

## Cost of Heart Failure Among Hypertensive Users of Nonspecific NSAIDs and COX-2-Specific Inhibitors

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### Abstract

**Objective:** To determine the costs of heart failure in hypertensive patients receiving celecoxib, rofecoxib, and nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) in clinical practice.

**Methods:** Stable hypertensive patients without a history of coronary heart disease and newly treated with celecoxib, rofecoxib, ibuprofen, naproxen, or diclofenac between January 1, 1999, and September 30, 2000, were identified from the LifeLink™ Integrated Claims Solutions employer database. The incidence rate of inpatient and outpatient heart failure claims was determined based on patients' time of exposure to study drugs after adjusting for confounding factors. The heart failure costs of managing inpatient and outpatient events were estimated as the total healthcare costs for patients with heart failure claims minus the total healthcare costs among matched control groups without heart failure claims. Healthcare costs were computed for the 0 to 30 days and 31 to 90 days following the initial outpatient or inpatient claim. Finally, the excess incidence rate of patients with inpatient and outpatient heart failure claims, relative to celecoxib, were multiplied by the heart failure cost of an inpatient and outpatient event to determine the incremental costs of heart failure associated with each of the study drugs relative to celecoxib.

**Results:** Among 55 396 patients, 707 patients had outpatient heart failure claims, and 229 patients had inpatient heart failure claims. In this study, rofecoxib-treated patients were 26% more likely to have an outpatient claim (rate ratio [RR] = 1.26; 95% confidence interval [CI], 1.06-1.48;  $P = .007$ ) and 52% more likely to have an inpatient claim (RR = 1.52; 95% CI, 1.15-2.02;  $P = .003$ ) for heart failure than celecoxib-treated patients. The

adjusted RR of heart failure claims was similar between celecoxib and NSAIDs. The average heart failure cost for a patient with an outpatient heart failure claim was \$1054 within 30 days and \$221 for the period 31 to 90 days after the initial outpatient heart failure claim (total 90-day cost of \$1275). The cost for a patient with an inpatient heart failure claim was \$5966 during the hospitalization. The 90-day posthospitalization heart failure cost was \$245 (total 90-day cost of \$6211 for hospitalization and follow-up). The total heart failure-related incremental cost per patient per day of use was \$0.15 for rofecoxib and \$0.04 for nonspecific NSAIDs relative to celecoxib.

**Conclusion:** The additional heart failure costs associated with the use of rofecoxib significantly add to its cost in patients with stable hypertension, relative to celecoxib and nonspecific NSAIDs. The higher heart failure costs of rofecoxib were attributable to the higher incidence of patients with inpatient and outpatient heart failure claims relative to celecoxib and nonspecific NSAID populations being compared.

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Nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) have also been associated with sodium and water retention as well as blood pressure (BP) elevations.<sup>1</sup> While sodium and water retention may have no clinical effect in most patients, for those patients with pre-existing congestive heart failure (CHF), or

those predisposed to developing CHF, sodium and water retention may have significant clinical implications.<sup>2,3</sup> For example, 2 recent analyses found an approximate 2-fold increase in the risk of CHF hospitalizations in elderly patients during periods of nonspecific NSAID use relative to periods of nonuse.<sup>2,3</sup> In patients with a history of heart disease, those hospitalized for CHF were 10.5 times more likely to have recently used nonspecific NSAIDs relative to the control group (odds ratio = 10.5; 95% confidence interval [CI], 2.5-44.9).<sup>3</sup>

Clinical trials have demonstrated that cyclooxygenase (COX)-2-specific inhibitors are significantly more effective than placebo in reducing pain and inflammation in patients with rheumatoid arthritis (RA) and osteoarthritis (OA).<sup>4-7</sup> COX-2-specific inhibitors are comparable in efficacy with nonspecific NSAIDs, but have a significantly reduced incidence of gastrointestinal ulcers and ulcer complications.<sup>5,8-10</sup>

Two recent studies of differing design compared CHF associated with rofecoxib and celecoxib treatment. The first study was a randomized clinical trial of patients aged 65 years and older with OA and treated hypertension, in which CHF, defined as new onset or worsening of CHF, was a secondary endpoint. In this trial, 1% of patients receiving rofecoxib 25 mg/day (4 of 399) experienced CHF, compared with 0% (0 of 412) of patients receiving celecoxib 200 mg/day at week 6 ( $P = .043$  by log-rank analysis).<sup>11</sup> The second study was an analysis based on spontaneous adverse event reports. This analysis found that celecoxib was associated with a statistically significant decreased risk of clinically significant new-onset edema ( $P = .045$ ) or worsening CHF and BP destabilization compared with rofecoxib.<sup>12</sup>

The current retrospective claims analysis was undertaken to determine the healthcare utilization and clinical practice costs of heart failure in patients receiving celecoxib, rofecoxib, and nonspecific NSAIDs. Since the incidence of heart failure is 2 to 3 times more common in persons with hypertension than in normotensive persons,<sup>13,14</sup> this analysis focused

solely on the higher-risk hypertensive patient population.

## ...PATIENTS AND METHODS...

### Data Resources

Data for this analysis were extracted from the LifeLink™ Integrated Claims Solutions employer database. This database contains information on all inpatient and outpatient medical care, including diagnoses and therapeutic procedures, and all outpatient prescriptions for approximately 1.8 million employees, dependents, and retirees. The LifeLink Integrated Claims Solutions employer database allows patients to be tracked longitudinally across multiple sites of care.

