Adherence and Dosing Frequency of Common Medications for Cardiovascular Patients

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Objectives: To compare adherence between once-daily (QD) and twice-daily (BID) dosing with chronic-use prescription medications used by patients with cardiovascular disease.

Study Design: Retrospective cohort database analysis.

Methods: Analysis consisted of 1,077,474 patients aged ≥18 years with a prescription index date from January 1 to December 31, 2007, for an antidiabetic, antihyperlipidemic, antiplatelet, or cardiac agent with QD or BID dosing. Adherence (medication possession ratio [MPR]) was the number of days of medication supplied between the first prescription fill date and the subsequent 365 days divided by 365 days. Overall mean MPR and comparisons between dosing frequency groups were assessed with a generalized estimating equation. Covariates included age at index date, gender, Charlson comorbidity index, therapeutic class, dosing frequency, and the interaction between therapeutic class and dosing frequency group.

Results: Overall, the adjusted mean MPR ± standard error (SE) value for QD agents was 13.6% greater than BID agents (0.66 ± 0.0006 vs 0.57 ± 0.0016; P <.01). The adjusted mean MPR value for QD agents was 2.9%, 17.5%, and 29.4% greater than BID agents in the antidiabetic, antihyperlipidemic, and antiplatelet therapeutic classes, respectively. For cardiac agents, the adjusted mean MPR value was similar between QD and BID agents. Carvedilol represented approximately 80% of the cardiac agents in the BID group. The adjusted mean MPR ± SE for carvedilol phosphate QD was 0.73 ± 0.0024 and 0.65 ± 0.0027 for carvedilol BID (11% difference; P <.01).

Conclusions: In this large analysis, the QD dosing regimen was related to greater adherence versus a BID regimen.

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For author information and disclosures, see end of text.

Cardiovascular disease (CVD) continues to be the leading cause of mortality in the western world. In the United States alone, more than 830,000 people die each year from CVD, which accounted for 34.3% of all deaths in 2006.[1] The prevalence of CVD in the US population is staggering, with 17.6 million, 5.8 million, and 6.4 million individuals living with coronary heart disease, heart failure, or a history of stroke, respectively.[1] These numbers are likely to rise with the increasing elderly population, which is anticipated to be 20% of the US population by 2030.[2]

Over the last decade, numerous clinical trials of medications have demonstrated significant benefit in treating patients with CVD and associated risk factors, such as diabetes mellitus, and are now highly recommended in clinical guidelines.[3-7] For these medications to provide their benefits, patients need to be adherent to the prescribed regimen. Adherence, as defined by the International Society for Pharmacoeconomics and Outcomes Research, is "the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as 'the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen.'"[8] While this is one definition of adherence, it can basically be explained as "Does the patient take the medication as prescribed?"

Despite evidence of significant clinical benefit, for patients with CVD, adherence is often suboptimal.[9-16] It has been estimated that 40% to 50% of patients with CVD may be nonadherent, and this reduction in adherence may be seen at approximately 3 to 6 months of therapy.[10-12] Medication nonadherence is a commonly recognized source of adverse patient outcomes and use of healthcare and associated costs.[16,17] Studies have demonstrated that nonadherence to therapies for hypertension, dyslipidemia, or chronic stable angina results in greater morbidity, increased risk for hospitalization, or greater mortality.[14,18-25] For example, data from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry have demonstrated that lack of adherence with the antiplatelet agent clopidogrel in patients with acute myocardial infarction was associated with a 10-fold increase in mortality (0.7% vs 7.5%; P <.0001) and increase in cardiac hospitalizations (14% vs 23%; P = .08) at the end of 1 year.[26]

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Take-Away Points

The current study is the first large-scale effort to validate the often-held assumption that the complexity of a cardiovascular dosing regimen impacts medication adherence.

- Across the 4 therapeutic classes studied (antidiabetic, antihyperlipidemic, antiplatelet, and cardiac), adherence for once-a-day regimens was 14% higher than for twice-daily agents.
- Regardless of dosing regimen, adherence for many patients remains suboptimal.
- Providing patients with access to simplified dosing regimens may be an important factor in maximizing therapeutic success.

