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

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Abstract

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 HbA1c levels.

Research Design & Methods: We analyzed an inception cohort of 2065 insured patients with type 2 diabetes newly started on hypoglycemic therapy and followed for at least three years between 1992 and 2001. Medication adherence was calculated by dividing the number of dispensed by prescribed doses for the first-prescribed hypoglycemic drug for the period between medication initiation and the next elevated HbA1c result measured at least three months later; intensification was defined as a dose increase or the addition of a second hypoglycemic agent.

Results: Patients were 55.4 (12.2) years old, 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 HbA1c compared to patients in the highest quartile (27% vs. 37% with increased regimens if HbA1c 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 HbA1c [95% CI: 1.11-1.93, p = 0.01].

Conclusions: Among insured diabetic patients with elevated HbA1c, level of medication adherence predicted subsequent medication intensification. Poor patient self-management behavior increases therapeutic clinical inertia.
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 over-estimates 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 influence 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 agent (a core patient-level behavior) and subsequent medication intensification among patients who remained above HbA1c goal.

Methods

Setting

Patients in this study were insured by Harvard Pilgrim Health Care (HPHC), a large HMO in New England, and cared for by Harvard Vanguard Medical Associates (HVMA), a multi-specialty 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).

Study Design

We conducted a prospective cohort analysis to assess the relationship between patient medication adherence to first-prescribed oral hypoglycemic agent and subsequent medication intensification within 6 or 12 months of their next elevated HbA1c (HbA1c > 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 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 ≥1 inpatient or ≥2 outpatient ICD-9 250.XX codes for diabetes and/or any dispensing of diabetes-specific medications.
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 one month). From an initial population of 20,837 adult patients with diabetes within our system, we identified 2843 patients with at least 3 years of continuous enrollment who were newly initiated on oral hypoglycemic medications. After excluding patients: 1) without a baseline HbA1c prior to medication initiation, 2) no subsequent refills, and/or 3) no elevated HbA1c results during the follow-up period (n = 778), 2065 eligible study subjects remained for analysis.

Measures

Our primary exposure of interest was adherence to first prescribed oral agent, measured from drug initiation date until the first elevated HbA1c result at least three months after the initiation date. We introduced this 3-month time lag between treatment initiation and the target elevated HbA1c to provide sufficient time for the initial treatment to impact HbA1c levels. Medication adherence was assessed by taking the ratio of medication dispensed (from pharmacy records) to the medication prescribed (as documented in the medical record). 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 gender 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 HbA1c level prior to medication initiation, body mass index (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 increase in dose of initially prescribed oral hypoglycemic medicine or 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 HbA1c result at least three 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 HbA1c. We categorized medication adherence to initially prescribed hypoglycemic drug in two ways: 1) We defined quartiles of adherence during the initial period prior to the target elevated HbA1c result and then compared the proportion of patients with subsequent medication intensification in the highest and lowest adherence quartiles; 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 six months of therapy (among patients with at least 6 months of baseline adherence data, n = 1456). 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, and chi-square 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 HbA1c 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 Meyer 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 2065 to 1033). 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 Harvard Pilgrim Health Care Human Studies Committee.

Results

Study Subjects

The 2065 eligible patients in our analytic cohort were 55.4 (12.2) years old, 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 HbA1c (including initial 3 month lag period), and 45.0 (22.3) months of follow-up observation time from this index HbA1c result.

Adherence

Mean adherence to first-prescribed oral hypoglycemic agent was 79.8% (19.3%). Compared to
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 HbA1c prior to medication initiation (Table 1). There were no significant differences in gender proportion, neighborhood income levels, 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 = 1020), with 42% of patients demonstrating “excellent” adherence (>90%, mean 97.6 [3%], n = 857), and fewer than 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 HbA1c (i.e. first elevated result three months or more 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” adherence (< 50%) (Figure 1 and Figure 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 HbA1c result (16.5 vs. 14.3 months, excluding 3-month lag period, p < 0.001), but had similar baseline HbA1c 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 to those in the lowest quartile (odds ratio [OR] 1.64, 95% confidence interval [CI]: 1.26 – 2.14, p < 0.001). In a final model that included age, gender, race, baseline HbA1c prior to medication initiation, number of concurrently prescribed medicines, and interval between medication initiation and next elevated HbA1c, higher baseline adherence conferred a 53% greater odds of medication intensification comparing highest vs. lowest quartiles (adjusted OR 1.53, 95% CI: 1.11-2.11), and 49% greater odds comparing “excellent” (>90%) vs. “poor” (<50%) baseline adherence (aOR 1.49, 95% CI: 1.18-1.88) (Table 2).

In the fully adjusted multivariate model controlling for baseline adherence quartiles, patient age (aOR 0.99 [0.99-1.001], p 0.08) and months between medication initiation and next elevated HbA1c (aOR 1.03 [0.95-1.11], p 0.53) were not independently associated with medication intensification. In addition, gender (aOR 1.1 [0.82-1.54] for men, p = 0.47), black race (aOR 0.84 [0.60 – 1.18], p = 0.30), and number of concurrently prescribed medicines (aOR 1.012 per medicine [0.99 – 1.03], p =0.37) remained not statistically associated with medication intensification. Results were similar in the model with “excellent” vs. “poor” baseline adherence except for small
but statistically significant decreased odds of intensification with increasing age (aOR 0.98 per year [0.97-0.99], p = 0.005) and increased odds with increasing interval from initiation to next elevated HbA1c (aOR 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 (19-25) months for patients with “excellent” vs. 29 (26-34) months for “moderate” vs. 58 (42 – unmeasured) months for “poor” baseline adherence. The hazard ratio for intensification was 1.39 (standard error 0.07) in a Cox proportional hazards model that compared patients with “excellent” vs. “poor” adherence with adjustment for age, gender, race, interval between medication initiation and next elevated HbA1c, and number of concurrently prescribed medicines (Table 2).

