDs. Since there were significant differences in demographic and

clinical characteristics among study drugs, adjustments were made for these confounding factors (eg, older age, female gender, higher prevalence of CVD) using multivariate analyses and direct adjustment methods.

Definition and Determination of the Incidence Rate of Patients With Blood Pressure Destabilization

Either of the following events reported at least 1 day after the start of COX-2-specific inhibitor or nonspecific NSAID therapy qualified as a BP destabilization event: (1) an increase in the daily dose of antihypertensive medication, and/or (2) initiation of a new antihypertensive medication. Because all patients were required to be on stable antihypertensive therapy at the time of the index prescription, any indication of BP destabilization was considered a new event. Patients were observed only until the first occurrence of BP destabilization.

Since no standard definition of BP destabilization based on claims data was available, we conducted a separate analysis using an alternate definition of BP destabilization based on physician diagnoses of hypertension indicative of BP destabilization. We identified 2 additional criteria: (1) 2 medical encounters (outpatient physician visit, emergency department visit, or hospitalization) occurring within 60 days during the exposure period of a study drug with a documented *International Classification of Diseases-ninth revision-Clinical Modification* (ICD-9-CM) diagnosis of hypertension (ICD-9 = 401-404); or (2) 1 medical encounter with a diagnosis of hypertension, which was accompanied by a switch to a different COX-2-specific inhibitor or nonspecific NSAID within 30 days after the hypertension claim. The purpose of this analysis was to see if cases identified by these alternative criteria (based on hypertension diagnoses) had a significant impact on the number of cases identified among study groups.

During the observation period, patients were defined as being on therapy only for the duration of the days' supply of each prescription. The time from the end of the

days' supply of 1 prescription until the day the following prescription was filled was defined as a break in therapy. A BP destabilization event was considered attributable to drug therapy if it occurred during the days-supply period or within 5 days following the end of the days' supply of any prescription. Observation for a given drug was stopped if a patient received a prescription for a different nonspecific NSAID or COX-2-specific inhibitor, the patient disenrolled from the plan, or the database period ended (March 31, 2001). Since ibuprofen, naproxen, and diclofenac all belong to the nonspecific NSAID class, we combined them into 1 group for the analysis.

Determination of Average Incremental Cost of Blood Pressure Destabilization Events

The incremental cost of BP destabilization was estimated by comparing the total healthcare costs for patients with an event to a matched control group without the event. The differences in the total costs between cases and controls (ie, incremental cost) were considered an estimate of the costs associated with managing the BP destabilization event.

The control group was comprised of hypertensive COX-2-specific inhibitor or nonspecific NSAID users who did not have BP destabilization during the observation period. Control patients were randomly selected and matched to those with BP destabilization on a 1-to-1 basis according to drug, age in 10-year intervals, gender, history of CVD, and history of diabetes. Patients who could not be matched on all criteria were matched by drug, age, and a combined measure of history of CVD and/or diabetes. In addition, when the 10-year age groups were too sparsely populated in the set of potential controls, adjacent age groups were combined to permit a 1-to-1 match between the cases and controls.

Among cases, healthcare costs were computed for 2 different follow-up periods: the 30 days following the outpatient claim (including the date of the event) and the 31 to 90 days following the outpatient event. Costs for the control group were

calculated based on a 0- to 30-day period and 31- to 90-day period following a randomly selected index date. Since it is very difficult to calculate outpatient BP destabilization-specific costs (eg, due to lack of defined episode of care, differences in medical coding at follow-up visits, and distinguishing resources as wholly, partially, or nonattributable to BP destabilization), costs within these 2 periods were computed as the total cost from all claims incurred during the respective time periods and were classified as inpatient, outpatient, outpatient pharmacy, and outpatient laboratory costs. All costs were determined from the insurer's perspective, including the amounts paid by private insurers, Medicare, and other secondary insurers, and not from the amount billed to the insurer. Costs of a BP destabilization event were aggregated across study groups.

To describe healthcare utilization for BP destabilization, 2 additional analyses were performed. First, the percentage of patients with at least 1 inpatient, outpatient, pharmacy, or laboratory claim was compared between cases and controls. Second, the distribution of costs by resource type (eg, inpatient, outpatient) for these claims was compared between cases and controls.