A number of factors may influence adherence, one being the complexity of the medication regimen.[10,27-30] Complexity of a prescribed medication regimen has been shown to be inversely related to patient adherence.[10,29] The complexity consists of 3 major domains: the number of medications prescribed, the complexity of administration, and daily dosing frequency.[30] For patients with CVD, who often take multiple medications, including the use of combination products, it can be difficult to significantly reduce the number of medications needed for optimal patient outcomes. The complexity of the administrations is not typically an issue in the management of chronic CVD since most medications are taken orally. Subsequently, the simplification of daily dosing frequency may have the most potential to improve drug adherence in patients with CVD.

While it may seem intuitive that a simplified dosing schedule would improve adherence, the literature investigating the relationship between adherence and daily dosing frequency is limited to smaller studies that are fairly old and meta-analyses of these previous studies.[16,30,31] The research has suggested that patients are more adherent to drugs with a once-daily (QD) dosing schedule compared with drugs requiring more frequent dosing, but there are concerns about the generalizability of the results. Another major limitation of the current data is that much of the data focus on a single drug or drug class. Additionally, the data are limited to the assessment of adherence of a single therapeutic class, such as only hypertension, dyslipidemia, or diabetes. There have been studies that have compared medication adherence across a variety of different disease states, but these analyses often included disease states that are unrelated, such as epilepsy, hypertension, and osteoporosis.[32,33] Recognizing the scarcity of broad-based multitherapeutic evidence related to adherence and the need to generate relevant data for the patients with CVD, this study attempts to estimate adherence from the broader multi-therapeutic perspective of classes of medications that are commonly used by patients with CVD. The objective of this study is to compare patient adherence between QD and twice-daily (BID) dosing with chronic-use prescription medications commonly used by patients across the spectrum of CVD with a large, recent, commercial database.

METHODS

Data Source and Data Selection

The study data are from the Thomson Reuters MarketScan Research Databases (Ann Arbor, Michigan). The MarketScan Commercial Claims and Encounters plus the Medicare Supplemental databases are large insurance claims databases with both working age employer-sponsored insurance and patients with Medicare Supplemental Insurance. Pharmacy claims contained quantities of drug dispensed, days supply, and costs.

Data were from July 1, 2006, to December 31, 2008. The first prescription fill date, or index date, for 1 or more of the drugs of interest, as described below, occurred between January 1 and December 31, 2007, and prescription data needed to be available for the entire period of time between 6 months prior to and 12 months after the index date. The unit of analysis was drug therapy for 1 year; therefore, patients were permitted to have prescription claims for more than 1 drug in this analysis.

Drugs were selected for inclusion in the study if they were in capsule or tablet form and could be grouped into 1 of the following therapeutic classes: antidiabetic (eg, metformin, thiazolidinediones, sulfonylureas), antihyperlipidemic (eg, statins, fibrates), antiplatelet (eg, clopidogrel, aspirin/dipyridamole, cilostazol), or cardiac agents (eg, ACE inhibitors, antiarrhythmic agents, alpha-beta blockers, calcium channel blockers). For each prescription claim, the quantity of pills per day was calculated. A drug was designated as having either QD or BID dosing if ≥80% of the claims had a quantity per day of either 1 or 2, respectively.

Patients in the analysis were 18 years or older and were required to be continuously enrolled in a health plan for inclusion in the study. Patient baseline comorbidities were quantified with a simple unweighted Charlson index score.[34] Patients with catastrophic healthcare costs (eg, index drug costs greater than $1000, pre-index prescription costs greater than $10,000, or pre-index medical costs greater than $100,000) were excluded from the analysis in order to capture a typical healthcare experience. Patients with prescription claims for less than a 30-day supply were excluded.

Adherence Measures

The adherence measure used in this analysis was the medication possession ratio (MPR). The MPR was defined as the number of days of medication supplied from the first prescription fill date up to 365 days divided by 365 days. Calculations of MPR greater than 1.0 were set to 1.0.

