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The Implications of Therapeutic Complexity on Adherence to Cardiovascular Medications

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Background: Patients with chronic disease often take many medications multiple times per day. Such regimen complexity is associated with medication nonadherence. Other factors, including the number of pharmacy visits patients make to pick up their prescriptions, may also undermine adherence. Our objective was to estimate the extent of prescribing and filling complexity in patients prescribed a cardiovascular medication and to evaluate its association with adherence.

Methods: The study population comprised individuals prescribed a statin (n = 1 827 395) or an angiotensin-converting enzyme inhibitor or renin angiotensin receptor blocker (ACEI/ARB) (n = 1 480 304) between June 1, 2006, and May 30, 2007. We estimated complexity by measuring the number of medications, prescribers, pharmacies, pharmacy visits, and refill consolidation (a measure of the number of visits per fill) during the 3 months from the first prescription. The number of daily doses was also measured in ACEI/ARB users. After this period, adherence was evaluated over the subsequent year. The relationship between complexity and adherence was assessed with multivariable linear regression.

Results: The statin cohort had a mean age of 63 years and were 49% male. On average, during the 3-month complexity assessment period, statin users filled 11.4 prescriptions for 6.3 different medications, had prescriptions written by 2 prescribers, and made 5.0 visits to the pharmacy. Results for ACEI/ARB users were similar. Greater prescribing and filling complexity was associated with lower levels of adherence. In adjusted models, patients with the least refill consolidation had adherence rates that were 8% lower over the subsequent year than patients with the greatest refill consolidation.

Conclusion: Medication use and prescription filling for patients with cardiovascular disease is complex, and strategies to reduce this complexity may help improve medication adherence.

Arch Intern Med. 2011;171(9):814-822.
Published online January 10, 2011.
doi:10.1001/archinternmed.2010.495

EFFECTIVE MEDICATIONS ARE central to the prevention and management of chronic diseases and their complications. Because many patients have multiple chronic conditions,[1] therapeutic regimens often involve multiple medications and frequent daily dosing. Such regimen complexity may undermine effective chronic disease management. For example, patients who are prescribed medications that must be taken multiple times per day are less likely to adhere to their treatments than patients with simpler dosing schedules.[2] Interventions that simplify treatment regimens by reducing dosing frequency[3] or by switching patients to fixed-dose medication combinations[4] result in substantial improvements in appropriate medication use.

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Other factors may also add complexity to a patient's medication regimen and adversely affect adherence but have not been previously evaluated. Patients interact with physicians to have medications prescribed and often visit pharmacies to fill their prescriptions. As a result, for patients prescribed equivalent numbers of medications and with equal levels of illness severity, those who make numerous trips to the pharmacy to pick up their medications or for whom multiple physicians write prescriptions or who fill prescriptions at many different pharmacies may have greater difficulty taking their medications as prescribed. These factors are of interest because they are potentially amenable to scalable adherence improvement interventions. For example, consolidation of prescription filling in a "pharmacy home" may help improve

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health care quality, analogous to the intended effects of a patient-centered medical home.[5]

Accordingly, we assembled a large, contemporary, nationally representative cohort of patients prescribed a long-term medication to estimate the extent of prescribing and regimen complexity and to evaluate their contribution to medication nonadherence.

METHODS

SETTING AND DESIGN

We used prescription claims data from CVS Caremark, Woonsocket, Rhode Island, a pharmacy benefit manager with more than 50 million beneficiaries throughout the United States, to assemble a cohort of patients who were prescribed a cholesterol-lowering statin or an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB) between June 1, 2006, to May 30, 2007. These agents were chosen because they represent the 2 most widely sold therapeutic classes to treat cardiovascular disease in the United States.[6] Separate cohorts were created for statin and ACEI/ARB users; patients who filled prescriptions for medications in both classes were included in both cohorts. We defined the index date as the first prescription date for any drug in the relevant class during the accrual period. We excluded patients who did not maintain continuous drug insurance benefits for the 1 year before and 15 months after the index date. Patients receiving pharmacy benefit coverage through CVS Caremark can fill prescriptions at any retail pharmacy (ie, not only CVS retail pharmacies), although mail-order prescriptions can only be filled through CVS Caremark's mail-order pharmacy.

For each patient, study time was divided into 3 periods. Therapeutic complexity (ie, the exposure) was measured during the 3-month period after and including the index date. Our complexity measures are described in greater detail in the following subsection. Medication adherence (ie, the outcome) was evaluated during the 12 months after therapeutic complexity was measured (ie, months 4 to 15 after the index date). The 12-month period before the index date was used to determine patient comorbidity.

Information contained in the prescription drug claims data included drug name, dosage, date dispensed, quantity dispensed, days supplied, pharmacy and prescriber identity, method of medication delivery (ie, retail or mail order), and cost. All traceable person-specific identifying factors were transformed into anonymous, coded study numbers to protect subjects' privacy. The institutional review board of Brigham and Women's Hospital approved the study.