Determination of Specific Incremental Per-Patient-Per-Day Cost of Using Study Drug

The estimation of the specific incremental per-patient-per-day cost of treatment with rofecoxib and 3 commonly used nonspecific NSAIDs, ibuprofen, naproxen, and diclofenac, was calculated in reference to celecoxib treatment. In this analysis, the excess adjusted incidence rate of BP destabilization for the study drugs relative to celecoxib was first calculated. Then, the adjusted excess incidence claim rate was multiplied by the average incremental cost of a BP destabilization event to obtain the drug-specific incremental cost per patient per day of using each study drug.

Statistics

Claims rates were computed as the total number of patients with at least 1 BP

destabilization event attributable to non-specific NSAID or COX-2-specific inhibitor therapy divided by the total days of exposure to the drug across all patients. Claims rates were expressed per 1000 patient-days of exposure. Poisson multiple regression models were used to compare incidence rates across groups after adjusting for all demographic and risk factors listed in **Table 1**.

Average incremental costs of a BP destabilization event were estimated by a weighted geometric mean using a natural logarithm transformation. The mean was weighted by adjusting the data to the demographic and clinical distribution of a standard population; the standard population was based on the age, gender, and history of CVD and diabetes characteristics of all the members of the study group. In this analysis, multiple regression models were run on the natural logarithm transformed cost values to compare costs between patients with and without BP destabilization. Then, based on the results from multiple regression, we estimated cost for patients with or without BP destabilization and the difference between the 2 groups (average incremental cost of BP destabilization) using direct adjustment. Statistical Analysis System (SAS) Release 8.02 (SAS Institute, Cary, NC) was used in all statistical comparisons.

...RESULTS...

Claims Rates for Blood Pressure Destabilization

A total of 53 510 patients who had a stable hypertensive condition received a total of 55 396 new prescriptions for a COX-2-specific inhibitor or non-specific NSAID. Among them, 11 375 patients had at least 1 outpatient claim for a BP destabilization event. When adjusted for age, gender, specialty of primary provider, medical history, type of BP medication, medications influencing hypertension, antidepressants, and anticoagulant drugs, patients treated with celecoxib were significantly less likely to have a claim for outpatient BP destabilization as compared with rofecoxib and non-specific NSAIDs (Table 1).

The adjusted outpatient claims rate was 2.66 per 1000 patient-days of exposure with rofecoxib, which was 17% higher than the rate of 2.27 per 1000 patient-days with celecoxib ($P < .001$). Similarly, the adjusted outpatient claims rate was 2.65 per 1000 patient-days with the non-specific NSAIDs, which was also 17% higher than the rate for celecoxib ($P < .001$). The adjusted outpatient claims rate was not significantly affected by patient gender, but patient age and specialty of primary providers were significantly associated with BP destabilization. Patients with a medical history of ischemic heart disease, heart failure, other forms of heart disease, cerebrovascular disease, or diabetes were 11% to 25% more likely to have an outpatient claim ($P < .001$) (Table 1). Moreover, patients receiving medications that influenced hypertension, including corticosteroids, sympathomimetics, and appetite suppressants, were 5% to 17% more likely to have a claim ($P < .05$). In addition, patients receiving antidepressants (risk rate [RR] = 1.08; 95% [CI], 1.03-1.13) and anticoagulant drugs (RR = 1.12; 95% CI, 1.04-1.20) also had significantly greater rates of BP destabilization claims ($P < .01$). In contrast, the claims rate was 10% lower in patients with a history of hyperlipidemia ($P < .001$) and 5% lower among those receiving estrogens ($P < .05$).

Using the "alternative" definition of BP destabilization, only 982 additional cases (less than 8% of total cases) were identified by adding 2 additional criteria to the previous criteria. Patients on non-specific NSAIDs had a slightly greater proportion of cases identified by using the alternative definitions compared with those taking celecoxib or rofecoxib. There was no difference in the proportion of new cases using this alternative definition between the celecoxib and rofecoxib groups. Therefore, the definition used in the original design seems appropriate and sensitive enough to identify BP destabilization cases without hypertension diagnosis.