Statistical Analyses

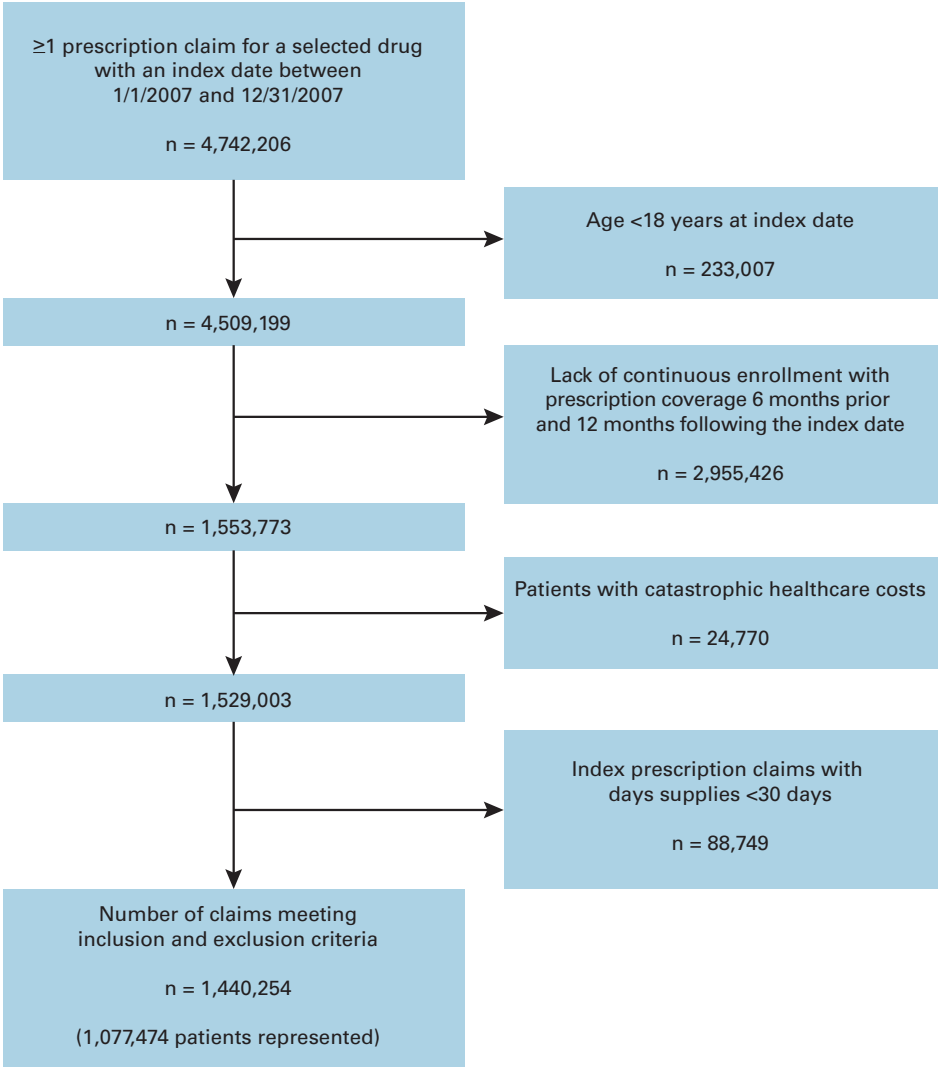
The primary objective was to compare the mean MPR values between the QD and BID groups. A generalized estimating equation (GEE) was used to estimate the mean MPR and to compare the dosing frequency groups. The GEE accounted for the correlations resulting from a patient presenting data for multiple drugs either within a therapeutic class or in different therapeutic classes. An exchangeable correlation structure was used in the GEE. Alternative to mean, MPR greater than 80% has been suggested as a measure of adherence and was also calculated. To account for differences in patient demographic and clinical characteristics, the multivariate model adjusted for the potential confounding variables (age at index date, gender, and Charlson comorbidity index) and included therapeutic class, dosing frequency (QD or BID), and the interaction between therapeutic class and dosing frequency group.