### Study Design

This was a historical cohort study conducted in 3 separate phases. First, the incidence rate of patients with inpatient and outpatient heart failure claims was determined based on patients' time of exposure to study drugs after adjusting for confounding factors (including older age, female gender, and cardiovascular [CV] risk factors). Second, the heart failure costs of managing an inpatient and outpatient event were estimated as the total healthcare costs for patients with heart failure claims minus the total healthcare costs among matched control groups without heart failure claims. For inpatient heart failure events, costs accrued during hospitalization, 0 to 30 days postevent and 31 to 90 days postevent, were all determined. Outpatient costs were computed for the 0 to 30 days and 31 to 90 days following the initial outpatient claim. Finally, the excess adjusted incidence rate for patients with inpatient and outpatient heart failure claims, relative to celecoxib, were multiplied by the heart failure cost of inpatient and outpatient events to determine the incremental costs of heart failure associated with each of the study drugs relative to celecoxib.

### Study Sample Selection (Patients)

The LifeLink database was reviewed to identify new users of celecoxib, rofecoxib,

ibuprofen, naproxen, and diclofenac between January 1, 1999, and September 30, 2000. If a patient did not previously fill a prescription for any nonspecific NSAID or COX-2-specific inhibitor within the preceding 180-day period, the initial study drug prescription qualified as an index prescription. It was possible for patients to have more than 1 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 during the 120 days immediately prior to the index prescription, and remained continuously enrolled in the database for 12 months prior to their COX-2-specific inhibitor or nonspecific NSAID index date.

Patients with at least 1 of the following diagnosis codes in the 12-month period prior to the COX-2-specific inhibitor or nonspecific NSAID index prescription were classified as having a history of heart disease: acute myocardial infarction (410.xx), heart failure (428.xx), ischemic heart disease (411.xx-414.xx), other forms of heart disease (420.xx-427.xx, 429.xx), cerebrovascular disease (430.xx-438.xx), or diseases of pulmonary circulation (415.xx-417.xx).

Patients with a history of heart failure in the 12 months prior to the index date were excluded from the analysis. A cohort of 50 940 patients who had received a total of 52 719 index prescriptions met all of the inclusion criteria. The demographics, medical history, and drug usage of this patient population are described elsewhere in this supplement.<sup>15</sup>

#### **Controlling for Differences in Baseline Risk of Heart Failure**

To understand potential differences in the baseline risk factors, we evaluated patient history for specific risk factors for cardiovascular disease (CVD) and disorders during the 12 months prior to their index date. A detailed description of CV channeling bias can be found in this issue

of the journal.<sup>15</sup> Since there were significant differences in demographic and clinical characteristics among study drugs, this study adjusted these confounding factors using multivariate analyses and direct adjustment methods.

#### **Determination of Rate of Patients With Heart Failure Claims**

The following heart failure codes, reported at least 1 day after the start of COX-2-specific inhibitor or nonspecific NSAID therapy, qualified for inclusion in the analysis. Inpatient heart failure stays were defined as: (1) Diagnosis-Related Group (DRG) code 124 (circulatory disorders except acute myocardial infarction with cardiac catheterization and complex diagnosis) accompanied by an *International Classification of Diseases* (ICD-9) discharge diagnosis code for heart failure (428.xx) or hypertensive heart disease with CHF (402.x1, 404.x1, 404.x3); (2) DRG code 127 (heart failure and shock) accompanied by ICD-9 discharge diagnosis codes for heart failure or hypertensive heart disease with CHF or rheumatic heart failure (398.91); or (3) DRG code was not for one of the events of interest, but one of the discharge diagnosis codes was for heart failure. Outpatient heart failure claims were identified by ICD-9-CM diagnosis code of 428.xx. Patients were observed only until the first occurrence of a heart failure claim.

During the observation period, patients were assumed to be on nonspecific NSAID or COX-2-specific inhibitor therapy only for the duration of the days' supply of each prescription. Any time between the end of the days-supply of 1 prescription and the date that the subsequent prescription was filled was assumed to be a break in therapy. Heart failure 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). For purposes of the incidence

rate calculations, patients were also only observed until the first occurrence of a heart failure claim.

#### **Determination of Average Incremental Cost of Heart Failure**

The cost of treatment associated with heart failure was estimated by comparing the total healthcare costs for hypertensive patients with heart failure claims to the total healthcare costs of a matched group of hypertensive patients without heart failure claims. Patients were matched on a 1-to-1 basis by drug, age (in 10-year intervals), gender, history of CVD, and history of diabetes. If 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. The incremental total cost (costs among cases and costs among controls) was considered an estimate of the costs of managing the heart failure event.

When heart failure occurred as an outpatient event, healthcare costs were computed for the 30 days following the outpatient claim (including the date of the event) and for 31 to 90 days following the outpatient event. Costs within these 2 periods were computed as the total cost from all claims incurred during the respective time periods because of the difficulty in calculating event-specific costs. Costs were also classified as inpatient, outpatient visit, 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.

To describe the healthcare utilization pattern for patients with heart failure in a medical insurance system, we compared the percentage of heart failure cases with at least 1 claim for inpatient, outpatient, pharmacy, and laboratory services to the percentage of control patients with at least 1 claim for these services. In addition, we compared the distribution of the costs for these claims between patients with and without heart failure.