Only 29 patients (.0043 per 1000 patient-days) had claims for an inpatient BP destabilization event. After adjusting for demographic and risk factors, the

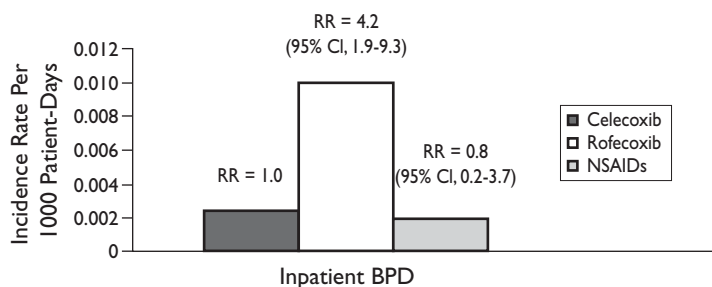
Table 1. Percentage of Patients With at Least 1 Blood Pressure Destabilization Outpatient Event During the Nonspecific NSAID or COX-2–Specific Inhibitor Exposure Period

	Number of Patients With Event	Days of Exposure	Adjusted Rate Ratio	95% CI of Adjusted Rate Ratio	Adjusted Rate per 1000 pt-d	Adjusted P
Drug Group (n)						
Celecoxib (20 915)	5740	2 527 114	1.00	ref	2.27	
Rofecoxib (12 952)	3460	1 322 883	1.17	1.12-1.22	2.66	<.001
Nonspecific NSAIDs (ibuprofen, naproxen, diclofenac) (21 529)	2175	879 717	1.17	1.10-1.23	2.65	<.001
Patient Age Categories						
60+	8896	3 546 610	1.00	ref	2.51	
50-59	2003	943 445	0.94	0.89-0.99	2.35	<.05
<50	476	239 659	0.81	0.81-0.97	2.02	<.05
Patient Gender						
Male	4343	1 805 632	1.00	ref	2.41	
Female	7032	2 924 082	0.99	0.95-1.04	2.38	NS
Primary Provider Specialty						
Family practice	3690	1 657 150	1.00	ref	2.23	
Internal medicine	3657	1 451 550	1.08	1.03-1.13	2.40	<.01
Orthopedic surgery	854	381 154	1.03	0.95-1.10	2.28	NS
Rheumatology	422	187 028	1.01	0.90-1.12	2.24	NS
Cardiology	294	101 263	1.12	0.99-1.27	2.50	.06
Neurology	185	75 156	1.06	0.91-1.22	2.35	NS
Other	1309	507 216	1.17	1.10-1.24	2.60	<.001
Unknown	964	369 197	1.14	1.06-1.22	2.53	<.01
Medical History						
Ischemic heart disease	2939	1 005 496	1.11	1.06-1.16	2.66	<.001
Other forms of heart disease	2741	892 037	1.13	1.08-1.19	2.72	<.001
Hyperlipidemia	2364	1 074 637	0.90	0.86-0.94	2.16	<.001
Diabetes	1906	657 663	1.14	1.08-1.20	2.74	<.001
Cerebrovascular disease	1153	374 745	1.11	1.05-1.19	2.68	<.001
Heart failure	938	222 287	1.25	1.16-1.34	3.01	<.001
Rheumatoid arthritis	280	119 187	0.96	0.84-1.08	2.30	NS
Myocardial infarction	210	63 674	1.06	0.92-1.22	2.54	NS
Diseases of pulmonary circulation	140	46 744	0.91	0.77-1.08	2.19	NS
Nephritis, nephrotic syndrome	137	37 509	1.17	0.98-1.39	2.81	.08
Acute renal failure	48	10 775	1.25	0.93-1.68	3.01	NS
Blood Pressure Medication Type						
Antihypertensive	10 219	3 922 040	2.32	2.17-2.48	5.58	<.001
Diuretic	5393	1 731 818	1.76	1.68-1.83	4.22	<.001
Combination	1253	554 031	1.50	1.41-1.60	3.62	<.001
Medications Influencing Hypertension						
Sympathomimetics	2769	1 097 876	1.05	1.00-1.10	2.52	<.05
Estrogens	2657	1 175 189	0.95	0.90-0.99	2.28	<.05
Corticosteroids	1754	675 173	1.06	1.01-1.12	2.55	<.05
Appetite suppressants	265	99 265	1.17	1.03-1.32	2.81	<.05
Erythropoietin	16	4621	1.00	0.61-1.64	2.40	NS
Cyclosporine	11	2975	1.20	0.66-2.17	2.88	NS
Antidepressants	2824	1 089 669	1.08	1.03-1.13	2.60	<.001
Anticoagulants	935	281 676	1.12	1.04-1.20	2.68	<.001

NSAID indicates nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; NS, nonsignificant; ref, reference variable.