The mean MPR adjusted for the model covariates and the standard error (SE) are presented, unless noted otherwise. *P* values less than or equal to 0.05 were considered statistically significant. No adjustments were made for multiplicity. All analyses were conducted with SAS (SAS Institute, Inc, Cary, North Carolina) version 9.2.

RESULTS

The sample sizes for the analysis, after applying the study inclusion and exclusion criteria, are presented in the **Figure**. The final analysis database contained 1,440,254 (QD: 1,384,226 and BID: 56,028) therapy observations. This represented 1,077,474 patients, and their baseline characteristics at the index event for a therapy are presented in **Table 1**. The average age of patients was 59 years for patients taking QD medications and 61 years for patients with BID medi-

Figure. Sample Selection Flow Chart



cations. Approximately 45% and 30% of the patients were in the Southern and North Central regions of the United States, respectively. Across the therapeutic classes, the average Charlson index score ranged from an average of 0.5 to 1.6 and the number of concomitant medications ranged from an average of 3 to 6. Approximately 80% of patients who took antidiabetic agents had a diagnosis of diabetes. Of patients in the antiplatelet agent class with a QD dosing frequency, 65% had a diagnosis of ischemic heart disease, and approximately 50% of patients in the cardiac agent class had a diagnosis of hypertension. For all patients, one-third had a diagnosis of hyperlipidemia. Approximately 50% of patients participated in a preferred provider organization insurance plan. For healthcare costs, the average cost of the index drug ranged from $30 for the antihyperlipidemic agent class with a BID dosing frequency to $255 for the antidiabetic agent class with the QD dosing frequency. Inpatient and outpatient pre-index medical costs ranged from an average of $3041 for patients in the antidiabetic agent class with a BID dosing frequency to $18,522 for patients in the antiplatelet agent class with a QD dosing frequency.

Overall, the adjusted mean MPR ± SE value for QD agents was 15.8% greater than BID agents (0.66 ± 0.0006 vs 0.57 ± 0.0016; P <.01) (**Table 2**). The adjusted mean MPR values for the QD agents were 3.0%, 21.2%, and 41.7% greater than for BID agents in the antidiabetic, antihyperlipidemic, and antiplatelet therapeutic classes, respectively (Table 2). In the antidiabetic therapeutic class, most of the QD agents were composed of pioglitazone and sitagliptin, which had MPRs of about 0.70. The BID agents in the antidiabetic therapeutic class were largely metformin combination products with an MPR ranging from 0.54 to 0.72. In the antihyperlipidemic therapeutic class, the QD agents were chiefly statins with a wide range of MPRs (0.50 to 0.67), while the BID agents were predominantly composed of gemfibrozil (MPR 0.50). The antiplatelet therapeutic class demonstrated the largest difference between QD and BID agents. This therapeutic class had a larger percentage of BID agents compared with QD agents versus the other therapeutic classes. The principal QD agent in the antiplatelet class was clopidogrel with an MPR of 0.71. The BID agents were primarily composed of aspirin/dipyridamole, cilostazol, and ticlopidine, which had MPRs of 0.56, 0.43, and 0.50, respectively.

Conversely, for the cardiac agent class, the adjusted mean MPR value was similar between QD and BID agents (0% difference). Further analysis of this therapeutic class identified that carvedilol represented approximately 80% of the total BID group of cardiac agents. Since carvedilol is also available in a QD formulation we conducted a comparison between the 2 carvedilol formulations. A GEE was also used to model carvedilol data. The model contained age, gender, and Charlson comorbidity index. There were a total of 36,081 therapy observations of carvedilol in the database (18,619 for carvedilol phosphate QD and 17,462 for carvedilol BID) among 34,339 patients. The adjusted mean MPR ± SE for carvedilol phosphate QD was 0.73 ± 0.0024 and for carvedilol BID it was 0.65 ± 0.0027, representing a 12.3% (P <.01) difference.