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

The estimation of the heart-failure-related cost of treatment with rofecoxib and 3 nonspecific NSAIDs (ibuprofen, naproxen, and diclofenac) was calculated and compared with the heart failure-related cost of treatment with celecoxib. The rofecoxib and nonspecific NSAID cost was expressed as the incremental heart failure cost per patient-day of drug use relative to celecoxib. The adjusted excess rate of patients with heart failure claims for the study drugs relative to celecoxib was calculated. Then, the adjusted excess rate was multiplied by the average cost of a heart failure event to obtain the drug-specific incremental cost per patient per day of drug use.

#### **Statistical Analysis**

Because the number of patients with events for inpatient and outpatient heart failure was low, the 3 nonspecific NSAIDs of interest (ibuprofen, naproxen, and diclofenac) were combined into a single group to obtain a stable estimate of the incidence rate of heart failure. Claim rates were computed as the total number of patients with at least 1 heart failure event attributable to nonspecific NSAID or COX-2-specific inhibitor therapy divided by the total days of exposure to the drug across all patients. Claim rates were expressed per 1000 patient-days of exposure. Poisson multiple regression models were used to compare incidence rates across cohorts after adjusting for all demographic and medical history variables. Specifically, the variables included in the model were age; gender; specialty of primary providers; medical history (myocardial infarction, ischemic heart disease, pulmonary circulation, heart failure, other heart disease, cerebrovascular diseases, hyperlipidemia, diabetes, RA, acute renal failure, and nephritis) and type of hypertension medication; medication influencing hypertension; and other medications.

Multiple regression analyses were used to estimate the cost of heart failure. Since

the number of patients with heart failure was low and there was an imbalance of baseline risk factors between study groups, costs of heart failure events were not analyzed by treatment group. Rather, average costs of a heart failure event were estimated across treatment groups by comparing the cost of all identified heart failure events among the combined study cohorts with their matched controls (see section above for details).

Due to the skewed distribution of the cost data, average costs of heart failure were estimated by a geometric mean using a natural logarithm transformation. The mean was weighted by adjusting the data to the aforementioned demographic and clinical distribution of a standard population, where the standard population was based on the characteristics of the combined heart failure cases and their matched controls. Multiple regression analysis models were run on the natural logarithm-transformed cost values. Then, based on the aforementioned characteristics of the standard population (combination of cases and controls), we estimated direct adjusted total healthcare utilization (cost) for patients with heart failure and their controls. Statistical Analysis System (SAS) (SAS Institute, Cary, NC) Release 8.02 was used in all statistical comparisons.

## ...RESULTS...

### Demographics

A total of 52 719 patient prescriptions (from 50 940 unique patients) were eligible for analysis. Patients receiving celecoxib and rofecoxib comprised 37.3% and 23.2% of the index prescriptions in the study group, respectively. Nonspecific NSAIDs were administered to the remaining 39.5% of patient prescriptions. There were significantly more female than male patients in the total study group ( $P < .001$ ), and older patients received significantly more COX-2-specific inhibitors ( $P < .001$ ) than nonspecific NSAIDs. None of the 50 940 patients filling the index prescriptions had a change in antihypertensive therapy or dose over the course of 180

days prior to their index COX-2-specific inhibitor or nonspecific NSAID treatment (Table 1).

### Claims for Heart Failure

In total, there were 707 outpatient and 229 inpatient heart failure claims over a period of 6.2 million days of exposure to the drugs of interest in both outpatient and inpatient groups (Tables 1 and 2). Most heart failure claims (89.7% and 96.1% for outpatient and inpatient claims, respectively) were reported in patients older than 60 years, with younger patients at significantly lower risk of having claims ( $P < .05$ ).

In this study, patients receiving rofecoxib were 26% (risk rate [RR] = 1.26; 95% CI, 1.06-1.48;  $P < .01$ ) more likely to have an outpatient claim for heart failure than patients receiving celecoxib after adjusting for confounding factors. Patients receiving rofecoxib also had a 52% higher risk of having an outpatient heart failure claim than celecoxib recipients (RR = 1.52; 95% CI, 1.15-2.02;  $P < .01$ ). There were no significant differences in the relative risk of inpatient or outpatient claims between patients receiving nonspecific NSAIDs compared with those receiving celecoxib (RR = 1.13; 95% CI, 0.91-1.41;  $P > .05$ , and RR = 1.13; 95% CI, 0.74-1.73;  $P > .05$  for outpatient and inpatient claims, respectively) (Tables 1 and 2).

Patients with a medical history of ischemic heart disease ( $P < .0001$ ) and other forms of heart disease ( $P < .0001$ ) were significantly more likely to have outpatient claims for heart failure than patients without these diseases and disorders, regardless of medication (Table 1). There was also a trend for patients with a history of diabetes and acute renal failure to make more outpatient heart failure claims ( $P = .06$ ). The risk of having an inpatient claim was significantly increased in all patients with a history of ischemic heart disease ( $P = .02$ ), other forms of heart disease ( $P = .01$ ), pulmonary circulation disorders ( $P = .02$ ), and diabetes ( $P = .005$ ) (Table 2). Patients with hyperlipidemia were less likely to have outpatient (RR = 0.78; 95% CI, 0.64-0.95;  $P = .01$ ) and inpatient heart fail-