claims rate was more than 4 times higher with rofecoxib than celecoxib (.010 vs .0024 per 1000 patient-days; RR = 4.17; 95% CI, 1.86-9.26; $P < .001$). The claims rate for inpatient BP destabilization in the combined nonspecific NSAID group (ibuprofen, naproxen, and diclofenac) did not differ significantly from celecoxib ($P = .77$) (Figure 1). An association between the inpatient claims rate and patient age, gender, specialty of primary provider, type of BP medication, medications influencing hypertension, or medical history (in most instances) was not evident due to the small number of events. However, the analysis did find that history of cerebrovascular disease (RR = 2.65, $P < .05$)

Figure 1. Comparison of Incidence Rates of Patients With at Least 1 Inpatient Blood Pressure Destabilization (BPD) Event Among Celecoxib, Rofecoxib, and Nonspecific NSAID Groups



P values are based on Poisson multiple regression models controlling for confounding factors listed in Table 1.

Table 2. Distribution of Demographic and Clinical Characteristics of Groups With or Without Outpatient Blood Pressure Destabilization*

Variable Description	Patients With Events		Patients Without Events		χ^2	<i>P</i>
	No.	%	No.	%		
Total Sample Size	11 375	100.0	11 375	100.0		
Drug Group (n)						
Celecoxib (20 915)	5740	50.5	5740	50.5	0.00	1.000
Rofecoxib (12 952)	3460	30.4	3460	30.4		
Ibuprofen (10 789)	986	8.7	986	8.7		
Naproxen (8840)	928	8.2	928	8.2		
Diclofenac (1900)	261	2.3	261	2.3		
Patient Age Categories						
75+	3829	33.7	3829	33.7	0.00	1.000
55-74	6246	54.9	6246	54.9		
<55	1300	11.4	1300	11.4		
Patient Gender						
Male	4343	38.2	4304	37.8	0.28	.594
Female	7032	61.8	7071	62.2		
History of Cardiovascular Diseases and Disorders	4981	43.8	4885	43.0	1.65	.199
History of Diabetes	1906	16.8	1883	16.6	0.17	.682
Primary Provider Specialty						
Family practice	3690	32.4	3736	32.8	70.28	<.001
Internal medicine	3657	32.1	3285	28.9		
Orthopedic surgery	854	7.5	949	8.3		
Rheumatology	422	3.7	356	3.1		
Cardiology	294	2.6	259	2.3		
Neurology	185	1.6	207	1.8		
Other	1309	11.5	1634	14.4		
Unknown	964	8.5	949	8.3		

*Patients were matched for drug, age in 10-year intervals, gender, history of cardiovascular disease (CVD), and history of diabetes. If perfectly matched controls could not be found, the cases were matched for drug, age, gender, and a combined history of CVD or diabetes. In addition, when the 10-year age groups were too sparsely populated in the set of potential controls, adjacent age groups were combined to permit a 1-to-1 match between cases and controls.

and acute renal failure (RR = 12.20, $P < .05$) was significantly associated with inpatient BP destabilization claims (data not shown in Table 1).

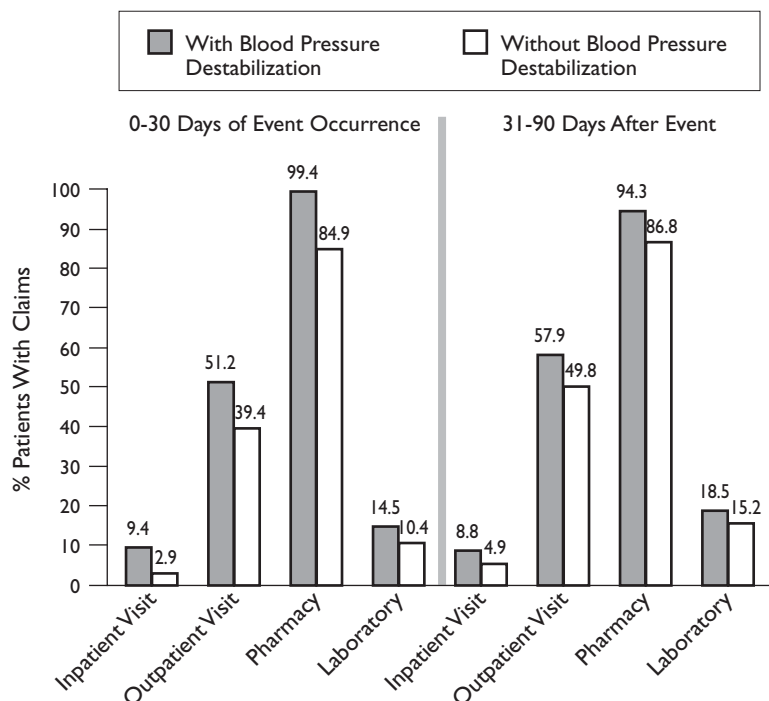
Estimation of Average Incremental Cost of Outpatient BP Destabilization Events

