Relationship Between Patient Medication Adherence and Subsequent Clinical Inertia in Type 2 Diabetes Glycemic Management

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OBJECTIVE — Clinical inertia has been identified as a critical barrier to glycemic control in type 2 diabetes. We assessed the relationship between patients' initial medication adherence and subsequent regimen intensification among patients with persistently elevated A1C levels.

RESEARCH DESIGN AND METHODS — We analyzed an inception cohort of 2,065 insured patients with type 2 diabetes who were newly started on hypoglycemic therapy and were followed for at least 3 years between 1992 and 2001. Medication adherence was assessed by taking the ratio of medication days dispensed (from pharmacy records) to medication days prescribed (as documented in the medical record) for the first prescribed hypoglycemic drug. Adherence was measured for the period between medication initiation and the next elevated A1C result measured at least 3 months later; intensification was defined as a dose increase or the addition of a second hypoglycemic agent.

RESULTS — Patients were aged (mean ± SD) 55.4 ± 12.2 years; 53% were men, and 19% were black. Baseline medication adherence was 79.8 ± 19.3%. Patients in the lowest quartile of adherence were significantly less likely to have their regimens increased within 12 months of their first elevated A1C compared with patients in the highest quartile (27 vs. 37%, respectively, with increased regimens if A1C is elevated, $P < 0.001$). In multivariate models adjusting for patient demographic and treatment factors, patients in the highest adherence quartile had 53% greater odds of medication intensification after an elevated A1C (95% CI 1.11–1.93, $P = 0.01$).

CONCLUSIONS — Among insured diabetic patients with elevated A1C, level of medication adherence predicted subsequent medication intensification. Poor patient self-management behavior increases therapeutic clinical inertia.

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Successful glycemic control in type 2 diabetes requires the effective use of prescribed medicines over time. Lack of medication intensification has recently been identified as a critical barrier to evidence-based care (1–5). Initial commentators on this so-called "clinical inertia" in diabetes management focused attention to a large extent on physician shortcomings, such as overestimates of care provided and lack of knowledge of care guidelines (6–9). There has been little attention paid to the patient's contribution to clinical inertia.

Efforts to provide evidence-based diabetes management may be hampered by patient attitudes and abilities, physician productivity requirements, and medical system or societal-level barriers to effective care (10,11). In particular, patients with diabetes are required to make significant behavioral and lifestyle changes over long periods of time to better control their disease (12). We hypothesized that patient-centered behavior such as medication adherence influences physicians' tendency to intensify medical therapy. To test this hypothesis, we analyzed an inception cohort of newly treated patients with type 2 diabetes to determine the relationship between patient medication adherence to initially prescribed oral hypoglycemic agents (a core patient-level behavior) and subsequent medication intensification among patients who remained above A1C goal.

RESEARCH DESIGN AND METHODS

— Patients in this study were insured by Harvard Pilgrim Health Care (HPHC), a large HMO in New England, and cared for by the Harvard Vanguard Medical Associates (HVMA), a multispecialty group practice in Massachusetts with an overall patient population of 300,000. Plan members had strong financial incentive to use the clinical and pharmaceutical services provided at HVMA facilities. The automated medical records system at HVMA captured data from all ambulatory encounters (including laboratory and pharmacy services) in a combination of both coded and narrative fields. Virtually all out-of-network care was captured by billing claims to HPHC. The validity and reliability of these data systems have been previously documented (13,14).

We conducted a prospective cohort analysis to assess the relationship between patient medication adherence to first prescribed oral hypoglycemic agents and subsequent medication intensification within 6 or 12 months of their next elevated A1C (A1C >7.0%). Our inception cohort was defined as all HPHC patients cared for within the HVMA population between 1992 and 2001 with type 2 diabetes who had at least 12 months of enrollment time before their first recorded

