Why Don't Diabetes Patients Achieve Recommended Risk Factor Targets? Poor Adherence versus Lack of Treatment Intensification

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BACKGROUND: Despite the availability of effective hypertension, hyperlipidemia, and hyperglycemia therapies, target levels of systolic blood pressure (SBP), LDL-cholesterol (LDL-c), and hemoglobin A1c control are often not achieved.

OBJECTIVE: To examine the relative importance of patient medication nonadherence versus clinician lack of therapy intensification in explaining above target cardiovascular disease (CVD) risk factor levels.

DESIGN: Cross-sectional assessment.

PARTICIPANTS: In 2005, 161,697 Kaiser Permanente Northern California adult diabetes patients were included in the study.

MEASUREMENT: "Above target" was defined as most recent A1c $\geq$7.0% for hyperglycemia, LDL-c $\geq$100 mg/dL for hyperlipidemia, and SBP $\geq$130 mmHg for hypertension. Poor adherence was defined as medication gaps for $\geq$20% of days covered for all medications for each condition separately. Treatment intensification was defined as an increase in the number of drug classes, increased dosage of a class, or a switch to a different class within the 3 months before or after notation of above target levels.

RESULTS: Poor adherence was found in 20–23% of patients across the 3 conditions. No evidence of poor adherence with no treatment intensification was found in 30% of hyperglycemia patients, 47% of hyperlipidemia patients, and 36% of hypertension patients. Poor adherence *or* lack of therapy intensification was evident in 53–68% of patients above target levels across conditions.

CONCLUSIONS: Both nonadherence and lack of treatment intensification occur frequently in patients above target for CVD risk factor levels; however, lack of therapy intensification was somewhat more common. Quality improvement efforts should focus on these modifiable barriers to CVD risk factor control.

KEY WORDS: diabetes mellitus; adherence, treatment intensification; hypertension; hyperlipidemia; quality of health care; cardiovascular disease.
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INTRODUCTION

Diabetes patients are at high risk for cardiovascular disease (CVD),[1–2] the leading cause of death, disability, and health care expenditure in the US.[3] Appropriate use of antihypertensive agents, lipid-lowering therapies, and glucose-lowering medications has been shown to lower CVD risk factor levels and to reduce the occurrence of CVD deaths and events in patients with diabetes.[4–13] Despite solid evidence for the efficacy of these therapies, they are often underutilized.[14–19] Underutilization of proven medications is a major barrier to improving the quality of heath care,[20] and may help explain recent reports suggesting widespread and persistent suboptimal control of systolic blood pressure (SBP), LDL-cholesterol (LDL-c), and hemoglobin A1c (A1c).[21–25] For example, national studies have shown that less than 10% of diabetes patients attain recommended goals for all 3 risk factors.[1,2]

The lack of appropriate medication therapy intensification by clinicians is a primary reason that patients fail to reach recommended targets for conditions such as hypertension, hyperglycemia, and hyperlipidemia.[26–32] Low rates of clinician responsiveness or "clinical inertia" in the face of elevated CVD risk factor levels have been associated with poorer levels of risk factor control.[30,31,33,34]

Another significant contributor to the underutilization of medications is the lack of patient adherence to the drug regimens prescribed by clinicians.[35] Approximately 10–30% of persons with type 2 diabetes have been reported to withdraw from prescribed regimens within 1 year of diagnosis,[36] and long-term persistence in use of lipid-lowering therapies and antihypertensives remains low.[37–39] Poor medication adher-

ence has been shown to be associated with disease progression, avoidable hospitalizations, disability, and death.[40–42]

Whereas both patient lack of adherence and clinician lack of appropriate therapy intensification for CVD risk factor control are well documented, the relative contributions of each to persistence of above target risk factor levels in diabetes is unknown. Understanding the relative importance of adherence versus clinical inertia may be particularly useful to health plans and providers planning interventions aimed at improving control of these CVD risk factors. The purpose of this descriptive, observational cohort study is to describe the proportions of diabetes patients with above target A1c, LDL-c, and SBP levels who have poor medication adherence during the past 12 months, and the proportions of those with no evidence of poor adherence who do not receive appropriate treatment intensification within 3 months. We also examine the proportion of patients in each category who achieve target risk factor levels within 6 months and determine whether being on maximal medical therapy regimens may help explain lack of treatment intensification.