All identified 11 375 patients who had at least 1 outpatient BP destabilization claim were matched with 11 375 patients who did not have claims for outpatient BP destabilization. The cases and controls did not differ significantly in terms of study drug used, patient age group, gender, history of CVD, or history of diabetes (Table 2). A significant difference ($P < .01$) was found in the specialty of the prescribing primary provider, but the proportion of each type of provider is quite comparable.

The cost for patients with an outpatient BP destabilization event during the periods within 30 days of occurrence and 31 to 90 days after the event was signifi-

cantly higher than the cost for those without an event. During the 0- to 30-day period (including initial treatment of event), the direct adjusted geometric mean cost was \$358.50 (95% CI, \$350.21-\$366.99; median cost: \$349.91) for those with BP destabilization compared with \$113.78 (95% CI, \$109.39-\$118.35; median cost: \$182.66) for those in the control group ($P < .001$). Similarly, during the 31- to 90-day period, the mean cost was \$421.79 (95% CI, \$407.88-\$436.19; median cost: \$512.44) and \$207.52 (95% CI, \$198.93-\$216.47; median cost: \$346.85) for those with and without outpatient BP destabilization, respectively ($P < .001$). Therefore, the incremental cost for those with BP destabilization compared with those without an event was \$244.72 per patient within the first 30 days and \$214.27 per patient between 31 and 90 days after the event. The average incremental cost for an outpatient BP destabilization event within the first 90 days of the event was \$458.99.

Figure 2. Comparison of Claims Between Hypertensive Patients With and Without an Outpatient Blood Pressure Destabilization (BPD) Event



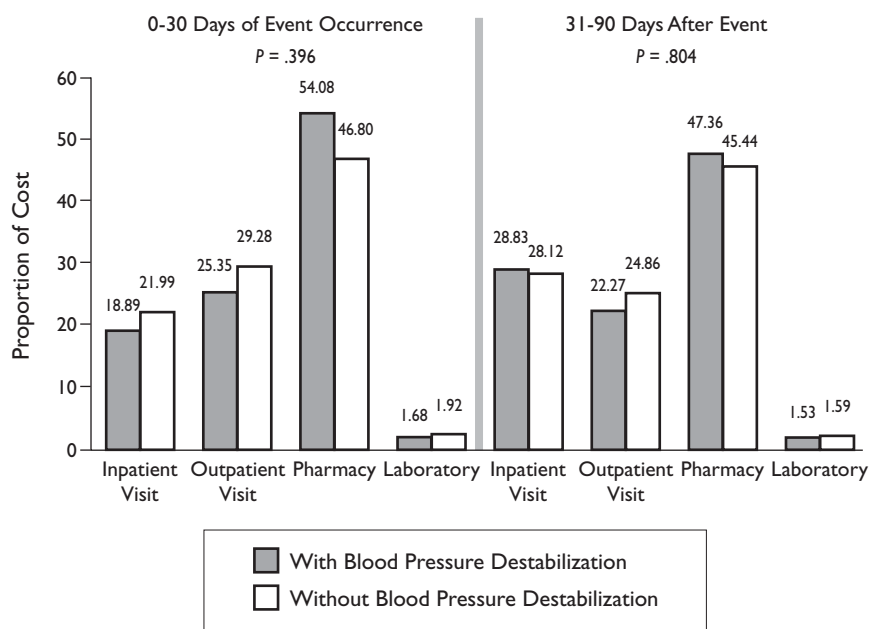
All $P < .001$. P values are based on χ^2 testing between patients with and without BPD.

Patients with BP destabilization were significantly more likely to have claims for inpatient and outpatient visits, outpatient pharmacy costs, and outpatient laboratory costs than those in the control group during both the 0- to 30-day and 31- to 90-day periods ($P < .001$) (Figure 2). However, the proportion of costs from each of these resources compared with total cost did not differ between the 2 groups, with pharmacy costs representing nearly half the total costs and inpatient costs and outpatient visit costs each accounting for approximately one fourth. Outpatient laboratory costs accounted for 1.5% to 1.9% of total costs (Figure 3).