**Table 1.** Risk Factors for Hypertensive Patients With at Least 1 Outpatient Heart Failure Claim

Variable	No. of Events	Days of Exposure (N = 6 201 086)	Adjusted Rate Ratio	95% CI	Adjusted Rate Per 1000 Patient Days	Adjusted P
<b>Total Patients</b>	707	6 201 086				
<b>Drug Group (n)</b>						
Celecoxib (19 663)	377	3 423 727	1.00	—	0.110	ref
Rofecoxib (12 218)	228	1 713 495	1.26	1.06-1.48	0.139	.007
Nonspecific NSAIDs (20 838)	102	1 063 864	1.13	0.91-1.41	0.124	.28
<b>Patient Age Categories</b>						
60+	634	4 688 263	1.00	—	0.135	ref
50-59	62	1 216 703	0.47	0.36-0.62	0.064	<.0001
<50	11	296 120	0.32	0.18-0.59	0.043	.0002
<b>Patient Gender</b>						
Female	444	3 874 183	1.00	—	0.115	ref
Male	263	2 326 903	0.89	0.75-1.06	0.102	.19
<b>Provider Specialty</b>						
Family practice	221	2 164 131	1.00	—	0.102	ref
Internal medicine	242	1 926 091	1.10	0.92-1.32	0.112	.31
Orthopedic surgery	46	496 844	0.89	0.65-1.22	0.091	.47
Cardiology	28	133 666	1.47	0.99-2.18	0.150	.06
Rheumatology	25	259 387	0.74	0.48-1.15	0.076	.18
Neurology	15	95 670	1.43	0.85-2.41	0.146	.18
Other	73	644 754	1.12	0.86-1.46	0.114	.39
Unknown	57	480 543	1.10	0.82-1.48	0.112	.51
<b>Medical History</b>						
Ischemic heart disease	250	1 275 254	1.62	1.37-1.92	0.185	<.0001
Other heart disease	244	1 106 251	1.75	1.48-2.08	0.200	<.0001
Hyperlipidemia	123	1 401 632	0.78	0.64-0.95	0.089	.01
Diabetes	122	867 066	1.21	0.99-1.48	0.138	.06
Cerebrovascular disease	85	498 850	1.01	0.81-1.28	0.115	.89
Rheumatoid arthritis	24	161 493	1.29	0.83-1.99	0.147	.25
Myocardial infarction	18	73 468	1.27	0.79-2.05	0.145	.33
Nephritis, nephrotic syndrome	12	42 693	1.45	0.78-2.70	0.165	.24
Pulmonary disease	10	53 431	0.88	0.47-1.66	0.100	.69
Acute renal failure	6	12 017	2.29	0.96-5.47	0.261	.06
<b>Blood Pressure Medication Type</b>						
Antihypertensive	609	5 256 081	1.06	0.84-1.34	0.121	.64
Diuretic	362	2 339 771	1.61	1.37-1.88	0.184	<.0001
Combination	64	731 949	1.04	0.79-1.37	0.119	.79
<b>Medications Influencing Hypertension</b>						
Sympathomimetics	185	1 426 077	1.22	1.03-1.45	0.139	.02
Corticosteroids	136	882 442	1.35	1.11-1.64	0.154	.0003
Estrogens	125	1 579 875	0.66	0.54-0.82	0.075	.0001
Appetite suppressants	14	133 346	1.24	0.72-2.11	0.141	.44
Erythropoietin	2	4043	2.11	0.52-8.55	0.241	.29
<b>Antidepressants</b>	192	1 438 894	1.23	1.03-1.45	0.140	.02
<b>Anticoagulant Drugs</b>	90	360 599	1.49	1.18-1.88	0.170	.0008

CI indicates confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; ref, reference variable.

**Table 2.** Risk Factors for Hypertensive Patients With at Least 1 Inpatient Heart Failure Claim

Variable	No. of Events	Days of Exposure (N = 6 279 665)	Adjusted Rate Ratio	95% CI	Adjusted Rate Per 1000 Patient-Days	Adjusted P
<b>Total Patients</b>	229	6 283 886				
<b>Drug Group (n)</b>						
Celecoxib (19 663)	118	3 473 954	1.00	—	0.0340	ref
Rofecoxib (12 218)	84	1 737 905	1.52	1.15-2.02	0.0517	.003
Nonspecific NSAIDs (20 838)	27	1 072 027	1.13	0.74-1.73	0.0384	.58
<b>Patient Age Categories</b>						
60+	220	4 762 868	1.00	—	0.0460	ref
50-59	7	1 224 325	0.18	0.09-0.40	0.0083	<.0001
<50	2	296 693	0.21	0.05-0.87	0.0097	.03
<b>Patient Gender</b>						
Female	154	3 931 836	1.00	—	0.0390	ref
Male	75	2 352 050	0.75	0.56-1.01	0.0293	.06
<b>Primary Provider Specialty</b>						
Family practice	75	2 188 663	1.00	—	0.0340	ref
Internal medicine	88	1 952 324	1.08	0.79-1.47	0.0367	.64
Rheumatology	10	263 543	0.77	0.38-1.56	0.0262	.46
Orthopedic surgery	9	502 510	0.52	0.26-1.04	0.0177	.06
Cardiology	8	138 086	1.11	0.53-2.32	0.0377	.78
Neurology	3	97 925	0.80	0.25-2.53	0.0272	.70
Other	22	653 359	1.04	0.65-1.68	0.0354	.86
Unknown	14	487 476	0.75	0.43-1.34	0.0255	.33
<b>Medical History</b>						
Other heart disease	79	1 135 253	1.48	1.10-2.00	0.0539	.01
Ischemic heart disease	78	1 303 878	1.42	1.05-1.91	0.0517	.02
Diabetes	48	879 045	1.59	1.15-2.21	0.0579	.005
Hyperlipidemia	32	1 416 465	0.71	0.49-1.04	0.0258	.08
Cerebrovascular disease	30	507 099	1.05	0.71-1.56	0.0382	.81
Rheumatoid arthritis	11	165 148	1.75	0.91-3.39	0.0637	.10
Pulmonary disease	9	54 101	2.27	1.14-4.51	0.0826	.02
Myocardial infarction	6	74 855	1.51	0.66-3.48	0.0550	.33
Nephritis, nephrotic syndrome	1	44 441	0.37	0.05-2.68	0.0135	.33
Acute renal failure	0	12 679	N/A	—	—	—
<b>Blood Pressure Medication Type</b>						
Antihypertensive	198	5 329 222	1.26	0.84-1.88	0.0459	.26
Diuretic	147	2 378 927	2.62	1.97-3.49	0.0954	<.0001
Combination	20	737 459	1.26	0.78-2.04	0.0459	.35
<b>Medications Influencing Hypertension</b>						
Sympathomimetics	55	1 449 508	1.10	0.80-1.50	0.0400	.56
Corticosteroids	48	897 021	1.49	1.07-2.09	0.0542	.02
Estrogens	29	1 599 260	0.43	0.28-0.64	0.0157	<.0001
Appetite suppressants	2	135 213	0.60	0.15-2.41	0.0218	.47
Erythropoietin	1	4048	3.26	0.46-23.34	0.1187	.24
<b>Antidepressants</b>	59	1 460 309	1.13	0.83-1.53	0.0411	.44
<b>Anticoagulant Drugs</b>	46	370 221	2.26	1.59-3.20	0.0823	<.0001