Comparisons were also completed using an MPR of greater than 80% adherence definition for the overall group and each subgroup (**Table 3**). These results are consistent with the overall findings of a significantly higher rate of adherence with the QD group compared with the BID group. The subgroup findings were also consistent, with a significantly higher rate of adherence with the QD group compared with the BID group for antidiabetic, antihyperlipidemic, and antiplatelet agents, and no difference in the general group of cardiac agents.

DISCUSSION

Using a large pharmacy claims database, we identified a 15.8% higher rate of adherence to medications with a QD dosing frequency compared with those given BID. To our knowledge, this unique analysis represents the largest single evaluation of adherence to medications commonly used by patients with CVD, while also providing data on specific classes of CVD medications. Most previous studies have either focused on a single disease state or have reported on multiple medical conditions that are typically unrelated (eg, CVD-related conditions and osteoporosis).[32,33]

Our results of improved adherence with a simplified dosing complexity (QD vs BID) are consistent with those found in older adherence studies and meta-analyses.[10,16,29-31,35-37] Some of these prior studies have demonstrated that patients taking drugs with a QD dosing frequency were more adherent to their therapy compared with those taking drugs with a BID frequency. Of note, in the meta-analysis by Claxton et al, QD dosing had an adherence rate of 79% compared with 69% for BID dosing.[31] While the adherence rates in the study by Claxton are higher than ours for both QD (66%) and BID dosing (57%), it should be noted that their meta-analysis only included studies using the medication event monitoring systems (MEMS), so patients were aware that their medication adherence was being monitored.[31] Therefore, questions remain about the differences in adherence between QD and BID dosing in the "real world" setting.

The use of pharmacy claims data allowed us to conduct a natural experiment of adherence, or a "real world" evaluation. In addition to pharmacy claims, adherence can be measured by a variety of methods including patient self-report, pill counts during follow-up visits, blood-level measurement,

Table 1. Characteristics of the Study Population by Therapeutic Class at the Index Event

	Antidiabetic Agents		Antihyperlipidemic Agents		Antiplatelet Agents		Cardiac Agents		Overall	
	QD	BID	QD	BID	QD	BID	QD	BID	QD	BID
Characteristic	(n = 72,152)	(n = 14,586)	(n = 532,480)	(n = 11,361)	(n = 39,222)	(n = 8577)	(n = 740,372)	(n = 21,504)	(n = 1,384,226)	(n = 56,028)
Age, y (mean, SD)	60 (13)	56 (12)	58 (13)	54 (13)	66 (13)	70 (13)	59 (15)	65 (14)	59 (14)	61 (14)
Women, %	46	46	49	39	39	47	50	42	49	43
Index region, %										
North Central	29	24	28	27	33	36	27	31	28	29
Northeast	9	8	9	6	9	9	9	7	9	8
South	46	57	43	40	42	39	45	44	44	46
West	16	11	19	26	15	16	19	18	19	17
Pre-index Charlson score (mean, SD)	1.2 (0.9)	1.1 (0.7)	0.5 (0.8)	0.5 (0.8)	1.4 (1.2)	1.6 (1.2)	0.6 (0.9)	1.3 (1.3)	0.6 (0.9)	1.2 (1.1)
Cardiovascular comorbidities, %										
Myocardial infarction	1	1	2	1	24	4	3	13	3	6
Ischemic heart disease	13	10	14	9	65	27	15	45	16	26
Congestive heart failure	4	2	3	2	12	8	6	32	5	15
Peripheral artery disease	4	3	3	2	17	30	4	9	4	9
Stroke	1	1	2	1	10	32	2	4	2	7
Diabetes	82	84	21	25	24	27	19	29	23	42
Hypertension	37	37	36	36	49	50	53	50	46	44
Hyperlipidemia	30	33	47	48	32	26	23	26	33	32
Number of concomitant medications at index (mean, SD)	6 (3)	5 (3)	3 (3)	4 (3)	5 (3)	5 (3)	4 (3)	6 (4)	4 (3)	5 (3)
Index insurance plan type, %										
Comprehensive	17	12	14	10	25	30	17	24	16	19
EPO	0.7	0.9	0.7	0.9	0.5	0.3	0.6	0.4	0.7	0.6
HMO	14	13	17	21	11	10	16	13	16	14
POS	9	12	10	10	8	6	10	8	10	9
POS with capitation	0.4	0.4	0.4	0.3	0.2	0.1	0.3	0.2	0.3	0.2
PPO	56	58	54	54	53	51	53	53	54	54
Cost of index drug, $ (mean, SD)[a,b]	255 (140)	234 (136)	102 (81)	30 (25)	155 (75)	115 (83)	54 (63)	118 (99)	86 (90)	130 (121)
Pre-index total medical costs, $, inpatient and outpatient (mean, SD)[a]	3701 (8438)	3041 (7315)	3980 (9603)	3194 (8143)	18,522 (18,962)	10,114 (14,155)	5323 (11,480)	13,176 (18,262)	5096 (11,206)	8045 (14,425)

