Using Administrative Data to Compare the Relative Effectiveness of Amlodipine vs Nifedipine CC

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Abstract

Objective: **To describe an approach for using claims data to compare the effectiveness of 2 similar drugs used for similar indications within a health maintenance organization.**

Study Design: **A database study comparing the effectiveness of amlodipine and nifedipine CC in the initial treatment of hypertension.**

Patients and Methods: **The claims records of Pennsylvania Medicaid patients between 18 and 64 years of age with continuous eligibility in 1994 were studied. Pharmacy, hospital, and outpatient claims data were merged, and adult patients receiving the target drugs for the specified indication were identified. The effectiveness of the 2 agents used were compared based on the concept that a change in dispensed medication suggested either an adverse event or lack of effectiveness. Adherence rates, adverse events, and pharmacy and nonpharmacy costs associated with the 2 agents were also compared.**

Results: **Patients receiving amlodipine and nifedipine CC as initial treatment for hypertension had similar demographic characteristics and numbers of comorbid conditions. More patients started on nifedipine CC switched to another calcium channel blocker (15.8% for nifedipine CC vs 10.3% for amlodipine). More patients started on amlodipine switched to another class of antihypertensive agent (13.2% for amlodipine vs 7.3% for nifedipine CC). Patients in both groups received adjunctive antihypertensive drugs at a similar frequency (35% for nifedipine CC vs 42%, for amlodipine). Rates of adherence were similar. In adherent patients, there was no difference in rates of reported adverse events. The nonpharmacy costs were similar between groups. Patients in the amlodipine group also had a trend toward higher overall pharmacy charges (all medications) and higher charges for antihypertensive medications other than the study drugs ($302 vs $188, *P*=.054).**

Conclusions: **Claims data are often the best available evidence for comparing the effectiveness of pharmaceuticals in real clinical practice. While these comparisons have inherent limitations, the accuracy of the assessment can be maximized by limiting the assessment to agents with the same specific indications. Other important elements include comparison of crossover rates to other pharmaceuticals in the same class, rates of addition of other pharmaceuticals in the same class, adherence, adverse events, and overall healthcare charges.**

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In this cost-conscious healthcare environment, the clinical advantage of a newly approved agent must justify its purchase price. Examples of clinical advantages include greater efficacy, ease of use, fewer adverse events, and improved patient adherence. Importantly, efficacy findings from clinical trials data may not reflect effectiveness in real clinical practice. Differences in patient demographics, ethnic backgrounds, and other patient characteristics may influence the efficacy of a drug.

Databases based on healthcare resource utilization records can help bridge this gap and provide

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real-world information about the charges and clinical benefits of healthcare interventions. In this study, we used a retrospective database analysis to compare the effectiveness of 2 long-acting dihydropyridine calcium channel blockers, amlodipine and nifedipine CC, for the initial treatment of uncomplicated hypertension.

··· METHODS ···

We conducted a retrospective comparison of treatment outcomes associated with these 2 drugs over a 9-month treatment period. The data source was the Pennsylvania (PA) Medicaid database. This database covers approximately 1.5 million lives and is comprised of about 50 million claim records per year. For this study, we compiled 3 Medicaid domain claim files: provider claims, outpatient pharmacy claims, and hospital discharge claims. We obtained claims for patients from October 1, 1993, to October 1, 1995. We also obtained patient-eligibility files to confirm coverage status.