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Abbreviations: HPHC, Harvard Pilgrim Health Care; HVMA, Harvard Vanguard Medical Associates.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

prescription for an oral hypoglycemic agent and at least 24 months enrollment time after initiation of therapy. Type 2 diabetes was defined from medical records based on one or more inpatient or two or more outpatient ICD-9 250.XX codes for diabetes and/or any dispensing of diabetes-specific medications in the prior year. Patients were excluded if a single baseline adherence value could not be calculated (e.g., initially prescribed multiple oral agents or insulin or switched from one drug to another within 1 month). From an initial population of 20,837 adult patients with diabetes within our system, we identified 2,843 patients with at least 3 years of continuous enrollment who were newly initiated on oral hypoglycemic medications. After excluding patients *1*) without a baseline A1C before medication initiation, *2*) no subsequent refills, and/or *3*) no elevated A1C results during the follow-up period ($n = 778$), 2,065 eligible study subjects remained for analysis.

Measures

Our primary exposure of interest was adherence to the first prescribed oral agent, measured from drug initiation date until the first elevated A1C result at least 3 months after the initiation date. We introduced this 3-month time lag between treatment initiation and the target elevated A1C to provide sufficient time for the initial treatment to impact A1C levels. Medication adherence was assessed by taking the ratio of medication dispensed (from pharmacy records) to the medication days prescribed (as documented in the medical record) for the first prescribed hypoglycemic drug. Adherence was measured for the period between medication initiation and the next elevated A1C result measured at least 3 months later; intensification was defined as a dose increase or the addition of a second hypoglycemic agent. Dispensed medication was assumed to be used in daily amounts equal to the prescribed amount while medication supply lasted. This adherence measure was calculated as the milligrams available per month from current and prior dispensings (e.g., 150 mg) divided by the amount prescribed per month (e.g., 300 mg) to obtain a percentage of the prescribed amount that was available for use (e.g., 50%) (15).

Patient age, race, and sex were taken from HPHC membership files. Patient race was available for 70% of the sample. In a previous study, we found 96% agreement between self-reported and medical record data on race classification for black and white patients in this setting, indicating that our race measure is highly reliable when available (16). As an indicator of socioeconomic status, we linked patient addresses to 1990 Federal census data to determine percent of low income (<$15,000 per year) residents in each patient's home census block. Other baseline covariates included last measured A1C level before medication initiation, BMI, number of physician visits and hospital days in the 12 months preceding medication initiation, and number of concurrently prescribed medicines at time of first oral hypoglycemic prescription.

Outcome assessment

The primary study outcome was medication intensification, defined as an increase in dose of initially prescribed oral hypoglycemic medicine or the addition of a second glucose-lowering agent to the initial regimen. We measured time to medication intensification beginning on the date of the first elevated A1C result at least 3 months after first medication initiation. Intensification was analyzed as both a binary variable (proportion intensified within 6 or 12 months) and as a time-to-intensification measure with censoring by enrollment end date.

Statistical methods

Our primary analytic goal was to assess the effect of initial hypoglycemic medication adherence on subsequent medication intensification among patients with elevated A1C. We categorized medication adherence to initially prescribed hypoglycemic drug in the following two ways: *1*) We defined quartiles of adherence during the initial period before the target elevated A1C result and then compared the proportion of patients with subsequent medication intensification in the highest and lowest adherence quartiles and 2) to facilitate clinical interpretation, we also present our results using the somewhat arbitrary but more clinically intuitive categories of "excellent" (>90%), "moderate" (50–90%), and "poor" (<50%) adherence rates.

Because the time interval used to calculate baseline adherence (14.9 ± 13.4 months) varied by patient, we also repeated all analyses restricting the adherence measurement to the first 6 months of therapy (among patients with at least 6 months of baseline adherence data, $n = 1,456$). Results of this analysis were very similar to the main analysis and are therefore not reported.