CI indicates confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; ref, reference variable.

ure (RR = 0.71; 95% CI, 0.49-1.04; *P* = .08) claims (Tables 1 and 2).

The type of antihypertensive medication taken by a patient also influenced the risk of a claim. Both outpatient and inpatient claims for heart failure were higher for patients receiving diuretics than for patients administered other antihypertensive drugs (*P* < .0001) (Tables 1 and 2).

The analysis also found that patients on corticosteroids, sympathomimetics, antidepressants, or anticoagulants had significantly higher outpatient heart failure claims (RR = 1.22-1.49; *P* < .05-*P* < .001) than nonusers. However, use of estrogens was associated with fewer outpatient heart

failure claims (RR = 0.66; 95% CI, 0.54-0.82; *P* = .0001) (Table 1). Similarly, compared with nonusers, patients on corticosteroids (RR = 1.49; 95% CI, 1.07-2.09; *P* = .02) had a significantly higher inpatient heart failure claims rate, as did patients on anticoagulants (RR = 2.26; 95% CI, 1.59-3.20; *P* < .0001). Again, use of estrogens was associated with fewer inpatient heart failure claims (RR = 0.43; 95% CI, 0.28-0.64; *P* < .0001) (Table 2).

### Incremental Costs of Heart Failure

Patients with a heart failure claim were matched on a 1-to-1 basis with 707 outpatients and 229 inpatients with no heart

**Table 3.** Distribution of Demographic and Clinical Characteristics Between Hypertensive Patients With and Without Heart Failure Claims\*

Variable Description	Outpatient Heart Failure Patients						Inpatient Heart Failure Patients					
	With Claims		Without Claims		$\chi^2$	<i>P</i>	With Claims		Without Claims		$\chi^2$	<i>P</i>
	N	%	N	%			N	%	N	%		
<b>Total Sample Size</b>	707	100.0	707	100.0			229	100.0	229	100.0		
<b>Drug Group (n)</b>												
Celecoxib (19 663)	377	53.3	377	53.3	0.000	1.000	118	51.5	118	51.5	0.000	1.000
Rofecoxib (12 218)	228	32.2	228	32.2			84	36.7	84	36.7		
Nonspecific NSAIDs (20 838)	102	14.4	102	14.4			27	11.8	27	11.8		
<b>Patient Age Categories</b>												
75+	332	47.0	332	47.0	0.000	1.000	143	62.4	143	62.4	0.000	1.000
55-74	370	52.3	370	52.3			83	36.2	83	36.2		
<55	5	0.7	5	0.7			3	1.3	3	1.3		
<b>Patient Gender</b>												
Female	444	62.8	444	62.8	0.000	1.000	154	67.2	154	67.2	0.000	1.000
Male	263	37.2	263	37.2			75	32.8	75	32.8		
<b>Primary Provider Specialty</b>												
Family practice	221	31.3	219	31.0	12.15	.096	75	32.8	62	27.1	6.69	.461
Internal medicine	242	34.2	221	31.3			88	38.4	88	38.4		
Orthopedic surgery	46	6.5	61	8.6			9	3.9	18	7.9		
Cardiology	28	4.0	21	3.0			8	3.5	9	3.9		
Rheumatology	25	3.5	22	3.1			10	4.4	7	3.1		
Neurology	15	2.1	8	1.1			3	1.3	3	1.3		
Other	73	10.3	104	14.7			22	9.6	20	8.7		
Unknown	57	8.1	51	7.2			14	6.1	22	9.6		
<b>History of Cardiovascular Diseases and Disorders</b>	403	57.0	403	57.0	0.000	1.000	135	59.0	135	59.0	0.000	1.000
<b>History of Diabetes</b>	122	17.3	122	17.3	0.000	1.000	48	21.0	48	21.0	0.000	1.000

\*Patients were matched for drug, age in 10-year intervals, gender, history of cardiovascular disease, and history of diabetes. 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. NSAIDs indicates nonsteroidal anti-inflammatory drugs.