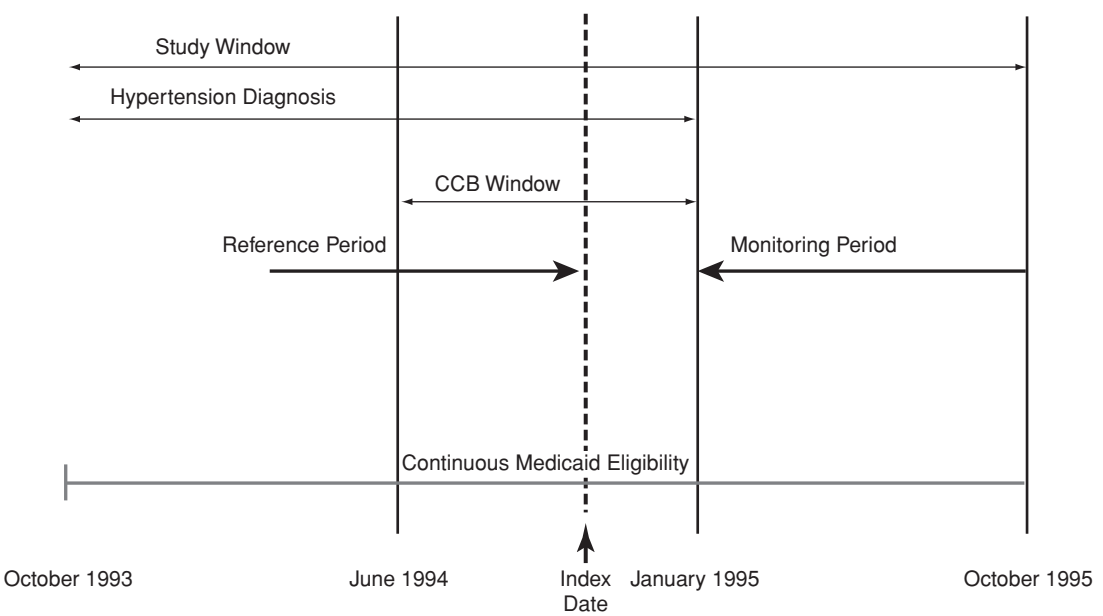
The inclusion/exclusion criteria were designed to minimize patient heterogeneity and effects of confounding by indication. The Figure illustrates the inclusion/exclusion approach. We first identified all patients who had a hypertension diagnosis (*International Classification of Diseases,* 9th Revision. Clinical Modification [ICD-9-CM] code 401) within a 15-month period (October 1993 through December 31, 1994) using the provider and hospital discharge databases. The patient identification numbers were then correlated with the pharmacy claim records. We included all patients who were dispensed a calcium channel blocker (CCB) between June 1994, and December 31, 1994 in the study; all other patients were excluded.

Additional Exclusion Criteria

The first CCB dispensing date for each patient was the *index date.* To ensure that all patients in the study were first-time CCB users, patients with a CCB prescribed 243 days (8 months) before their index date were excluded. All patients with claims records in the preceding 243 days with ICD-9-CM billing codes suggestive of cardiovascular complications were also excluded. Excluded complications included myocardial infraction (410), angina pectoris (411, 413), and cardiovascular disorders (430-438).

We considered the dispensing rates of other CCBs prescribed after amlodipine or nifedipine CC as an

Figure. The Inclusion/Exclusion Approach



indicator of amlodipine and nifedipine CC effectiveness, since the dispensing of a second CCB may suggest crossover to another CCB. In addition, we analyzed eligibility records to rule out lack of access to care as a confounding variable, and we excluded patients who were not continuously enrolled in Medicaid for 8 months prior to and 9 months following their index date. Patients younger than 18 years of age and patients older than 64 years of age at the time of initial CCB prescription were excluded. At age 65 years, an unknown percentage of the population switches to Medicare, and different reimbursement procedures had potential to confound the analyses.

Analyses

We then monitored prescriptions of the eligible patients from January 1995 through October 1995 (See Figure). We compared age and gender, and we compared level of comorbidity using the Charlson-Deyo Index score[1] (Table 1). The Charlson-Deyo Index scores were calculated using all outpatient ICD-9-CM codes reported during the 243 days before the initial CCB prescription and during any subsequent outpatient visits in the 9-month observational period. Patients were stratified into 3 levels of severity based on the Charlson-Deyo Index scores: none (0 points), mild (1 point), and moderate or severe (≥2 points).