Estimation of Specific Incremental Cost Per Patient Per Day

The adjusted incidence rate of claims for outpatient BP destabilization was higher with rofecoxib (adjusted incidence rate [adj IR] = 2.66 per 1000 patient-days) and nonspecific NSAIDs (adj IR = 2.65 per 1000 patient-days) compared with celecoxib (adj IR = 2.27 per 1000 patient-days) ($P < .001$ for all comparisons). The difference in the adjusted rate of patients

Figure 3. Comparison of Proportion of Cost by Resource Between Hypertensive Patients With and Without an Outpatient Blood Pressure Destabilization Event (BPD)



P values are based on χ^2 testing between patients with and without BPD. The proportion was calculated by: cost of each specific resource/sum of 4 studied resources x 100

with at least 1 outpatient BP destabilization claim compared with celecoxib was \$0.39 for rofecoxib and \$0.38 for the non-specific NSAID group. When the excess incidence rate was multiplied by the average incremental cost for an outpatient BP destabilization event relative to celecoxib, the specific incremental attributable cost of BP destabilization was \$0.18 and \$0.17 per patient per day of treatment with rofecoxib or a nonspecific NSAID, respectively (Table 3). Slightly more than half of this incremental attributable cost was realized within the first 30 days of the event.

Incremental costs were not estimated for inpatient BP destabilization because the sample size was too small and did not provide a stable result.

...DISCUSSION...

This study analyzes real-life data from patients with stable hypertension. The results of this observational study show that compared with celecoxib, there are

considerable additional costs in terms of monetary values as well as physical values associated with BP destabilization when using rofecoxib and 3 commonly used non-specific NSAIDs. These additional costs will have a substantial impact on the total cost of therapy in treating patients with stable hypertension. The higher incidence of BP destabilization can be explained by a higher adjusted rate of outpatient claims for BP destabilization for the rofecoxib and non-specific NSAID groups in comparison with celecoxib. In addition, the adjusted incidence of inpatient BP destabilization claims among rofecoxib users was 4 times higher than that for celecoxib users and the non-specific NSAIDs group, which, to be conservative, were not incorporated into the incremental estimates. Thus, the study showed that both inpatient and outpatient BP destabilization were more strongly associated with rofecoxib than with celecoxib. The outpatient BP destabilization claims were also more strongly associated with non-specific NSAIDs than celecoxib.

Table 3. Attributable Incremental Cost of Outpatient Blood Pressure Destabilization Related to Rofecoxib and 3 Commonly Used Nonspecific NSAIDs Compared With Celecoxib

	Rofecoxib	Nonspecific NSAID
Relative Risk (Adjusted RR)	1.172	1.168
Difference of Adjusted Rate of Patient With at Least 1 BP Destabilization Claim (Compared With Celecoxib)	0.39	0.38
Incremental Attributable Cost of BP Destabilization Per Patient Per Day of Nonspecific NSAIDs or Rofecoxib Treatment		
Total cost in 90 days of occurrence of event	\$0.18	\$0.17
0-30 days of occurrence of event	\$0.10	\$0.09
31-90 days after event	\$0.08	\$0.08

NSAID indicates nonsteroidal anti-inflammatory drug; RR, risk rate; BP, blood pressure.

In addition to serious medical complications, BP destabilization can have costly financial implications. In this analysis, patients with outpatient BP destabilization had significantly higher adjusted health-care costs ($P < .001$) than a control group without BP destabilization matched for age, gender, and history of CVD and diabetes. The higher costs were evident within the first 30 days after the event, and they persisted at higher levels in the period 31 to 90 days after the event. During both periods, patients with BP destabilization were significantly more likely to have claims for inpatient care, physician visits, pharmacy costs, and laboratory tests (all $P < .001$). Nevertheless, between treatments the proportion of costs attributed to each of these resources remained unaffected. Adjusted incremental costs for the 31- to 90-day period (\$3.57/d) were considerably lower than those for the 0- to 30-day period (\$7.89/d), suggesting the study design and time period are appropriate for this analysis.