MEASURES OF THERAPEUTIC COMPLEXITY

For each patient, we defined the following measures of therapeutic complexity: the total number of prescriptions and number of different prescriptions filled, the number of fills for medications in different drug classes and for drugs that are intended for long-term use (ie, maintenance medications), the number of physicians who wrote medication prescriptions, the total number of pharmacies and number of different pharmacies at which prescriptions were filled, the number of pharmacy visits (for non–mail-order prescriptions), and the consolidation of these refills. Maintenance medications are those that are intended for long-term use and were identified from the Wolters Kluwer Medi-Span Master Drug Database[7] and the First Data Bank National Drug Data File Plus Database.[8] For the ACEI/ARB analysis, we also measured the number of daily medication doses.

Refill consolidation was calculated by subtracting from 1 the quotient of the number of visits and the number of medications filled; possible values for the measure range between 0 and 1, with higher values representing fewer visits per fill (ie, more consolidation). For example, a patient who made 12 visits to the pharmacy to fill 12 prescriptions would have a consolidation score of 0, whereas a patient who made 3 visits to the pharmacy to fill 12 prescriptions would have a synchronization score of 0.75. Because mail-order fills are likely to impose much less burden on patients than visits to retail pharmacies, we did not include the days on which patients filled mail-order prescriptions in the count of pharmacy visits; patients who filled their prescriptions only by mail order were considered to have a refill synchronization score of 1 (ie, maximum synchronization). For patients who filled at both mail-order and retail pharmacies, the consolidation measure was based on all fills (ie, in the denominator of the quotient) but only face-to-face visits at retail pharmacies (ie, in the numerator). For example, a patient who filled 6 prescriptions at retail pharmacies on 2 visits and 6 prescriptions by mail order would have a consolidation score of 0.83 (ie, $1-2/[6+6]$). Because the number of medications a patient fills influences refill consolidation, we adjusted for the number of concurrently prescribed medications in our multivariate models (described in greater detail in the "Statistical Analysis" subsection).

MEDICATION ADHERENCE

We estimated adherence by calculating the number of days the medication was available or the "proportion of days covered" for each drug class prescribed over the 12-month adherence assessment period.[9] To do this, we first created a "supply diary" for each patient-day by stringing together consecutive fills of each medication class based on dispensing dates and reported days' supply. All drugs dispensed within a therapeutic class (ie, statins or ACEI/ARBs) were considered as interchangeable. When a dispensing occurred before the previous dispensing should have run out, new medication use was assumed to begin the day after the end of the old dispensing. If a patient accumulated more than 180 days' supply on a given day, the accumulated supply was truncated at 180 days. The number of days of medication the patient had on hand at the beginning of the adherence assessment period (ie, from dispensings that occurred during the complexity assessment period) were added to the supply diary.

COVARIATES

A number of patient characteristics were assessed as of the date of cohort entry. These included age, sex, and income. Data on socioeconomic status were obtained by linking zip code of residence with data from the US Census, which specified the median income of the geographic population associated with each zip code. Income was categorized into quintiles. We determined the nature of each patient's drug coverage using enrollment files and categorized patients into the following groups: directly employer sponsored, health insurer carve-out (ie, beneficiaries who are fully insured through a commercial health insurer but whose prescription drug coverage is "carved out" and provided separately by a pharmacy benefit manager), Medicare, or other (which includes Medicaid beneficiaries, cash card holders, and offshore customers). We assessed patient morbidity by calculating a Pharmacy Risk Group (PRG) score, which is determined using proprietary algorithms based on filled prescription claims data during the year prior to the index date.[10] Pharmacy Risk Group scores predict future resource use and expenditure and thus allow for risk adjustment in the absence of medical claims data.

We calculated each patient's mean monthly medication copayment for statins or ACEI/ARBs, as appropriate, by adding

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Table 1. Baseline Characteristics of Patients Receiving Statin and ACEI/ARB Prescriptions