To determine the effectiveness of nifedipine CC and amlodipine, we defined 3 proxies for effectiveness. The proxies were based on the concept that a change in dispensed medication suggested either an adverse event or lack of effectiveness.[2] Although changes could be due to other causes, it is likely that these causes were randomly distributed between groups. The 3 proxies included:

- Change in treatment regimen to another type of CCB within the monitoring period;
- Evidence of a change to another class of antihypertensive drug; and
- Evidence of the addition of another class of antihypertensive drug to the treatment regimen.

Adherence was calculated using a modification of the approach described by Monane et al.[3] The total number of days' supply of drug dispensed during the monitoring period, excluding the last prescription, was determined; this allowed us to estimate the percentage of the monitoring period with adequate dosing coverage. Because the hospitalization rate was low in this group of patients, it was not necessary to adjust compliance for time in the hospital. Patients whose drug supply was adequate to cover ≥70% of the observation period were considered *adherent.* Patients who received ≤30% of the doses required to cover the observation period were *nonadherent.*

To identify potential adverse drug reactions in adherent patients, the rates of ICD-9-CM codes consistent with potential adverse drug events in adherent patients were compared. We assessed the following adverse events: chest pain (786.5), headache (784.0), flushing (782.62), dizziness/vertigo (780.4), edema (782.3), palpitations (785.1), myocardial infarction (410.9), angina (410.9, 413, 413.0, 413.1, 413.9, 411.1, 411.89), and stroke (436).

To compare the cost of care in therapeutically adherent patients, data on 3 areas of medical resource use were compiled: pharmacy (divided into total charges and hypertensive care charges), outpatient medical services (excluding emergency room visits), and inpatient and emergency room services. To compare overall charges and charges in each category, we used ordinary least squares regression with an indicator variable for the type of antihypertensive medication dispensed and adjusted charges for the patient's level of comorbid disease.

Table 1. Demographic Characteristics

	Nifedipine CC (n=151)*	Amlodipine (n=316)*
Age (mean, y)	48.2	49
Sex		
Male	39	39
Female	61	61
Race		
Caucasian	56	64
Other	44	36
Charlson-Deyo Index score		
0	82	72
1	13	20
≥2	5	8

*Other than the age, all values are expressed as percentages.

··· RESULTS ···

We identified 134,476 patients as hypertensive during the 9-month monitoring period. Of these patients, 44,997 were dispensed CCBs. Within this group, 3.5% received either nifedipine CC or amlodipine. After applying the criteria for initial treatment of uncomplicated hypertension and continuous eligibility, the resulting patient sample was: 467; 151 nifedipine CC and 316 amlodipine.

Demographics/Comorbid Disease Severity

Patient demographics and severity of comorbid disease appeared comparable between study drugs (Table 1). There was a slight trend toward a greater number of minority patients (Pearson chi-square: 2.5, P=.11) and less comorbidity (Pearson chi-square: 4.7, P=.09) in the nifedipine CC group.

Effectiveness

Of patients started on nifedipine CC, 15.8% (95% confidence interval [CI]: 11.8% to 20.3%) had a prescription for a second CCB; 10.3% (95% CI: 8.1% to 12.1%) of patients started on amlodipine were prescribed a second CCB. The proportion of patients with apparent cross-over to another class of antihypertensive agent, however, was higher for amlodipine patients. Based on the defined criteria, 7.3% of the nifedipine CC patients and 13.2% of the amlodipine patients had a change in medication (P=.058). The proportion of therapeutically adherent patients who had another class of antihypertensive medication added to their nifedipine CC or amlodipine regimen was similar between groups. Thirty-five percent of patients started on nifedipine CC and 42% of patients started on amlodipine had another antihypertensive drug added to their regimen (P=.40).