BID indicates twice daily; EPO, exclusive provider organization; HMO health maintenance organization; n, therapy observations; POS, point of service; PPO, preferred provider organization; QD, once daily; SD, standard deviation.
[a]Costs refer to the total cost received by the provider (plan cost and patient out-of-pocket costs).
[b]Cost of study drug at the index prescription.

Table 2. Mean MPR by Therapeutic Class

Therapeutic Class (n, therapy observations)	Adjusted Mean MPR ± SE QD (n = 1,384,226)	Adjusted Mean MPR ± SE BID (n = 56,028)	% QD Difference From BID	*P*
Overall	0.66 ± 0.0006	0.57 ± 0.0016	+15.8%	<.01
By therapeutic class				
Antidiabetic agents	(n = 72,152) 0.69 ± 0.0012	(n = 14,586) 0.67 ± 0.0027	+3.0%	<.01
Antihyperlipidemic agents	(n = 532,480) 0.63 ± 0.0005	(n = 11,361) 0.52 ± 0.0031	+21.2%	<.01
Antiplatelet agents	(n = 39,222) 0.68 ± 0.0017	(n = 8577) 0.48 ± 0.0040	+41.7%	<.01
Cardiac agents	(n = 740,372 0.63 ± 0.0004	(n = 21,504) 0.63 ± 0.0024	0%	.50

BID indicates twice daily; MPR, medication possession ratio; QD, once daily; SE, standard deviation error.

and the use of MEMS. The MEMS is thought to be one of the most accurate methods for measuring adherence because the technology allows for the recording of the exact date and time the pill bottle is opened. The major limitation to MEMS is that adherence assessment can be confounded by the fact that patients are aware that their medication adherence is being monitored, and thus this method may not measure "real world" adherence.

There was a large variation in adherence across the therapeutic groups within our study. The largest difference was demonstrated in the antiplatelet agents therapeutic groups, with an almost 30% improvement in adherence between QD and BID, with no difference seen in the therapeutic group of cardiac agents. While our rates of adherence vary between the different therapeutic classes, these rates fit within the range demonstrated with QD dosing (35% to 97%) and BID dosing (38% to 90%) in the meta-analysis by Claxton and colleagues.[31] Furthermore, other studies have demonstrated different rates of adherence between therapeutic classes. The analysis by Briesacher et al found an adherence rate of 72.3% for agents used for hypertension and only 36.8% for agents used for management of gout.[32] Yeaw et al found an adherence rate of 72% for those taking antidiabetic agents, and 37% among those taking prostaglandin analogues.[33]

The similarity in adherence rates between QD and BID dosing in the therapeutic class of cardiac agents was an unexpected finding. One reason for this finding could be the heterogeneity of the medications and medical conditions included in this group. The cardiac agents therapeutic class included medications used in the management of hypertension, heart failure, arrhythmias, and ischemic heart disease. Since medication adherence is multifactorial, the mix of medications and medical conditions within this broad category may not allow for an accurate analysis of the impact of dosing complexity alone on adherence. Additionally, upon closer examination of the BID group of cardiac agents, we observed that carvedilol represented approximately 80% of the therapeutic class. We therefore surmise that the lack of difference in the cardiac agents therapeutic group may be due to the high rate of adherence with carvedilol BID. As demonstrated in our subanalysis, however, even the relatively high adherence rate of carvedilol BID can be increased by 12.3% by moving to