We assessed baseline differences in demographic and clinical characteristics using *t* tests, Wilcoxon rank-sum tests, and χ^2 tests, as appropriate. We used logistic regression with medication intensification at 12 months as the dependent variable and quartile of adherence as the primary explanatory variable of interest. Baseline A1C and other clinical variables significantly associated with the outcome in univariate analysis ($P < 0.1$) were included in the model. In addition, we created cumulative incidence curves (1 − Kaplan-Meier estimator) and used Cox proportional hazards modeling to assess time to intensification with censoring for all patients without intensification based on their end of enrollment date. Missing data, particularly race status (missing in 30% of subjects), led to significant attrition in the number of patients contributing to the final models (from 2,065 to 1,033). However, sensitivity analyses demonstrated that the effect of baseline adherence on subsequent medication intensification remained robust despite this attrition. All analyses were conducted using SAS version 9.1, and final statistical significance was defined as a *P* value <0.05. The study was approved by the Massachusetts General Hospital Institutional Review Board and the HPHC Human Studies Committee.

RESULTS — The 2,065 eligible patients in our analytic cohort were aged 55.4 ± 12.2 years; 52.5% were men, and 18.5% were black. Patients were followed for a mean of 107.6 ± 18.6 months of continuous enrollment, including 47.8 ± 22.5 months preceding first oral hypoglycemic agent, 14.9 ± 13.4 months between medication initiation and first elevated A1C (including an initial 3-month lag period), and 45.0 ± 22.3 months of follow-up observation time from this index A1C result.

Adherence

Mean adherence to first prescribed oral hypoglycemic agent was 79.8 ± 19.3%. Compared with patients in the highest adherence quartile (adherence >97%, $n = 516$), patients in the lowest quartile (adherence <66%, $n = 517$) were significantly younger, more often black, and had slightly lower baseline A1C before medication initiation (Table 1). There were no significant differences in sex proportion, neighborhood income levels,

Table 1—*Characteristics of overall cohort (n = 2,065) and comparing highest (>97%, n = 516) with lowest (<66%, n = 517) quartiles of baseline medication adherence*

	Total cohort	Highest quartile	Lowest quartile	*P*
Age (years)	55.4 ± 12.2	57.5 ± 11.8	54.1 ± 12.6	<0.001
Women (%)	47.5	52.5	51.5	0.73
Race (%)				
White	48.6	56.1	39.5	
Black	18.5	13.2	23.8	<0.001
Other or unknown	32.9	30.7	36.7	
Census tract income	39,674 (15,921)	40,470 (15,966)	39,835 (18,517)	0.57
Clinic visits, prior year	4.5 (6.2)	4.5 (4.2)	4.6 (4.2)	0.62
BMI (kg/m^2)	33.0 (7.2)	33.6 (6.8)	32.3 (7.1)	0.006
Concurrent medications	7.8 (7.7)	7.9 (7.7)	8.3 (8.2)	0.45
Total enrollment time (months)	108 (19)	107 (18)	107 (19)	0.98
A1C level preceding first medication initiation (%)	9.4 (2.2)	9.7 (2.1)	9.3 (2.3)	0.003
Time to initiation (months)	1.5 (4.6)	1.3 (4.8)	1.8 (4.7)	0.09
Time to next elevated A1C (months)	15.0 (13.4)	11.9 (11.8)	15.0 (12.7)	<0.001

Data are means ± SD, median (interquartile range), or *n* (%) unless otherwise indicated. Highest and lowest quartiles are of adherence to first prescribed hypoglycemic medication. *P* values are for highest vs. lowest quartile comparisons.

number of visits in the preceding year, or overall enrollment time between the two quartiles (Table 1).

Nearly half of the cohort (48%) had moderate baseline adherence (defined as 50–90% adherence, mean 72.1 ± 11%, $n = 1,020$), with 42% of patients demonstrating excellent adherence (>90%, mean 97.6 ± 3%, $n = 857$) and <10% with poor adherence (<50%, mean 40.8 ± 9%, $n = 188$).

Medication intensification

One-third (33.3%) of the overall cohort had their regimens intensified within 12 months of the index A1C (i.e., first elevated result ≥3 months after initial hypoglycemic medication prescription). Patients in the highest adherence quartile were significantly more likely to have their regimens intensified than patients in the lowest quartile (37.4% intensified vs. 26.7% intensified, $P = 0.02$). Similarly, patients with excellent adherence (>90%) were more likely to have their regimens intensified than patients with moderate (50–90%) or poor (<50%) adherence (Figs. 1 and 2).