Adherence

Mean adherence rates were similar between groups (nifedipine CC=55%, amlodipine=57%). In both groups, adherence was bimodally distributed, with the largest groups of patients either completely adherent or completely nonadherent. The percentage of patients considered adherent (41% for nifedipine CC, 42% for amlodipine) and nonadherent (36% for nifedipine CC, 33% for amlodipine) were similar between groups.

Adverse Events

There were no statistically significant between-group differences in the incidence of adverse events reported in therapeutically adherent patients, as indicated by ICD-9-CM codes (Table 2).

Economic Analyses

Nonpharmacy Charges. Nonpharmacy charges were similar for both agents. The mean number of physician visits was 2.8 for nifedipine CC and 2.9 for amlodipine, and the difference was not statistically significant after adjusting for degree of comorbidity. The percentage of patients requiring hospitalization was also similar (6.4% for nifedipine CC, 6.0% for amlodipine), as was the proportion of patients requiring emergency room visits without hospitalization (1.6% for nifedipine CC, 0.7% for amlodipine). Additionally, utilization of other hospital-based services was similar between groups (21% for nifedipine CC, 27% for amlodipine).

When the nonpharmacy charges associated with both agents were controlled for comorbidities (using the multivariate approach to analyzing charges using ordinary least squares regression, however, there was a trend toward a lower overall average medical charge in patients dispensed nifedipine CC ($6703 for nifedipine CC, $8783 for amlodipine).

Prescription Charges. As expected, prescription charges for all antihypertensive medications were higher for patients who initiated therapy with amlodipine (mean antihypertensive medication charge per patient: $627 for amlodipine patients vs $434 for nifedipine CC patients, P<.0001). In part, this is because amlodipine is a more expensive drug; mean per-patient charges for the study medications were $327 for nifedipine CC and $458 for amlodipine ($P$<.0001).

Patients whose initial therapy was amlodipine also tended to have higher charges for other antihypertensive medications. For adherent patients who began therapy with nifedipine CC and had other medications added (n=22), charges for other antihypertensive medications averaged $188. For patients who initiated therapy with amlodipine and had other medications added (n=56), charges for other antihypertensive medications averaged $302 ($P$=.054).

Patients in the amlodipine group tended to have higher overall pharmacy charges (all medications, antihypertensive and otherwise). This was especially true for patients with more severe comorbidities (higher Charlson-Deyo Index); that is, the most severely ill patients tended to have significantly higher overall prescription charges when their initial antihypertensive therapy was amlodipine. In patients without complicating illnesses, the difference in total prescription cost between

groups was $293 (least squares estimate). In the most severely ill patients (Charlson-Deyo Index ≥2), however, the cost difference was $2545 (Table 3). This interaction between the Charlson-Deyo Index and the overall pharmacy charge explained 34% of the total variance in prescription charges.

··· DISCUSSION ···

Health maintenance organizations and insurers are developing large repositories of claims data that may provide insight into the effectiveness of healthcare interventions in real clinical practice. This study describes the combined use of pharmacy, inpatient, and outpatient claims data to compare the effectiveness of 2 dihydropyridine calcium antagonists for the initial treatment of uncomplicated hypertension. The results suggest that nifedipine CC was as effective as but less expensive than amlodipine.

Measures of Effectiveness

Although pharmacy claims provide less-than-ideal evidence of a change in a patient's drug regimen, the 3-proxy methodology used in this study may have important implications for assessing pharmaceutical effectiveness in clinical practice. Earlier studies of adherence using database records generally attempted to exclude patients who had a change in regimen during the observation period. In our analysis, we chose to take advantage of apparent changes in regimen as a marker of a lack of effectiveness. We combined data on the sequence of prescriptions with data about patient adherence. This extends previously published work in which researchers suggested continued dispensing of a drug over time as an indicator of effectiveness.[2] In addition, patients in this study had rates of adherence similar to those reported in previous studies of Medicaid patients with hypertension,[3,4] and this helps to validate our findings.