Table 3. Percentage of Patients Who Experienced ≥80% Adherence (MPR) Adjusted for Covariates

Therapeutic Class (n, therapy observations)	Percentage of Patients QD	Percentage of Patients BID	*P*
Overall	46	41	<.0001
By therapeutic class			
Antidiabetic agents	54	49	<.0001
Antihyperlipidemic agents	44	30	<.0001
Antiplatelet agents	59	34	<.0001
Cardiac agents	46	46	.9565

BID indicates twice daily; MPR, medication possession ratio; QD, once daily.

the QD carvedilol formulation. This higher rate of adherence between carvedilol formulations is similar to the overall rate of increase demonstrated in the overall study (15.8%).

As with most studies, the current analysis is subject to limitations and assumptions. There are a number of limitations involved in using claims data to identify dosing regimens and adherence. We are unable to determine the intended duration of the prescriptions with the claims data. Additionally, because it is not included directly in the claims, the dosing regimen (QD or BID) was calculated as the quantity dispensed divided by the days' supply. It was assumed that a value of 2 was equal to 1 tablet twice a day; however, it is possible that a patient taking 2 tablets once a day would be misclassified into the BID group. While there is no way to determine the frequency of this, misclassifying QD regimens as BID would make the results of this study more conservative, as it would bias against detecting a difference between the 2 groups.

As the name implies, the MPR, as calculated by claims data, is limited to providing information on a patient's possession of a medication and not necessarily its use. The MPR has, however, been widely used and validated as a measure of adherence.[38,39] Furthermore, more direct measures of patient adherence, such as blood levels, pill counts, and electronic monitoring, are not feasible in a sample as large or geographically dispersed as the current study.

An additional limitation to using claims data in a retrospective cohort study is that the subjects are neither randomized nor equally distributed. In the current study, the number of therapy observations on QD therapy is almost 25 times as large as the number with a BID therapy and it is impossible to determine from the claims data all of the factors that influence a patient's treatment choice. There are likely to be some underlying differences between the 2 populations, which is why the current study used a multivariable model to control for potential confounders. Claims data are also imperfect in that diagnosis codes are limited to the top 5 diagnoses for each claim, which means that chronic conditions may not appear in a claim over the 6-month observation period used in this study.

Another limitation is that in 2006, during the study time frame, a number of pharmacy chains introduced low-cost generic programs which enabled patients to buy selected generic medications for approximately $4 per month. Pharmacy chains may not submit claims for patients who pay with cash. Consequently, patients who filled prescriptions with these programs after the index date may appear as nonadherent to their medication in the insurance claims database.[40]

It should also be noted that data on the use of over-the-counter medications, such as aspirin, are not available from claims data. Scarcity of empirical evidence makes it difficult to ascertain how aspirin may have influenced adherence of other drugs and the antiplatelet class in particular. For example, a large European observational study found patients prescribed concomitant aspirin and statin reported higher adherence compared with either drug alone,[41] while a large randomized cohort study in the United States found no clear influence of baseline platelet drug use on aspirin adherence.[42]

Finally, another limitation of the current study is that it used adherence, and not clinical outcomes, as its end point. While it is unclear whether the difference in adherence identified in this study will impact clinical outcomes, there is enough literature around each of these conditions to suggest that improved adherence is linked to improved outcomes.[8]

CONCLUSIONS

In the largest evaluation to date of adherence to medications commonly used by patients with CVD, this study found a once-daily dosing regimen was related to a 16% higher rate of adherence over a twice-daily regimen. While the study did not compare clinical outcomes related to the adherence difference, it is likely that such an increase would lead to improved clinical outcomes.[8] Providing patients with access to simplified dosing regimens may be an important factor in maximizing therapeutic success.

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