The group of patients intensified within 12 months was also slightly younger (54.4 vs. 56.0 years, $P = 0.008$) and had a 2-month longer interval between medication initiation and next elevated A1C result (16.5 vs. 14.3 months, excluding the 3-month lag period, $P < 0.001$) but had similar baseline A1C levels (9.4 vs. 9.4, $P = 0.58$) and proportion with black race (23 vs. 26%, $P = 0.27$).

Multivariate models

Patients in the highest baseline adherence quartile had 64% greater odds of medication intensification at 12 months compared with those in the lowest quartile (odds ratio [OR] 1.64 [95% CI 1.26–2.14], $P < 0.001$). In a final model that included age, sex, race, baseline A1C before medication initiation, number of concurrently prescribed medicines, and interval between medication initiation and next elevated A1C, higher baseline adherence conferred a 53% greater odds of medication intensification comparing highest versus lowest quartiles (adjusted OR 1.53 [1.11–2.11]) and 49% greater odds comparing excellent (>90%) with poor (<50%) baseline adherence (1.49 [1.18–1.88]) (Table 2).

In the fully adjusted multivariate model controlling for baseline adherence quartiles, patient age (adjusted OR 0.99 [95% CI 0.99–1.001], $P = 0.08$) and months between medication initiation and next elevated A1C (1.03 [0.95–1.11], $P = 0.53$) were not independently associated with medication intensification. In addition, sex (1.1 [0.82–1.54] for men,

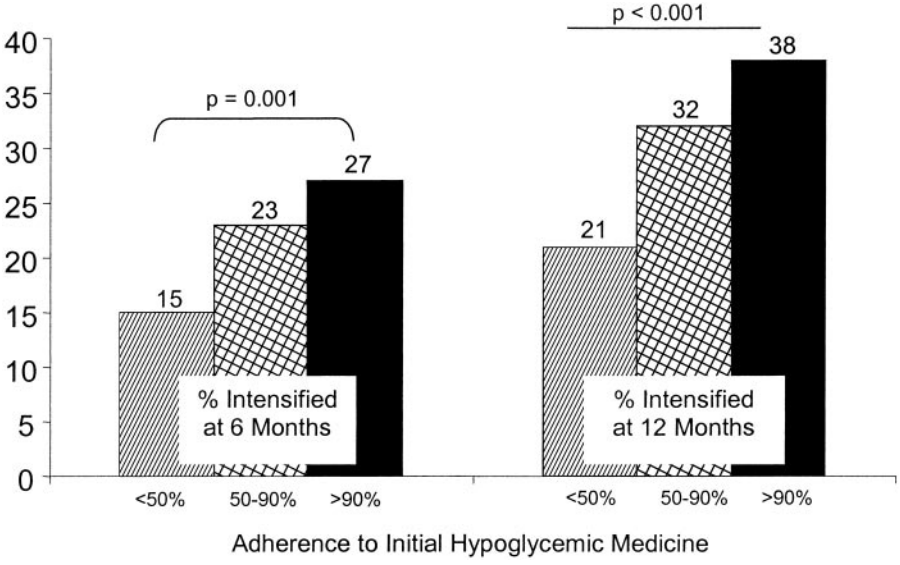

Figure 1—*Medication intensification within 6 and 12 months of first elevated A1C result following treatment initiation among patients with type 2 diabetes, stratified by level of adherence to initial hypolycemic medication (<50%, 50–90%, and >90% adherence).*