Our results suggest that, when the need to switch antihypertensive therapy arose, the choice of initial antihypertensive agent was indicative of the physician's subsequent prescribing practices. Patients who initiated antihypertensive therapy with nifedipine CC switched to another CCB more often than patients who initiated therapy with amlodipine. Conversely,

Table 2. Rates of Reported Adverse Events in Therapeutically Adherent Patients

	Nifedipine CC (n=62)*	Amlodipine (n=134)*	*P*
Palpitations	1.6	0.7	.56
Edema	1.6	2.4	.80
Dizziness	8.0	4.4	.40
Flushing	1.6	0	.12
Headache	12.9	7.5	.22
Chest pain	12.9	17.3	.44
Angina	0	0	—
Myocardial infarction	0	0	—
Stroke	1.6	0	.14
Any predefined complication	35.5	26.2	.18

* Values are expressed as percentages.

Table 3. Interactions Between Charlson-Deyo Index Scores, Prescribed Drug Therapy, and Total Pharmacy Cost Over the 9-Month Observation Period*

Charlson-Deyo Index	Drug	Pharmacy Charges ($) (Mean ± SE)
0	Nifedipine CC	1103 ± 146
0	Amlodipine	1396 ± 108
1	Nifedipine CC	1343 ± 429
1	Amlodipine	1765 ± 195
≥2	Nifedipine CC	2068 ± 536
≥2	Amlodipine	4604 ± 317

*Ordinary least squares regression was used to estimate charges. The resulting model shows an adjusted R^2 of 0.37. Interactions between the Charlson-Deyo Index score, initial drug, and charges were statistically significant at the $P<.001$ level.

when switching from amlodipine to another agent, physicians more often prescribed another drug class. The reason(s) for this difference is unknown.

This study also suggests that amlodipine and nifedipine CC were equally effective for the studied indication. Similar proportions of adherent patients in both groups received adjunctive antihypertensive drugs during the observation period, and initiation of treatment with amlodipine was not associated with reduced charges for medical care.

Adverse Events

Although the adverse event rates were similar between groups, adverse events in this study were likely to have been underreported when compared with clinical trials. Adverse events were captured only when documented as a primary, secondary, or tertiary diagnosis on outpatient billing records.

Economic Analyses

The increased pharmacy charges in the amlodipine group was not attributable to any differences in pharmacy benefits; all patients had similar pharmacy benefits and bore similar charges for the purchase of medications. It is possible that physicians who choose amlodipine may generally prefer drugs with similar brand identity (eg, drugs marked as high-cost/high-benefit preparations). These prescribing preferences might lead to large differences in pharmaceutical charges for the most ill patients, as observed in this study. Research suggests that physicians attribute some prescribing choices to patient demand and personal clinical experience.[5]

Limitations

This study was not an evaluation of *comparative efficacy* of amlodipine and nifedipine CC. Rather, it was a study of their *relative effectiveness* in clinical practice. Although we used a defined treatment indication and controlled for differences in comorbid conditions, assessments may have been confounded by demographic variances. Additionally, the accuracy of the 3 proxies of effectiveness has not been rigorously tested, although the proxy results are consistent with those of recent prospective clinical trial studies of dihydropyridine CCB agents.[6-8]

Due to these limitations, clinicians and researchers should use care when interpreting the results of comparisons based on claims data. For example, if one drug in this comparison was systematically employed to treat more severe cases of hypertension, additions of therapy or changes in regimen might not reflect differences in effectiveness. Therefore, careful selection of the indication for the comparison is essential. The construct of the administrative data records prevented a precise determination of the cause of changes in medication or why these changes occurred.

··· CONCLUSION ···

Administrative data can be used to compare the relative effectiveness of 2 drugs in clinical practice. Key elements of the comparison include differences in therapeutic effects (including evidence of crossover to another agent, addition of another agent, and adherence to the target agent), differences in rates of reported adverse effects, and differences in healthcare resource use. This type of evidence may not be ideal but will often be the best available to make informed judgments about the effectiveness of pharmaceuticals in specific clinical settings.

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