Discussion
In this large cohort of commercially-insured patients with type 2 diabetes newly started on oral hypoglycemic therapy, we found that medication adherence to initially prescribed drug was strongly related to subsequent medication intensification among patients with elevated HbA1c. Patients with poor adherence and elevated HbA1c levels were less likely to have their regimen increased than patients with good adherence and elevated HbA1c 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 two years for the majority of patients. This pattern exposes a general lack of alacrity in blood sugar 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 glycermia 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 who have pointed to clinical inertia as a key barrier to effective diabetes management (5, 20). Prior studies have identified several factors that are correlated with greater medication intensification, including absolute level of HbA1c (2, 4) and systematic features of the clinical practice 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 at a management decision point may shed further light on these potentially unrecognized patient cues.

While daily medication taking 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, 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 health maintenance organization who had fewer barriers to care (e.g. prescription costs, primary care physician access) than the general population (29). Moreover, differences in medication co-pays 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 Hba1c 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.
ACKNOWLEDGEMENTS

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Table 1: Characteristics of overall cohort (n = 2065), and comparing highest (> 97%, n = 516) vs. lowest (<66%, n = 517) quartiles of baseline medication adherence

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort</th>
<th>Highest Quartile</th>
<th>Lowest Quartile</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>55.4 (12.2)</td>
<td>57.5 (11.8)</td>
<td>54.1 (12.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, %</td>
<td>47.5</td>
<td>52.5</td>
<td>51.5</td>
<td>0.73</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-White</td>
<td>48.6</td>
<td>56.1</td>
<td>39.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>-Black</td>
<td>18.5</td>
<td>13.2</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>-Other or Unk.</td>
<td>32.9</td>
<td>30.7</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Census Tract Income</td>
<td>39,674 (15,921)</td>
<td>40,470 (15,966)</td>
<td>39,835 (18,517)</td>
<td>0.57</td>
</tr>
<tr>
<td>Clinic Visits, prior year</td>
<td>4.5 (6.2)</td>
<td>4.5 (4.2)</td>
<td>4.6 (4.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33.0 (7.2)</td>
<td>33.6 (6.8)</td>
<td>32.3 (7.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Concurrent meds, n</td>
<td>7.8 (7.7)</td>
<td>7.9 (7.7)</td>
<td>8.3 (8.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Total enrollment time, months</td>
<td>108 (19)</td>
<td>107 (18)</td>
<td>107 (19)</td>
<td>0.98</td>
</tr>
<tr>
<td>HbA1c level preceding first medication initiation</td>
<td>9.4 (2.2)</td>
<td>9.7 (2.1)</td>
<td>9.3 (2.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to initiation, months</td>
<td>1.5 (4.6)</td>
<td>1.3 (4.8)</td>
<td>1.8 (4.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Time to next elevated HbA1c, months</td>
<td>15.0 (13.4)</td>
<td>11.9 (11.8)</td>
<td>15.0 (12.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers are means (standard deviations), median (IQR), or number (percent); Highest and Lowest Quartiles are of adherence to first prescribed hypoglycemic medication; P-values are for Highest vs. Lowest Quartile comparisons; HbA1c = hemoglobin A1c
<table>
<thead>
<tr>
<th>Intensification at 12 months</th>
<th>Crude OR</th>
<th>p-value</th>
<th>aOR</th>
<th>p-value</th>
<th>Crude OR</th>
<th>p-value</th>
<th>aOR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st vs. 4th Quartile</td>
<td>1.64</td>
<td>&lt;0.001</td>
<td>1.53</td>
<td>0.01</td>
<td>1.53</td>
<td>&lt;0.001</td>
<td>1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.26 – 2.14)</td>
<td>(1.11 – 2.11)</td>
<td>(1.27 – 1.86)</td>
<td>(1.18 – 1.88)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox model</td>
<td>Crude HR</td>
<td>p-value</td>
<td>aHR</td>
<td>p-value</td>
<td>Crude HR</td>
<td>p-value</td>
<td>aHR</td>
<td>p-value</td>
</tr>
<tr>
<td>Hazard Ratios</td>
<td>1.52</td>
<td>&lt;0.001</td>
<td>1.41</td>
<td>&lt;0.001</td>
<td>1.46</td>
<td>&lt;0.001</td>
<td>1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standard Error</td>
<td>(0.08)</td>
<td>(0.10)</td>
<td>(0.06)</td>
<td>(0.07)</td>
<td></td>
<td></td>
<td></td>
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</table>

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. OR = odds ratio, HR = hazard ratio ('a' = adjusted); Models adjusted for age, gender, race, number of concurrently prescribed medicines at time of oral hypoglycemic initiation, baseline Hemoglobin A1c prior to medication initiation, and time from medication initiation to first elevated Hemoglobin A1c.
Figure 1: Medication intensification within 6 and 12 months of first elevated HbA1c 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 HbA1c result at least three months after initiation oral hypoglycemic therapy, stratified by “Excellent” (>90%, n = 857), “Moderate” (50-90%, n = 1020), and “Poor” (< 50%, n = 188) adherence to first-prescribed oral hypoglycemic medicine.
References