Characteristic	All Patients	Prevalent Users			New Users		
		Mail Order Only	Retail Only	Mixed	Mail Order Only	Retail Only	Mixed
Statins							
Patients, No.	1 827 395	250 011	815 844	349 178	44 894	289 971	77 497
Age, mean (SD), y	62.5 (12.8)	64.2 (11.5)	62.7 (13.2)	64.4 (11.7)	61.5 (11.3)	58.3 (13.6)	61.2 (12.2)
Male sex, %	48.6	41.6	50.3	47.8	46.8	49.9	53.6
Income, mean (SD), $	55 464.47 (19 984.73)	57 394.82 (19 960.30)	54 625.60 (20 221.89)	57 559.16 (20 285.46)	58 450.71 (20 047.96)	53 021.46 (18 656.77)	56 041.16 (19 264.56)
Insurance type, %							
Employer	61.5	88.3	44.9	85.3	62.7	49.8	86.7
Health plan	14.7	6.7	19.4	7.8	10.9	19.4	7.5
Medicare	18.7	4.3	29.7	6.1	5.8	20.7	5.1
Other	5.1	0.7	6.0	0.8	20.6	10.1	0.7
PRG risk score, mean (SD)	1.6 (2.0)	1.0 (1.3)	1.4 (1.8)	1.6 (2.0)	1.5 (1.8)	2.1 (2.4)	2.7 (2.8)
Monthly copayments, mean (SD), $							
Statins	17.27 (18.69)	12.91 (10.23)	20.27 (21.85)	13.35 (10.80)	11.99 (11.47)	19.11 (22.28)	13.64 (12.12)
Other medications	14.40 (28.86)	8.54 (9.21)	15.54 (28.23)	13.87 (29.95)	8.83 (12.93)	17.83 (38.97)	14.13 (31.22)
ACEI/ARB							
Patients, No.	1 480 304	174 996	750 608	270 750	25 483	208 259	50 208
Age, mean (SD), y	62.6 (13.9)	64.6 (12.2)	62.7 (14.3)	64.6 (12.4)	61.8 (11.7)	58.2 (15.0)	62.1 (13.0)
Male sex, %	48.8	41.4	51.6	47.9	43.2	47.0	48.6
Income, mean (SD), $	53 815.92 (18 992.51)	55 908.80 (19 089.56)	52 600.72 (18 824.91)	56 199.21 (19 502.53)	58 309.71 (19 686.10)	52 257.74 (18 074.76)	56 018.86 (19 263.75)
Insurance type, %							
Employer	58.4	88.5	42.5	85.2	56.1	49.0	87.9
Health plan	14.9	6.5	19.0	7.8	11.7	18.5	7.0
Medicare	19.7	4.2	29.6	6.2	6.0	19.8	4.5
Other	7.0	0.8	8.9	0.8	26.2	12.7	0.6
PRG risk score, mean (SD)	1.5 (1.9)	1.0 (1.4)	1.3 (1.8)	1.6 (2.0)	1.4 (1.7)	1.9 (2.3)	2.6 (2.8)
Monthly copayments, mean (SD), $							
ACEI/ARB	11.55 (13.02)	9.07 (7.97)	12.55 (14.56)	9.85 (8.93)	9.94 (9.24)	12.67 (15.28)	10.38 (10.11)
Other medications	14.87 (27.72)	8.93 (8.59)	16.04 (28.22)	13.12 (25.58)	9.14 (9.37)	18.86 (38.01)	13.98 (26.26)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PRG, Pharmacy Risk Group.

together the copayments for all medications in the class dispended during the complexity assessment period, dividing this by the total number of days of medication supplied for these prescriptions, and then multiplying the result by 30.

STUDY STRATA

Adherence differs systematically for patients newly initiated on therapy compared with long-term medication users[11] and for patients who receive their prescriptions via mail order compared with those who fill at retail pharmacies.[12] Accordingly, we divided each of our cohorts into 6 predefined strata based on whether patients had received a prescription for any member of the therapeutic class in the 12 months prior to the index data (ie, 2 strata: new or prevalent users) and how they received their prescriptions (ie, 3 strata: retail only, mail order only, or a combination of mail order and retail) during the complexity assessment period.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize measures of therapeutic complexity. Because of the overlapping nature of some of the measures (eg, total number of fills and number of unique medications) and colinearity of some measures with our outcome (eg, patients who have a greater number of total fills are by definition more adherent), we evaluated the bivariate relationship between the following measures of complexity and medication adherence: (1) the number of unique medications, (2) the number of prescribers, (3) the number of unique pharmacies, (4) refill synchronization, and (5) doses per day (for the ACEI/ARB analyses). We created multivariable linear models to evaluate the relationship between these variables and adherence, controlling for patient demographics, comorbidity, and medication costs.

The analyses were first performed for the entire cohort and then repeated in each of the 6 strata described in the previous subsection. We also repeated our analyses using nonlinear versions of our predictor variables. Because these analyses gave rise to identical inferences, we present the results based on the linear version of our measures below. To evaluate the influence of our decision to only consider retail pharmacies in the count of pharmacies at which patients filled prescriptions, we repeated our analyses after adding an additional pharmacy to all patients filling by mail order (in whole or in part). Finally, we repeated our analyses using an alternative morbidity measure—the number of distinct medications filled by each patient in the year prior to their index date.[13] All analyses were performed using SAS version 10.2 statistical software (SAS Institute Inc, Cary, North Carolina).

RESULTS

Our statin cohort and ACEI/ARB cohorts consisted of 1 827 395 and 1 480 304 patients, respectively; 664 675 patients (20.1% of the total sample) were included in both