**Table 4.** Comparison of Total Cost Between Hypertensive Patients With and Without an Outpatient or Inpatient Heart Failure Claim

Type of Claim and Time Period	With Heart Failure Claim			Without Heart Failure Claim			Adjusted <i>P</i>	Incremental Cost	
	Average Cost (\$)*	95% CI (\$)	Median Cost (\$)†	Average Cost (\$)*	95% CI (\$)	Median Cost (\$)†		Average Cost (\$)	Median Cost (\$)
<b>Outpatient Claim</b>									
0-30 days postevent	1167.33	1057.62-1288.39	1027.40	113.07	96.46-132.52	190.37	<.001	1054.26	837.03
31-90 days postevent	500.41	422.70-592.38	703.75	279.59	237.58-329.01	399.46	<.001	220.82	304.29
<b>Inpatient Claim</b>									
During hospital stay	5966.38	5315.76-6696.62	5721.83	0.00	0.00-0.00	0.00	<.001	5966.38	5721.83
0-30 days postevent	268.74	197.78-365.03	446.46	92.43	67.96-125.60	163.86	<.001	176.31	282.60
31-90 days postevent	324.90	229.10-460.56	717.90	256.65	193.30-340.65	405.76	NS	68.25	312.14

\*Direct adjusted geometric mean.

†Median cost is unadjusted.

CI indicates confidence interval; NS, not significant.

failure claims (controls) (Table 3). Significant differences in costs were observed between hypertensive patients with and without an outpatient heart failure claim at both 0 to 30 days and 31 to 90 days postevent ( $P < .001$ ) (Table 4). The average incremental cost for outpatient heart failure claimants was \$1054 within the first 30 days postevent (average \$1167 for heart failure claimants less average of \$113 for controls) and \$221 for the 31- to 90-day period (average \$500 for heart failure claimants less average of \$280 for controls). Similarly, compared with controls, patients who made inpatient heart failure claims had average incremental costs of \$5966 during hospitalization and \$176 within 0 to 30 days postevent ( $P < .001$ ) (Table 4).

Patients with an inpatient heart failure claim were significantly more likely to have claims for inpatient and outpatient services ( $P < .001$ ), pharmacy ( $P < .01$ ), and laboratory ( $P < .05$ ) than controls during the 0- to 30-day postevent period (Table 5). They also had significantly more inpatient ( $P < .001$ ) and outpatient ( $P = .057$ ) claims during the 31- to 90-day period. Patients

with an outpatient heart failure claim were also significantly more likely than controls to have claims for inpatient and outpatient services, pharmacy, and laboratory (all  $P < .001$ ) during the 0- to 30-day period, and significantly more inpatient and outpatient claims during the 31- to 90-day period ( $P < .001$ ).

The distribution of cost by resource type differed significantly between patients with outpatient heart failure claims and controls ( $P < .001$ ) (Table 6). For example, among patients with at least 1 outpatient heart failure claim, inpatient hospital costs comprised 52.4% of total costs compared with 26.7% of costs among controls in the 0- to 30-day period. Similarly, the distribution of costs differed between hospitalized heart failure cases and their controls. For patients with an inpatient heart failure claim, the proportion of costs in the 0 to 30 days following hospital discharge was 26.3% compared with 42.4% in the 0- to 30-day period among controls. At 31 to 90 days postevent, the inpatient costs for the cases was higher than controls (38.4% vs 21.6%;  $P < .001$ ).

The attributable cost of heart failure was higher in the rofecoxib group than in the celecoxib and nonspecific NSAID groups. The incremental outpatient and inpatient heart failure claims-related per-patient-per-day costs for rofecoxib treatment were \$0.15 higher than that for celecoxib. The incremental heart failure-related per-patient-per-day cost for non-specific NSAID treatment was only \$0.04 in comparison with celecoxib (Figure). The proportion of incremental cost due to outpatient heart failure claims for rofecoxib was 24%, while this proportion for non-specific NSAIDs was 42%. For both rofecoxib and nonspecific NSAIDs, most incremental attributable costs (73% for rofecoxib and 56% for nonspecific NSAIDs) were associated with hospitalization. In addition, the greatest outpatient cost was claimed during the period of 0 to 30 days (83% for rofecoxib and 83% for nonspecific NSAIDs).

...DISCUSSION...

Heart failure is a common chronic condition, affecting approximately 4.8 million Americans, with an additional 400 000 new cases each year.<sup>14</sup> The elderly have a far greater risk of developing heart failure than younger people,<sup>14</sup> a finding paralleled in the current analysis. The disease adds a significant burden to the healthcare system, with approximately \$18 billion spent annually on its overall care.<sup>14</sup>

The current retrospective claims analysis highlights the substantial costs associated with hospitalization for heart failure. Hypertensive patients with an outpatient claim for heart failure had an average incremental cost of more than \$1000 within the first 30 days postevent compared with patients without such claims. The average incremental cost for an inpatient claim was even higher, at around \$6000, due to the cost of initial hospitalization. These results are consistent with those of other studies looking at the costs for hospitalization from heart failure.<sup>16,17</sup>

The current study also demonstrated that patients receiving rofecoxib were at a significantly higher risk of developing

**Table 5.** Comparison of Healthcare Resource Claims Between Hypertensive Patients With and Without Outpatient or Inpatient Heart Failure Claims