The results of this analysis are consistent with those of 2 randomized prospective clinical trials comparing the effects on BP control of celecoxib and rofecoxib in hypertensive elderly OA patients. They suggest that the difference between celecoxib and rofecoxib may be the consequence of direct renal effects of the rofecoxib molecule or its metabolites rather than a pharmacologic

class effect of the COX-2-specific inhibitors.^{10,11} An alternative hypothesis is that celecoxib may inhibit carbonic anhydrase, leading to lower blood pressures. In a randomized clinical trial of 810 older hypertensive OA patients, rofecoxib 25 mg qd was significantly more likely than celecoxib 200 mg qd to cause clinically significant elevations in systolic hypertension (17% vs 11%, $P = .032$), as defined by an increase in systolic BP >20 mm Hg to an absolute level >140 mm Hg.¹⁰ This increase in systolic BP should lead to a change in antihypertensive medication according to current guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI),¹⁴ which is consistent with one of the definitions used for BP destabilization in the present study. In a second randomized clinical trial of 1092 older hypertensive OA patients, rofecoxib 25 mg qd was again more likely than celecoxib 200 mg qd to cause clinically significant elevations in systolic BP (15% vs 7%, $P < .001$).¹¹

The differences seen between celecoxib and rofecoxib in this study and in randomized clinical trials are consistent with a survey of patients from the National Data Bank for Rheumatic Diseases.¹⁵ Patients using celecoxib, rofecoxib, or nonspecific NSAIDs completed a questionnaire concerning hypertension. After controlling for age, gender, and arthritis

diagnosis, the incidence of patient-reported increases in BP among hypertensive patients was significantly higher with rofecoxib compared with patients not using nonspecific NSAIDs or COX-2-specific inhibitors (odds ratio [OR] = 1.55, $P < .001$), whereas patients taking celecoxib or nonspecific NSAIDs were not at significantly increased risk compared with nonusers (OR = 1.16 and 1.12, respectively; $P = .17$ and $.22$, respectively). Similarly, patients receiving rofecoxib were more likely to report difficulty controlling their BP.

In the present observational study, celecoxib had a significantly lower adjusted rate of claims for outpatient BP destabilization than the nonspecific NSAIDs. As noted in the survey described above, the incidence of patient-reported increases in BP and the incidence of difficulty in controlling BP were comparable for celecoxib and nonspecific NSAIDs.¹⁵ Similarly, in the multinational SUCCESS-I trial, more than 13 000 patients with OA were randomly assigned to treatment with celecoxib 200 or 400 mg daily, naproxen 1000 mg daily, or diclofenac 100 mg daily for 12 weeks.¹¹ The incidence of BP changes ≥ 15 mm Hg did not differ significantly between celecoxib and the nonspecific NSAIDs for systolic BP (8.4% vs 9.3%) or diastolic BP (6.8% vs 6.7%). Moreover, investigators reported a similarly low rate of aggravated hypertension in patients treated with celecoxib or nonspecific NSAIDs (0.3%). It is unclear why the results comparing celecoxib with the nonspecific NSAIDs in the present observational study differ from those in the other studies. However, each study differed in several fundamental ways, including measured outcome, study design, patient population, and clinical setting.

Furthermore, the study did not find a significant difference in inpatient BP destabilization between nonspecific NSAIDs and celecoxib (.0024 vs .0019 per 1000 patient-days; $P = .77$). Inpatient diagnosis based on diagnosis-related group codes may be a more reliable measure for a disease or condition than the definition of BP destabilization used in this study. These

inpatient results may suggest that celecoxib and nonspecific NSAIDs may have a similar risk for BP destabilization, but the risk with rofecoxib is significantly higher.

The BP destabilization-related cost per patient per day of celecoxib use was considerably lower than that of rofecoxib and the 3 studied nonspecific NSAIDs. The BP destabilization-specific incremental cost was \$0.18 more per day for rofecoxib than for celecoxib. For example, with over 4.7 million patient-days of drug exposure in the 3 drug groups during the study period, we estimate that treating the entire group with celecoxib would result in outpatient BP costs that were \$850 000 lower, as compared with treating the entire group with rofecoxib. Meanwhile, the BP destabilization-specific incremental cost for nonspecific NSAIDs (ibuprofen, naproxen, and diclofenac) was \$0.17 per day relative to celecoxib, indicating that celecoxib is associated with lower attributable costs for managing BP destabilization events than both rofecoxib and nonspecific NSAIDs. While cost issues are an important consideration in selecting drug treatment, the ultimate cost to the patient in terms of development or exacerbation of a serious medical condition must also be taken into account when prescribing COX-2-specific inhibitor therapy.