METHODS

Study population. This study was developed and approved by the Steering Committee of the Translating Research in Action for Diabetes (TRIAD) Study and conducted in 1 of TRIAD's 6 Translational Research Centers, Kaiser Permanente Northern California (KP). KP is an integrated health care delivery system providing comprehensive medical care to a diverse population of approximately 3.2 million members in Northern California.[43] Patients were selected for the study from the KP diabetes registry if they were identified as having diabetes before January 1, 2005 and were continuously enrolled with an active drug benefit during all of 2004 and 2005. Continuous enrollment was required so that adherence and treatment intensification could be accurately assessed throughout 2005. Eligible patients were further assessed for the presence of clinically recognized hypertension and hyperlipidemia before January 1, 2005 (see the Appendix for definitions) using KP automated clinical databases. The validity and reliability of the KP diabetes registry; its laboratory, clinical, and pharmacy databases; and the utility of these databases for assessing both treatment intensification and medication adherence have been documented.[44,45]

Definitions of Target Levels. Patients were defined as being above target levels of A1c if they had an A1c laboratory value ≥7.0% at any point during 2005, using the first measurement in 2005 for each patient if multiple above target values were noted. Similarly, those diabetes patients with hyperlipidemia were defined as above target for LDL-c if they had any LDL-c value ≥100 mg/dL during the year. Those with hypertension were defined as above target for blood pressure if they had at least 2 consecutive SBP readings of ≥130 mm Hg. Two consecutive readings were required because of the greater lability of blood pressure measures; 1 measure was considered sufficient for LDL-c and A1c as HEDIS guidelines recommend 1 LDL-c and A1c test per year. To assess if the relative importance of adherence versus clinical inertia observed at these risk factor target cut points, in a second sensitivity analysis, we defined being above target as A1c ≥8.0%; LDL-c ≥130 mg/dL; and 2 SBP readings of ≥140 mm Hg.

Adherence to Medications. Adherence to medications was calculated with KP prescription databases using the validated continuous, multiple interval measure of gaps in therapy (CMG) method.[46–48] Validation research has shown the CMG method to be significantly associated with objective measures of medication use such as serum/urine drug levels, physiological drug effects such as blood pressure, and increased comorbidity and cost.[47] This method is defined as the proportion of days the patient *should* have been on medication therapy during which the patient did not have medication available. For each individual condition (hyperglycemia, hypertension, and hyperlipidemia), CMG was first calculated separately for each medication class filled at least twice in the 12 months before the last date above target levels were observed in 2005. Individual class adherence was then combined into a single measure for all medications prescribed for a single condition, weighting the estimate for each medication class by the number of days from the first to last fill in the 12-month period. Medications filled only once were not included in the analysis because CMG cannot be calculated from single fills. Because many prior studies have found significant clinical effects when cumulative days of refill gaps equal or exceed 20%,[42,49,50] we defined poor adherence for each condition as a weighted nonadherence measure of ≥20% across all medications prescribed for the condition.

Treatment intensification. Treatment intensification was assessed for each condition from KP prescription databases during the 3 months before and the 3 months after first measurement of above target levels in 2005. Intensification was defined as any one of the following 3 occurrences: (a) an increase in the number of drug classes; (b) an increase in the daily dosage of at least 1 ongoing drug class; or (c) a switch to a medication in a different drug class. Seven medication classes were tabulated for hypertension (ace inhibitors, angiotensin antagonists, beta adrenergic blockers, calcium channel blockers, thiazides/related diuretics, potassium-sparing diuretics, and loop diuretics); 5 for hyperlipidemia (statins, bile acid resins, fibrates, niacin, and ezetimibe), and 4 for diabetes (sulfonylureas, metformin, thiazolidinediones, and insulin);[44] combination pills were considered as consisting of 2 classes. Daily dosages were categorized as low (near initial starting doses), medium (maintenance range), or high (above maintenance range) based on package insert recommendations and inspection of actual dosage distributions. This analysis focuses on treatment intensification in patients with no evidence of poor adherence, as these patients are the most appropriate targets for treatment intensification interventions and prescribing additional medications for patients in poor adherence may be less effective.