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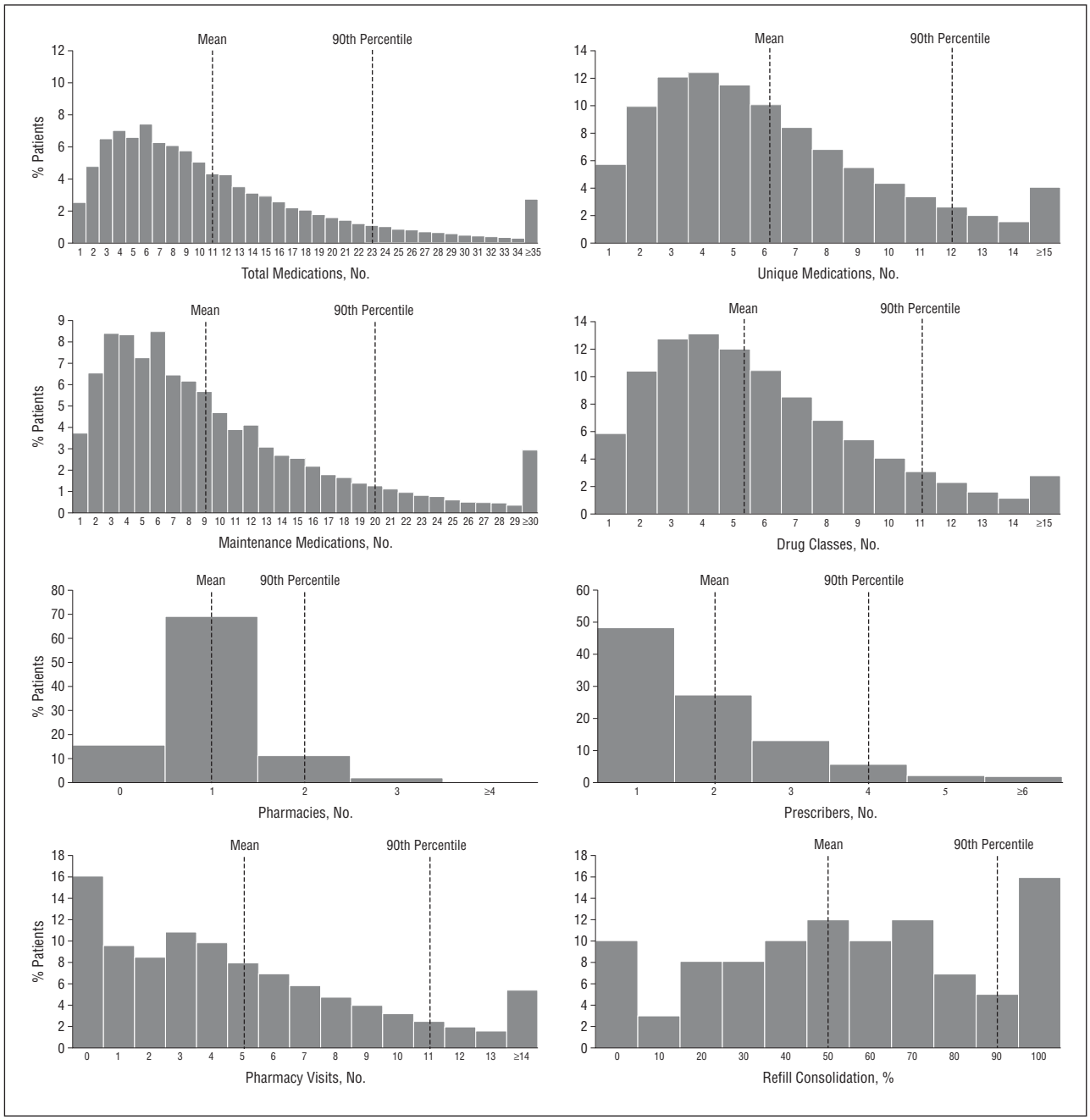

Figure 1. Estimates of therapeutic complexity over a 90-day period among statin users.

study groups. Patients in both cohorts had a mean age of 63 years, were evenly split between sexes, and had mean incomes above $50 000 per year, and the majority received drug coverage directly through employer-sponsored insurance or via a health plan (**Table 1**).

Approximately 80% of patients in both cohorts were prevalent medication users (ie, had received a prescription for a member of the therapeutic class within the prior 12 months). Patients who received their medications by mail (either entirely or in part) had higher median incomes, were more likely to have employer-sponsored insurance, and paid lower monthly copayments than patients who filled their prescriptions at retail pharmacies. Within categories of new and prevalent use, patients who filled only by mail order had lower levels of illness severity.

THERAPEUTIC COMPLEXITY

The nature of medication filling by statin users during the 3-month complexity assessment period is shown in **Figure 1**. Over this period, patients filled a mean of 11.4 medications at 5.0 visits to the pharmacy. The majority (9.7) of fills were for maintenance medications and represented a mean of 5.9 different drug classes. Patients filled a mean of 6.3 different medications (ie, each medication was filled a mean of 1.8 times). On average, prescriptions were written by 2