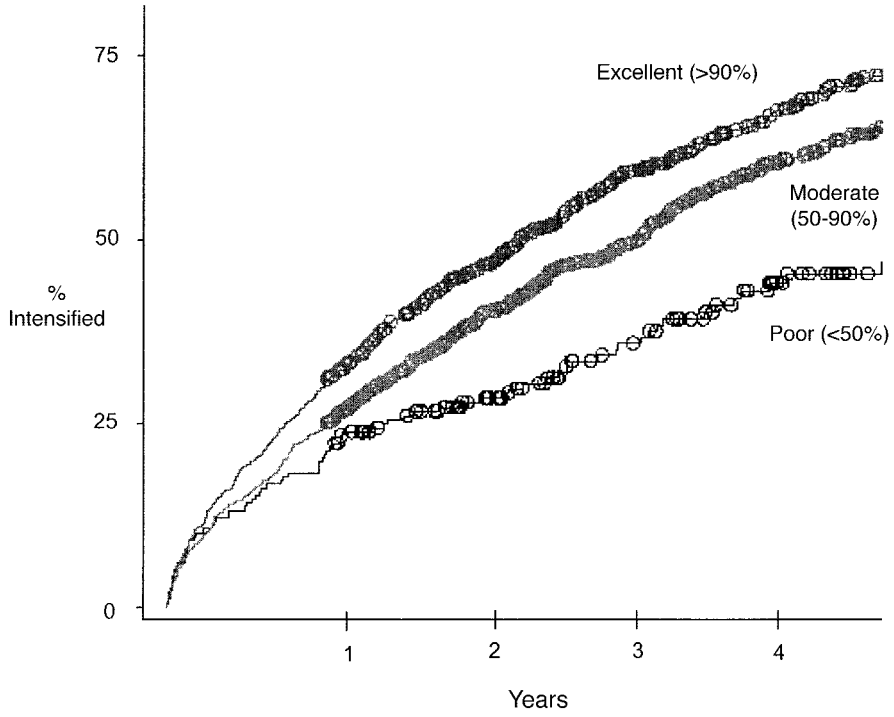

Figure 2—*Cumulative incidence curves of time to medication intensification from first elevated A1C result at least 3 months after initiation oral hypoglycemic therapy, stratified by excellent (>90%,* n *= 857), moderate (50–90%,* n *= 1,020), and poor (<50%,* n *= 188) adherence to first prescribed oral hypoglycemic medicine.*

$P = 0.47$), black race (0.84 [0.60–1.18], $P = 0.30$), and number of concurrently prescribed medicines (1.012 per medicine [0.99–1.03], $P = 0.37$) remained nonstatistically associated with medication intensification. Results were similar in the model with excellent versus poor baseline adherence except for a small but statistically significant decreased odds of intensification with increasing age (0.98 per year [0.97–0.99], $P = 0.005$) and increased odds with an increasing interval from initiation to next elevated A1C (1.02 per month [1.01–1.03], $P = 0.005$).

Applying survival analysis methods that account for censoring, we found that median time to intensification was 22 months (95% CI 19–25) for patients with excellent versus 29 months (26–34) for moderate versus 58 months (42–unmeasured) for poor baseline adherence. The hazard ratio for intensification was 1.39 (SE 0.07) in a Cox proportional hazards model that compared patients with excellent versus poor adherence with adjustment for age, sex, race, interval between medication initiation and next elevated A1C, and number of concurrently prescribed medicines (Table 2).

CONCLUSIONS — In this large cohort of commercially insured patients with type 2 diabetes newly started on oral hypoglycemic therapy, we found that medication adherence to the initially prescribed drug was strongly related to subsequent medication intensification among patients with elevated A1C. Patients with poor adherence and elevated A1C levels were less likely to have their regimen increased than patients with good adherence and elevated A1C levels. This study provides strong evidence linking the domains of patient behavior (specifically, medication adherence) and physician actions (e.g., subsequent medication management among patients not meeting goals of glycemic therapy).

Our analysis also underscores the generally slow rate of medication intensification at a critical period of diabetes management when patients are transitioning to oral drug therapy. Even among the most adherent patients in our cohort, regimen intensification was delayed for nearly 2 years for the majority of patients. This pattern exposes a general lack of alacrity in blood glucose control during a phase that many patients might be considered to have "mild" diabetes. Given the cumulative effect of hyperglycemia over time (17,18) and the finding that patients with improved insulin sensitivity to maintain near-normal glycemia levels may have better preserved pancreatic function (19), this observation highlights a substantial opportunity to improve diabetes care by increasing attention on effective management at earlier phases of the disease.