Type of Claim, Time Period, and Resource	Patients With Claims for Resource Use, %			
	With Claim	Without Claim	$\chi^2$	P*
<b>Outpatient Heart Failure Claim</b>				
0-30 Days Postevent				
Inpatients	31.8	4.7	174.77	<.001
Outpatients	100	39.3	425.65	<.001
Pharmacy	91.4	84.9	14.29	<.001
Laboratory	25.2	9.2	63.45	<.001
31-90 Days Postevent				
Inpatients	18.5	7.6	36.87	<.001
Outpatients	64.4	53.3	17.77	<.001
Pharmacy	88.3	88.4	0.01	.934
Laboratory	16.50	14.0	1.77	.183
<b>Inpatient Heart Failure Claim</b>				
0-30 Days Postevent				
Inpatients	22.7	3.5	37.13	<.001
Outpatients	63.8	41.9	21.90	<.001
Pharmacy	88.6	79.9	6.59	<.01
Laboratory	15.3	8.7	4.65	<.05
31-90 Days Postevent				
Inpatients	26.2	7.4	28.87	<.001
Outpatients	64.2	55.5	3.63	.057
Pharmacy	84.7	89.5	2.35	.125
Laboratory	18.3	12.7	2.82	.093

\*P values are based on  $\chi^2$  testing between patients with and without a heart failure claim.

inpatient or outpatient heart failure claims than those taking celecoxib. As a result, rofecoxib was also associated with higher per-patient-per-day costs attributable to heart failure, particularly during hospitalization for heart failure. Hypertension, edema, and heart failure often occur concomitantly. For example, hypertension is often a precursor to heart failure, while uncontrolled hypertension has been documented as a precipitating factor for decompensated heart failure.<sup>18</sup> Edema is a concomitant sign and symptom of heart failure.<sup>19</sup> Since rofecoxib is

**Table 6.** Comparison of Cost Distribution Between Hypertensive Patients With and Without Outpatient or Inpatient Heart Failure Claims

Type of Claim, Time Period, and Resource	Proportion of Cost by Resources,* %			
	With Claim	Without Claim	$\chi^2$	<i>P</i> <sup>†</sup>
<b>Outpatient Heart Failure Claim</b>				
0-30 Days Postevent				
Inpatients	52.40	26.68	112.16	<.001
Outpatients	30.39	25.85		
Pharmacy	15.97	46.25		
Laboratory	1.24	1.21		
31-90 Days Postevent				
Inpatients	29.36	47.79	50.79	<.001
Outpatients	24.84	16.89		
Pharmacy	44.26	34.20		
Laboratory	1.54	1.11		
<b>Inpatient Heart Failure Claim</b>				
0-30 Days Postevent				
Inpatients	26.27	42.38	23.22	<.001
Outpatients	34.86	24.98		
Pharmacy	37.49	31.86		
Laboratory	1.37	0.78		
31-90 Days Postevent				
Inpatients	38.43	21.63	35.39	<.001
Outpatients	23.15	29.03		
Pharmacy	37.41	48.25		
Laboratory	1.01	1.09		

\*The proportion was calculated by: (cost of each specific resource/sum of 4 studied resources) × 100.

<sup>†</sup>*P* values are based on  $\chi^2$  testing between patients with and without a heart failure claim.

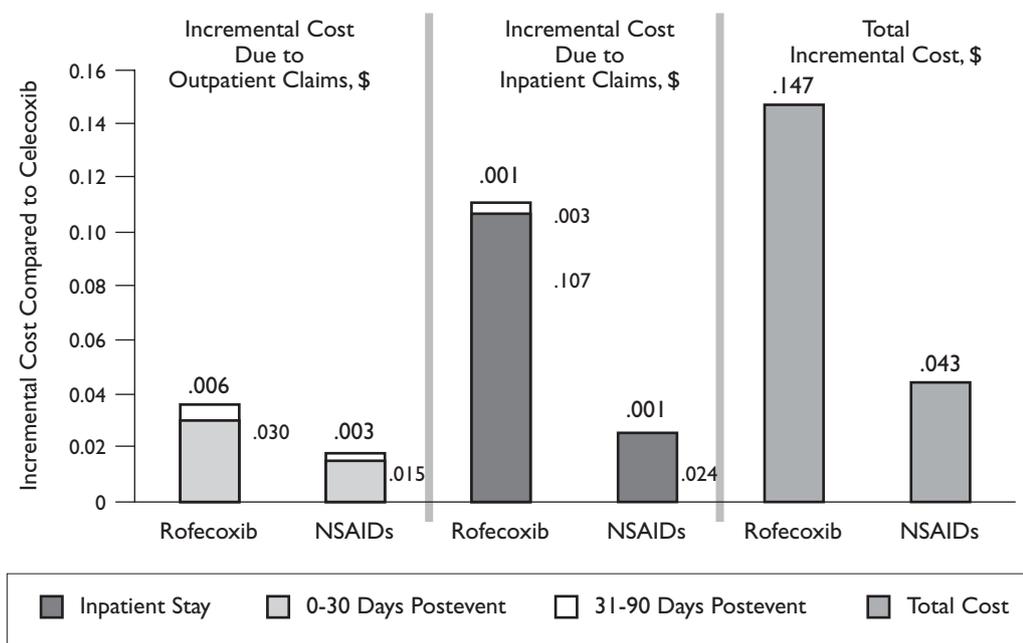
associated with a significantly higher risk of BP destabilization in elderly, hypertensive patients with OA than is celecoxib, it follows that rofecoxib would be associated with a higher incidence of heart failure claims than celecoxib in this patient group.<sup>11</sup> These findings are consistent with a recent clinical trial where, among OA patients aged 65 years and older with treated hypertension, the risk of new-onset or worsening of existing CHF was

significantly higher for rofecoxib compared with celecoxib (*P* = .043).<sup>11</sup> The higher risk of heart failure claims with rofecoxib relative to celecoxib and NSAIDs in this study demonstrates the additional costs of using rofecoxib in patients with stable hypertension. For example, with over 6.2 million patient-days of drug exposure in the 3 cohorts during the study period, we estimate that treating the entire cohort with celecoxib would result in outpatient and inpatient heart failure costs that were \$942 000 and \$253 000 lower, respectively, as compared with treating the entire cohort with rofecoxib.