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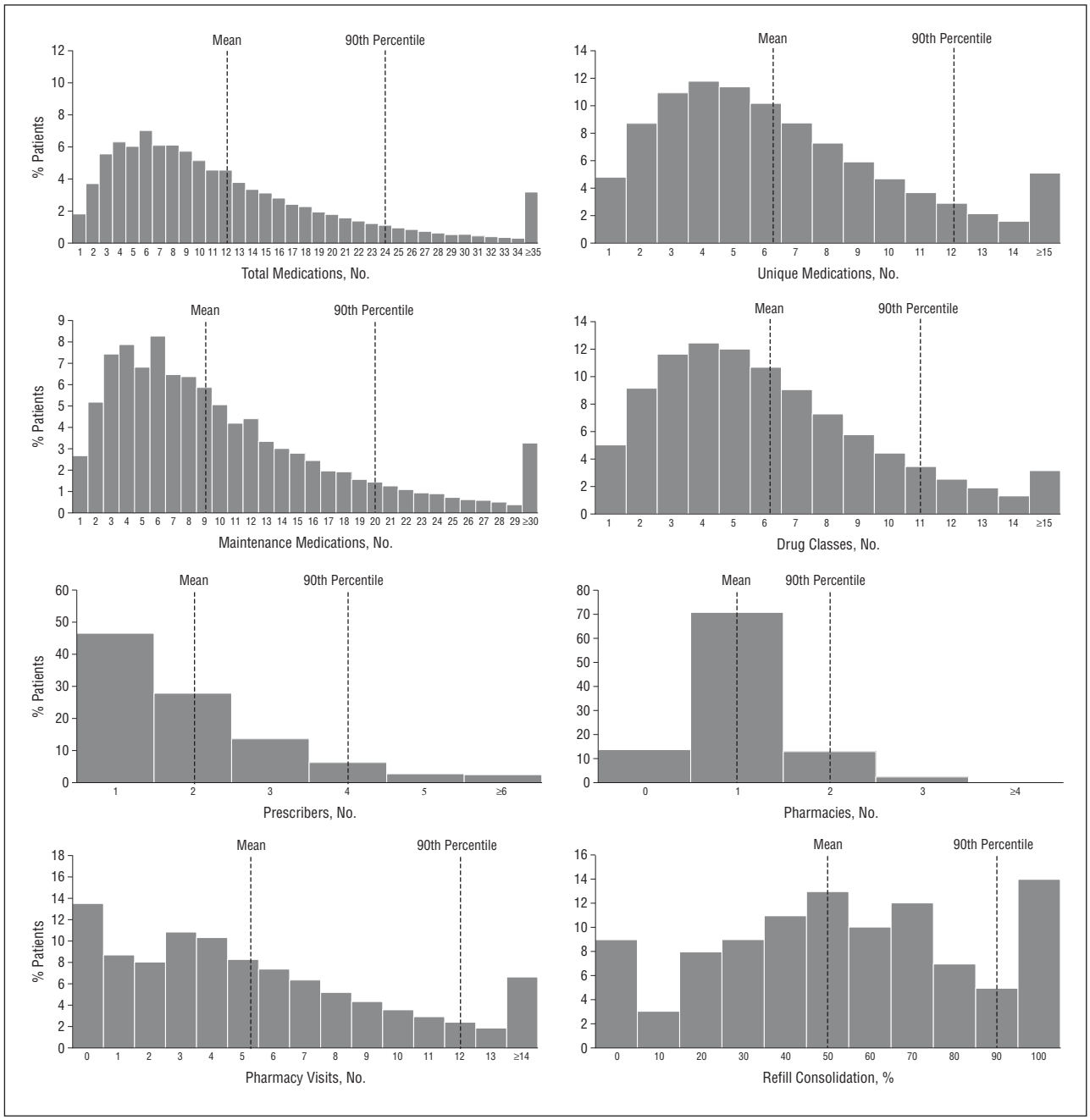

Figure 2. Estimates of therapeutic complexity over a 90-day period among angiotensin-converting enzyme inhibitor/angiotensin receptor blocker users.

different prescribers and filled at 1 pharmacy. During the 3-month period, the 90th percentile thresholds for prescribing and filling complexity were as follows: 23 total medications filled (ie, 10% of statin users filled prescriptions for 23 or more medications), 19 maintenance medications, 12 unique medications, 11 different drug classes, 4 prescribers, 2 pharmacies, and 11 visits to the pharmacy. Medication filling patterns for the ACEI/ARB cohort were similar (**Figure 2**). In addition, patients took this class of medications a mean of 1.1 times per day; 10% filled prescriptions for an ACEI/ARB with instructions to take it 2 or more times per day.

RELATIONSHIP BETWEEN COMPLEXITY AND MEDICATION ADHERENCE

Mean medication adherence in the statin and ACEI/ARB cohorts was 68.6% and 66.4%, respectively. The univariate and multivariate relationship between the measures of therapeutic complexity and adherence are presented in **Table 2**. After controlling for demographics, comorbidity, and copayments, independent predictors of worse medication adherence included a greater number of prescribers, visits to more pharmacies, and less refill consolidation. For example, each additional pharmacy at which patients filled a prescription during the 3-month complex-

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Table 2. Relationship Between Adherence and Complexity Measures for Statin and ACEI/ARB Users[a]

Predictors (Referent)	All Statin Users		All ACEI/ARB Users	
	Unadjusted[b]	Adjusted[b]	Unadjusted[b]	Adjusted[b]
Patient demographics				
Age ≥65 y (vs <65 y)	6.57	5.35	4.61	3.39
Male (vs female)	–1.71	–2.44	–0.07	–0.60
Income per quintile	1.38	1.72	0.76	0.98
Copayments				
Mean monthly copayments for index class, per tertile[c]	–2.77	–1.52	–1.56	–0.89
Mean monthly copayments for all other drugs, per tertile	–2.11	–0.82	–1.35	–0.59
Morbidity score	–0.62	–1.32	–0.43	–0.97
Complexity measures				
Daily dose, per additional dose	NA	NA	–0.01	–0.25
Unique medications, per additional medication	0.57	0.89	0.46	0.69
Prescriber, per additional practitioner	0.11	–0.25	–0.07	–0.31
Unique retail pharmacies, per additional pharmacy	–2.43	–1.60	–2.82	–2.02
Refill consolidation, full (vs none)[d]	13.35	8.42	12.60	8.12
Intercept	NA	58.86	NA	63.60