In 2 separate randomized trials in elderly hypertensives with OA, celecoxib 200 mg/d was associated with a lower incidence of clinically significant edema and BP destabilization than rofecoxib 25 mg/d.^{10,11} An analysis of the LifeLink™ claims database to determine the incidence of outpatient edema associated with celecoxib, rofecoxib, and nonspecific NSAIDs was also conducted. Patients treated with rofecoxib (adjusted RR = 1.23; 95% CI: 1.03-1.48) were significantly more likely to have outpatient edema than those treated with celecoxib (RR = 1.0), while there was no difference between patients receiving nonspecific NSAIDs (adjusted RR = 1.08; 95% CI: 0.86-1.36) and those taking celecoxib. However, there are a number of potential difficulties with such an analysis of the claims database. First, edema is described by a single

ICD-9 code (782.3, edema) within a set of codes titled “Symptoms, signs, and ill-defined conditions (780-789).” Physicians may not code edema reliably because it is but one, relatively obscure 4-digit code within a set of heterogeneous ICD-9 codes. Second, edema is often accompanied by diagnosis of more serious conditions, such as heart failure, which physicians are presumably more likely to include on the physician claim. Finally, since edema is generally a less serious condition from the patient’s perspective, not all patients will seek physician care. These caveats notwithstanding, the edema results reported above are consistent with clinical trial and claims results for nonedema end points reported in this supplement.

Study Limitations and Strengths

Because the study is based on insurance claims databases, it is difficult to determine a causal relationship between BP destabilization and the study drugs. However, determining a causal relationship is not the focus of this study. The study was designed to distinguish total healthcare utilization associated with BP destabilization during exposure to the study drugs. Since the methodology of identifying BP destabilization is the same across study groups, any bias—from identifying cases to estimation of cost figures—that may affect the results will be similar across treatment groups. Therefore, relative differences among study groups will provide very important information.

A second limitation was the ability to attribute resource utilization and costs to managing outpatient-treated events. Whereas hospitalized events have an identifiable episode of care and a single set of discharge diagnosis codes, outpatient events have no defined episode, and each outpatient medical encounter may have different diagnostic codes. At least 2 approaches have been used in published retrospective cost analyses to attribute costs: an “attribution-based” approach, in which resources and costs related to managing the condition of interest are identified and counted; and a “global” approach, where the costs of managing an event are

estimated as the incremental costs among those with an event minus the costs among a control group without an event.¹⁶ While both approaches have limitations, the global approach may overestimate costs, if costs unrelated to managing the event occur preferentially among the event group relative to the control group. When interpreting these results, one must consider this bias.¹⁷ In this study, cases were matched to controls on cardiovascular and demographic factors related to resource utilization and costs in an attempt to control for any potential bias.

Finally there is the absence of actual BP readings available in the claims data. Changes in hypertensive medication use, such as increasing the dose or initiating new antihypertensive drugs, were used to define a BP destabilization event; however, these events were unconfirmed because of the lack of BP data. Because a literature search did not reveal any other study that attempted to identify BP destabilization from claims data, the definition of BP destabilization was developed a priori. Another issue arising from use of claims data is a possible underestimation of BP destabilization. Many clinically significant elevations in BP may have gone undetected, particularly since BP elevation is an asymptomatic condition. A surveillance bias may also affect incidence reports if physicians treating one treatment group were more vigilant at monitoring BP destabilization than physicians treating another group.

While the database does cover retirees, it primarily contains medical insurance claims data from commercial insurers of employees of large corporations and their dependents. As such, results from this study may not be generalizable to elderly populations. It is important to include data from the elderly, since they may be at higher risk for BP destabilization and related events.

Despite these limitations, using an observational study has allowed evaluation of a variety of dosages of drugs and representation of drug effect at “usual” clinical practice dosages (clinical trials may be restricted to 1 dosage of the study drug). In

addition, this study presents costs and incidence rates from clinical practice to estimate the economic impact of BP destabilization. Traditionally, economic evaluations often apply event rates from clinical trials, which may not represent event rates in clinical practice, to externally applied practice patterns and costs. Due to study protocol influences, economic evaluations based on clinical trial data may have limited external validity. By using a single real-life data source for both incidences and costs, these data may be more representative of clinical practice costs and incidence rates for BP destabilization.

Implications of the Results

Hypertension is common among arthritis patients. Celecoxib had a significantly lower rate of BP destabilization claims and their associated costs compared with rofecoxib and the nonspecific NSAIDs. In addition to the acquisition cost of the drug, economic evaluations of medications should consider the costs of managing adverse consequences of drug therapy, as well as the personal consequences to the patient in terms of developing or exacerbating a serious medical condition. These factors should be considered when selecting a COX-2-specific inhibitor therapy for hypertensive arthritis patients.

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