Our study builds on the work of others (5,20) who have pointed to clinical inertia as a key barrier to effective diabetes management. Prior studies have identified several factors that are correlated with greater medication intensification, including absolute level of A1C (2,4) and systematic features of the clinical practice

Table 2—*Treatment intensification by baseline adherence, comparing highest vs. lowest quartile and excellent (>90%) vs. poor (<50%)*

	1st vs. 4th quartile				Excellent vs. poor adherence			
	Crude OR	*P*	Adjusted OR	*P*	Crude OR	*P*	Adjusted OR	*P*
Intensification at 12 months	1.64	<0.001	1.53	0.01	1.53	<0.001	1.49	<0.001
95% CI	(1.26–2.14)		(1.11–2.11)		(1.27–1.86)		(1.18–1.88)	
	Crude HR	*P*	Adjusted HR	*P*	Crude HR	*P*	Adjusted HR	*P*
Cox model (HR ± SE)	1.52 ± 0.08	<0.001	1.41 ± 0.10	<0.001	1.46 ± 0.06	<0.001	1.39 ± 0.07	<0.001

n = 516 (1st adherence quartile) vs. 517 (4th adherence quartile) patients and 857 (excellent adherence) vs. 188 (poor adherence) patients. Lower adherence category serves as the referent for the higher adherence category. Models adjusted for age, sex, race, number of concurrently prescribed medicines at time of oral hypoglycemic initiation, baseline A1C prior to medication initiation, and time from medication initiation to first elevated A1C. HR, hazard ratio.

in which care is delivered (21). Published clinical trials have demonstrated that physician education (1) and clinical process level interventions (22) can reduce clinical inertia. The results of our analysis broaden the framework for understanding clinical inertia by demonstrating the impact of patient behavior on the complex process of medication adjustment.

Our results must be interpreted in the context of the study design. Large administrative and clinical datasets provide sufficient sample size to examine important trends in care within various strata, but they are subject to unmeasured confounding and generally lack extensive contextual detail. Thus, it is not known from our report whether physicians were aware of their patients' level of medication adherence. Data from other clinical contexts suggest that physicians are poor judges of patient adherence rates (23,24). Thus, the association discovered here between patient adherence and subsequent medication intensification may also reflect the influence of other correlated but unmeasured behavioral and attitudinal patient factors that influence physicians' decisions to intensify treatment. Qualitative studies of patient-physician interactions from a management decision point may shed further light on these potentially unrecognized patient cues.

While taking daily medication is a behavior largely in the domain of the patient, other studies have shown that physicians can significantly influence this behavior by the level of trust they engender (25,26) and by their skills in communicating and motivating patients to engage in health-improving behaviors (27,28). Further research should address whether interventions to improve physician-patient communication about medication use and adherence would result in greater rates of subsequent dose intensification.

Although use of pharmacy claims to measure adherence may be less accurate than more intensive adherence measurement methods (e.g., electronic pill bottles, individual patient surveys, and pill counts), two major strengths of this approach are that *1*) in a closed system such as ours, where patients have a strong financial and logistic incentive to fill prescriptions at in-house pharmacies, lack of medication refill reliably indicates lack of adherence; and *2*) in contrast to the directly monitored adherence measures, patients do not alter their adherence behavior in response to the measurement process.

Our study was conducted among insured patients cared for within a single large HMO who had fewer barriers to care (e.g., prescription costs and primary care physician access) than the general population (29). Moreover, differences in medication copays among enrolled patients were minimal. This design helps to isolate the relationship between adherence and intensification but may limit generalizability to other patient populations.

In summary, among patients with type 2 diabetes and similar access to high-quality care, those patients with worse adherence to their first prescribed oral hypoglycemic drug were less likely to have their regimen intensified after an elevated A1C than similarly hyperglycemic patients with good baseline adherence. Increased focus on the patient's role in medication intensification may provide greater insight and lead to more effective solutions to the problem of clinical inertia.

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