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NA, not applicable.
[a] Data are given as percentage change in adherence.
[b] $P < .001$ for all parameters.
[c] Statins or ACEI/ARB as appropriate.
[d] Higher values represent greater refill consolidation.

ity assessment window was associated with a 1.6 percentage point reduction in statin adherence over the subsequent year. Controlling for the number of medications a patient was prescribed, patients with no consolidation of their refilling (ie, the fewest medications filled per pharmacy visit) had adherence rates that were 8.4 percentage points lower than those patients with complete consolidation (ie, the most medications filled per pharmacy visit). Similar results were seen in the ACEI/ARB cohorts. In addition, in the ACEI/ARB cohort, a greater number of daily doses was associated with slightly worse adherence (0.25 percentage points per additional daily dose). In both cohorts, filling prescriptions for more concurrent medications was associated with better adherence.

Analyses in the prespecified subgroups provide similar inferences to those for the overall cohort, although the results differed in magnitude (**Table 3**). The impact of refill consolidation was particularly large for patients newly initiated on therapy who received their prescriptions by combination of mail order and at retail pharmacies. For example, among this subgroup, ACEI/ARB users with maximum refill consolidation were 14% more adherent than patients with no refill consolidation. The impact of the number of daily doses was also somewhat larger for this group of patients; adherence fell by 2.4% for each additional daily medication dosage.

In sensitivity analyses where mail-order pharmacies were considered as part of the overall pharmacy count, the impact of each additional pharmacy on adherence was smaller in magnitude than in our primary results (ie, –0.80% and –1.01% per additional pharmacy in statin and ACEI/ARB users, respectively), while the impact of refill consolidation was slightly larger (ie, adherence was 10.1% and 10.5% higher for patients with maximum as compared with minimum consolidation in statin and ACEI/ARB users, respectively). Using an alternative morbidity measure (the number of unique medications patients consumed in the prior 12 months) had no impact on our findings.

COMMENT

Our study of a large cohort of individuals filling prescriptions for a statin or ACEI/ARB demonstrates the enormous complexity faced by patients with cardiovascular disease in contemporary practice. During a 3-month period, patients filled prescriptions for a mean of 11.4 medications, representing a mean of 5.9 different drug classes. More striking, during this same time frame, 10% of patients filled prescriptions for 23 or more medications, 12 or more unique medications, and 11 or more different drug classes, had prescriptions written by 4 or more prescribers, filled them at 2 or more pharmacies, and made 11 or more visits to the pharmacy.

While some of this complexity is unavoidable in the effort to treat chronic diseases and prevent their complications, our results highlight the association between complexity and medication adherence. Several other studies have examined the negative impact of regimen complexity (ie, the number of daily doses a patient must consume) on adherence, and our results confirm those findings.[2,14] However, our study is the first, to our knowledge, to broaden the definition of complexity and evaluate the relationship between patterns of prescribing and filling and appropriate medication use. In specific, controlling for the number of medications used, patients who made visits to more unique pharmacies and those who filled fewer medications per visit (ie, had less refill consolidation) were substantially less adherent to their prescribed therapy. The magnitude of these effects were particularly large for patients who had newly initiated therapy and who filled their prescriptions at both retail pharmacies and via mail order. Adherence rates drop quickly af-

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Table 3. Multivariate Relationships Between Complexity and Subsequent Adherence for Statin and ACEI/ARB by Medication Use Category[a]

Predictors (Referent)	All Patients	Prevalent Users[b]			New Users[b]		
		Mail Order Only	Retail Only	Mixed	Mail Order Only	Retail Only	Mixed
Statins							
Patient demographics							
Age ≥65 y (vs <65 y)	5.35	2.57	5.52	2.26	−0.52[c]	3.47	1.82
Male (vs female)	−2.44	−1.60	−2.16	−2.00	−3.12	−3.32	−3.58
Income, per quintile	1.72	0.69	1.64	0.86	1.92	2.11	1.70
Copayments							
Mean monthly statin copayments, per tertile	−1.52	−1.29	−1.61	−0.87	−2.43	−3.83	−2.13
Mean monthly copayments for other drugs, per tertile	−0.82	−0.41	−0.91	−0.93	0.04	−0.30	−1.31
Morbidity score	−1.32	−0.82	−1.01	−0.54	−1.12	0.46	−0.23
Complexity measures							
Unique medications, per additional medication	0.89	0.59	0.64	0.20	1.30	0.78	0.10
Prescriber, per additional practitioner	−0.25	−0.03[c]	−0.13	−0.24	1.64	0.02[c]	0.14[c]
Unique retail pharmacies, per additional pharmacy	−1.60	NA[d]	−1.35	−1.39	NA[d]	−2.68	−1.14
Refill consolidation, full (vs none)[e]	8.42	NA[d]	5.38	3.15	NA[d]	6.14	9.20
Intercept	58.86	71.42	66.09	72.17	56.21	45.33	57.19
ACEI/ARB							
Patient demographics							
Age ≥65 y (vs <65 y)	3.39	1.60	3.34	0.92	−0.26	0.54	0.67
Male (vs female)	−0.60	−0.68	−0.55	−0.50	−1.00	−2.19	−2.23
Income, per quintile	0.98	0.46	1.01	0.55	1.11	1.00	0.94
Copayments							
Mean monthly ACEI/ARB copayments, per tertile	−0.89	−1.09	−1.40	−0.49	−1.20	−1.67	−0.42
Mean monthly copayments for other drugs, per tertile	−0.59	0.07	−0.23	−0.55	−0.03	−0.87	−1.32
Morbidity score	−0.97	−0.45	−0.63	−0.38	−0.78	0.56	−0.32
Patient demographics							
Doses per day, per additional dose	−0.25	−1.36	−0.49	−0.43	−2.32	−0.71	−2.42
Unique medications, per additional medication	0.69	0.51	0.49	0.07	0.99	0.75	−0.17
Prescriber, per additional practitioner	−0.31	−0.27	−0.17	−0.49	1.05	−0.09[c]	−0.19[c]
Unique retail pharmacies, per additional pharmacy	−2.02	NA[d]	−1.51	−1.24	NA[d]	−2.75	−1.43
Refill consolidation, full (vs none)[e]	8.12	NA[d]	4.16	3.43	NA[d]	1.52	14.05
Intercept	63.60	75.73	69.96	75.27	63.45	51.10	61.82