The current study limited analysis of heart failure data to stable hypertensive patients only to study the heart failure claims and related costs in a population of patients more susceptible to heart failure events. In 2 previous reports, the use of nonspecific NSAIDs resulted in an approximate 2-fold increase in the risk of hospitalization for heart failure.<sup>2,3</sup> Our study population differed from those in other reports.<sup>2,3</sup> Using a cohort design, Heerdink and colleagues<sup>2</sup> evaluated CHF hospitalizations in patients taking both diuretics and nonspecific NSAIDs versus those taking only diuretics, while Page and Henry<sup>3</sup> used a case-control design to compare the odds of exposure to NSAIDs among patients hospitalized with a primary diagnosis of CHF (cases) to controls hospitalized without CHF. The authors from both of these studies suggested that the effect of nonspecific NSAID use was to precipitate CHF in patients already susceptible, rather than the result of pathophysiologic changes induced by nonspecific NSAIDs. Consistent with the results from clinical studies,<sup>9,20,21</sup> the current analysis demonstrated that the incidence of heart failure events was comparable in patients treated with either celecoxib or nonspecific NSAIDs.

The current data support recent clinical findings cited above. In a recent study comparing rofecoxib and celecoxib, new-onset or worsening of existing CHF was significantly more common in patients on rofecoxib than celecoxib (*P* = .043).<sup>11</sup>

**Figure.** Attributable Incremental Inpatient and Outpatient Heart Failure Cost Per Patient Per Day of Rofecoxib and Nonspecific NSAIDs Treatment in Comparison With Celecoxib



Another study using the World Health Organization/Uppsala Monitoring Centre safety database of almost 2 million spontaneous adverse event reports from 57 countries also reported a significantly greater proportion of heart failure among all reported adverse drug reactions in patients receiving rofecoxib than celecoxib.<sup>22</sup> Similarly, in an analysis of the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial results of rofecoxib 50 mg/d versus naproxen 1000 mg/d in patients with RA, rofecoxib demonstrated a significantly higher rate of CHF adverse events than the naproxen group (RR = 2.11; 95% CI, 0.96-4.67).<sup>23</sup>

Previous reports have shown the association between hypertension and CHF,<sup>13,14,18</sup> and unstable hypertension and CHF.<sup>18</sup> For example, Ghali et al reported that uncontrolled hypertension was the second most commonly cited precipitating factor, behind lack of compliance with diet or drugs, for hospitalizations due to decompensated heart failure in a select population.<sup>18</sup> Hypertension is a major contributor to CHF morbidity and mortality,

doubling or tripling the risk of CHF compared with normotensives.<sup>13,14</sup> Some additional risk factors for CHF in hypertensive patients include various preexisting CV conditions and diabetes,<sup>13</sup> conditions that also led to significantly more claims for CHF in the current study, regardless of drug therapy. Although nonspecific NSAIDs generally have no effect on the BP of normotensive patients, they can elevate BP in hypertensive patients.<sup>2</sup> Unfortunately, approximately one third of hypertension is undiagnosed,<sup>24</sup> leaving many patients at risk for increased BP and CHF when using nonspecific NSAIDs.

**Study Limitations**

There are limitations to our analyses that should be mentioned. First, we used heart failure diagnoses based on ICD-9 and DRG codes on billing claims to identify patients with heart failure, and did not confirm the diagnosis of heart failure with the patient’s physician or through medical chart review. This approach, however, was consistent with the objec-

tive of our study: to identify the economic impact of health failure associated with the study drugs. Since the methodology of identifying heart failure cases is the same across study cohorts, it is unlikely there was any bias for identifying heart failure associated with any particular study drug over another. However, it is important to note that this study was not designed to evaluate the etiologic relationship between heart failure and the study drugs. Such a study would require a more rigorous case identification and confirmation than was used here.

A second limitation is the extent to which these results can be applied to different populations. The study population was identified from the healthcare claims of commercial health insurance plans consisting of employees, retirees, and their dependents. The study results may only apply to plans with similar demographic, clinical, and socioeconomic characteristics. The study results, however, provide a good indication of the patient populations at increased risk of heart failure claims, notably, older individuals, those with a CV or renal history, and those using diuretics and other hypertensive medications. Nonetheless, the results of this study are consistent with the results reported in different study populations in that there is higher risk of heart failure with rofecoxib relative to nonspecific NSAIDs and celecoxib.<sup>11,12,23</sup>

In summary, the results from this retrospective analysis indicate that the incremental cost of heart failure events in stable hypertensive patients is high. In addition, in this analysis, the risk of both outpatient and inpatient heart failure events is significantly higher among those prescribed rofecoxib than those prescribed celecoxib or nonspecific NSAIDs. Thus, the total incremental cost per patient per day for heart failure events was higher for rofecoxib than for celecoxib.

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