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NA, not applicable.
[a] Data are given as percentage change in adherence.
[b] $P < .001$ for all parameters except where indicated.
[c] P value not significant.
[d] Patients who filled prescriptions only by mail were considered to have no pharmacy visits and maximum refill consolidation.
[e] Higher values represent greater refill consolidation.

ter patients begin therapy,[15] and thus patients who are new to therapy may be especially prone to the consequences of filling complexity if they fill their medications at both mail order and retail pharmacies.

With the exception of 1 subgroup of ACEI/ARB users, we found that patients with larger numbers of concurrently prescribed medications had higher rates of subsequent adherence. The existing literature evaluating this relationship has reported mixed results. For example, Grant and colleagues[16] studied patients newly initiated on a statin therapy and, similar to our results, found adherence to be approximately 1 percentage point higher for each additional concurrent medication these patients were prescribed. Chapman et al[11] found lower rates of adherence to lipid-lowering and antihypertensive therapy for patients consuming greater numbers of other medications, a result that is consistent with the improvements in adherence that result from switching patients to combination pills[4] and which may reflect true difficulties that patients face in following complex treatment regimens. In contrast, being prescribed more medications may influence patients' perceptions of illness and motivate better adherence. Having filled more medications in the past may represent behavioral characteristics of patients who are also more likely to be highly adherent in the future. It is also possible that there is a threshold effect for the number of concurrent medications that modifies its relationship with adherence.

Because nonadherence is associated with excess morbidity and mortality,[17,18] our findings suggest that therapeutic complexity may undermine the goals of chronic disease management. In addition, these results highlight an essential aspect of the therapeutic cascade that may be particularly burdensome and which few clinicians likely consider when making prescribing decisions. As such, our findings highlight the potential benefit of efforts to reduce prescribing and filling complexity by encouraging filling by mail order[12] and/or reducing the frequency with which they must fill (eg, by providing 90-day supplies of medications).

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In addition, our results suggest the potential for novel adherence improvement interventions aimed at improving refill consolidation at individual pharmacies and on individual visits. For example, the creation of a "pharmacy home" may centralize and simplify medication access. Such an intervention would need to be prospectively and rigorously evaluated and could include providing financial incentives for patients to fill at a single pharmacy or altering pharmacy benefits to facilitate refill consolidation, for example, by authorizing early renewals for a short period or providing patients with longer supplies of medications so that subsequent refills could all occur at the same visit.

These functions may support other effective adherence improvement activities carried out by pharmacists.[19] Furthermore, in addition to improving adherence, this strategy may provide patients with the opportunity to have longitudinal relationships with pharmacists, creating benefits in other aspects of medication quality, such as the improved ability to detect drug-drug interactions and improved safety. By consolidating pharmacologic care at a single pharmacy, a more complete history of medication use will be available to the pharmacy and that data can be used to optimize drug utilization review. Because such an intervention does not rely on changing a patient's therapeutic regimen or the nature of communication between physicians and pharmacists, it may be a scalable approach that could be implemented soon.

There are several limitations to our analysis. We studied a large cohort of patients receiving prescription drug benefits through a national pharmacy benefit manager. The patients in our cohort represented a broad range of demographic characteristics, including Medicare beneficiaries, but the results may not be generalizable to other groups such as the uninsured. We relied on pharmacy claims data to perform our analyses, and thus we did not have access to detailed clinical or behavioral information about patients in our cohort. As such, we are unable to identify the specific reasons why patients chose to fill prescriptions on multiple visits or pharmacies, and thus the results of our observational study should be interpreted as hypothesis generating. Because patients with greater degrees of prescribing and filling complexity may differ in systematic ways from those with less complexity, we are unable to exclude the possibility of unmeasured confounding by factors such as health-seeking behavior or organizational skills that may be associated with different levels of adherence. In some cases, patients may consciously decide to fill prescriptions on multiple visits or at different pharmacies, for example, to better manage their out-of-pocket expenditures, although we would expect that these purposeful choices are likely to be associated with greater, not lower, levels of long-term adherence. Similarly, we are unable to account for differences in plan design, such as the use of disease management programs, which may have influenced patient's medication taking behavior. It is possible that our data sources did not capture claims for patients who paid cash for low-cost "$4" generic medications. While these missing claims may cause outcome misclassification (ie, these patient would appear less adherent), they would also make filling patterns appear less complex and thus bias our results to the null. Finally, although pharmacy refill claims are widely believed to be a valid method for assessing compliance,[20] this measure does not indicate with certainty which medications a patient actually consumes.

In conclusion, our analysis of patients filling prescriptions for 2 common cardiovascular medication classes demonstrates the substantial complexity that health system factors contribute to medication use by patients with chronic disease and the negative impact of this complexity on medication adherence.

Accepted for Publication: July 21, 2010.
Published Online: January 10, 2011. doi:10.1001/archinternmed.2010.495
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Author Contributions: Drs Choudhry and Shrank and Ms Pakes had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Choudhry, Fischer, Avorn, Schneeweiss, Brennan, and Shrank. *Acquisition of data:* Choudhry, Liberman, and Shrank. *Analysis and interpretation of data:* Choudhry, Fischer, Avorn, Liberman, Schneeweiss, Pakes, Brennan, and Shrank. *Drafting of the manuscript:* Choudhry and Pakes. *Critical revision of the manuscript for important intellectual content:* Choudhry, Fischer, Avorn, Liberman, Schneeweiss, Pakes, Brennan, and Shrank. *Statistical analysis:* Choudhry, Schneeweiss, and Pakes. *Obtained funding:* Choudhry, Avorn, and Shrank. *Administrative, technical, and material support:* Choudhry, Liberman, Pakes, Brennan, and Shrank. *Study supervision:* Choudhry, Avorn, Liberman, Schneeweiss, and Shrank.
Financial Disclosure: Drs Liberman and Brennan are employees of CVS Caremark.
Funding/Support: This work is supported by a research grant from CVS Caremark. Dr Shrank is supported by a career development award from the National Heart, Lung and Blood Institute (HL-090505).

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INVITED COMMENTARY

ONLINE FIRST

Prescription Refill Management and Its Effect on Adherence

Individuals with multiple comorbid medical conditions, or multimorbidity, must perform numerous self-care activities, including the management of multiple prescription medications. Though such medications have proven efficacious in large clinical studies, in the real world their therapeutic effectiveness is subject to the complexities of prescribing, obtaining, and taking medications appropriately. In this issue of the *Archives*, Choudhry and colleagues report the association of therapeutic complexity with patient adherence to 2 cardiovascular medications purchased through a national pharmacy benefits manager. The authors assessed complexity based on the number of medications, prescribers, pharmacies, pharmacy visits, and proportion of medications filled per pharmacy visit (ie, refill consolidation). Adherence to a statin or ACEI/ARB was ascertained during a 1-year period by calculating the percentage of time the medication was available based on refill records.

Overall adherence was approximately 68%, slightly higher than in prior studies.[1-3] In adjusted analyses, a higher number of prescribers, more visits to pharmacies, and lower refill consolidation predicted worse medication adherence. In addition, in subgroup analyses, the effect was larger among individuals recently started on therapy with cardiovascular medications and who used both mail-order and retail pharmacies. In essence, greater therapeutic complexity, as reflected by both prescribing and filling behaviors, was associated with lower medication adherence.

The study by Choudhry et al highlights the fragmentation of prescription management by drawing attention to the intricacies of managing a complex medication regimen. Prior research has operationalized medication complexity based largely on the number of medications, doses, or times of administration.[4] However, such measures do not account for patients who may have multiple prescribers, shop around for lower prices by filling generic medications for $4 or $5 at retail pharmacy chains, use both mail-order and retail pharmacies, and have refills due on different dates. Each of these practical issues adds complexity to patients' medication management, and as we learn from this study, adherence suffers.

Aiming to improve adherence, health care providers can encourage patients to simplify their pattern of filling medications by using a single pharmacy or synchronizing refill dates. Having a pharmacy home, as the authors propose, might also be helpful for maintaining an accurate medication list and avoiding drug-drug interactions. Though the present study does not provide direct evidence for these practices, their potential to improve adherence is intriguing.

This study is not without limitations. The authors' method of calculating refill adherence may overestimate adherence; a preferred approach is the cumulative medication gap.[5] The cohort lacked data on uninsured individuals and retail purchases of discount medications; therefore, complexity may be underestimated for some patients. The measure of refill consolidation warrants additional study. Refill consolidation, calculated as 1 – (pharmacy visits/prescriptions filled), may be misleading if viewed in isolation because, as the authors point out, it is affected by the number of prescriptions. In the authors' example, a patient who visits the pharmacy 12 times to fill 12 prescriptions has a refill consolidation score of 0, which indicates no consolidation of refills. However, a patient who

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