To allow a full 3 months follow-up, we extended the observation into 2006 for those whose above target values were first identified in the final quarter of 2005, excluding the small number of these patients who were no longer with KP in 2006. In assessing both medication adherence and treatment

intensification in diabetes, we excluded patients who were using insulin at the time above target A1c levels were noted because neither can be accurately identified in prescription databases.

Data Analyses. For each condition separately (hyperglycemia, hyperlipidemia, and hypertension), we first determined the proportions of patients above versus at or below target levels. Among patients who were above target, we then determined the proportions with poor adherence to medications, no current medications or evidence of poor adherence but no treatment intensification, or no evidence of poor adherence and treatment intensification within 3 months before to 3 months after the observation of above target risk factor levels. As adherence and treatment intensification for insulin are both difficult to assess using automated databases, we limited our analysis of hyperglycemia to patients who were not on insulin at baseline. In measuring treatment intensification, we also examined the proportion who were either already on, or whose treatment intensification moved them to, maximal medical therapy (MMT). MMT was defined as: 4 classes of antihypertensive drugs for hypertension; ezetimibe (at any dose), 80 mg simvastatin, or 40 mg atorvastatin for hyperlipidemia; and any insulin starts for diabetes (as exact insulin dosages could not be assessed).

To assess whether those patients who had no evidence of poor adherence and received a timely treatment intensification were more likely to achieve target risk factor values within 6 months than either patients in poor adherence or had not received a treatment intensification, we looked ahead 6 months after the determination of above target risk factor levels for each patient to see what proportions achieved targets according to the definitions given above.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA). This study was reviewed and approved by Kaiser Permanente's Institutional Review Board.

RESULTS

A total of 161,697 diabetes patients met the criteria for inclusion into the study (Table 1). The average age was 61; 48% were female; and 46% were Caucasian. Of these patients, 81% also had hypertension and 85% also had hyperlipidemia. Control levels could be assessed (i.e., at least 1 risk factor value was available in 2005) for 84%, 92%, and 88% of eligible patients for A1c, LDL-c, and SBP, respectively.

Risk Factor Levels, Adherence, and Intensification for Hyperglycemia. Of the 122,967 diabetes patients not using insulin at their baseline assessment (Fig. 1), 53% had above target A1c levels at some point during 2005. Within the 'above target' group, 23% were poorly adherent to their oral antiglycemic medications. Another 30% had no evidence of poor adherence but did not receive treatment intensification in the 3 months before or 3 months after above target levels were assessed. The remaining 47% of above target patients received treatment intensification, including approximately one third who were begun on insulin. By design, no patient was on MMT (insulin) at baseline.

Risk Factor Levels, Adherence, and Intensification for Hyperlipidemia. Of diabetes patients with hyperlipidemia, 53% were above target at some point during 2005 (Fig. 2). Among those above target, 21% were poorly adherent to hyperlipidemia medications, 32% had no evidence of poor adherence and received treatment intensification, and almost half (47%) had no evidence of poor adherence but had not received a treatment intensification surrounding the determination of above target levels. Less than 10% of patients not receiving treatment intensification were already at MMT, and less than 10% of those who did undergo intensification were moved to MMT (data not shown).

Risk Factor Levels, Adherence, and Intensification for Hypertension. Of diabetes patients with hypertension, 47% were above target at some point during 2005 (Fig. 3). Within this group, 20% were poorly adherent to their antihypertensive medications, 36% had no evidence of poor adherence and received treatment intensification, and 43% had no evidence of poor adherence but had not received treatment intensification surrounding determination of above target SBP levels. Less than 10% of patients not receiving treatment intensification

Table 1. Patient Characteristics—2005 Adult Diabetes Patients, KPNC

	All Patients	Patients for Whom Control Can be Assessed		
	Diabetes	Diabetes Not on Insulin at Baseline	Diabetes with Hyperlipidemia Diagnosis	Diabetes with Hypertension Diagnosis
Total, *N* (%)	161,697	122,967 (76.0)	120,030 (91.8)	121,206 (88.0)
Age, mean (SD)	61.0 (13.0)	61.9 (12.4)	62.4 (12.0)	62.9 (12.2)
Female, *N* (%)	76,902 (47.6)	58,136 (47.3)	57,173 (47.6)	60,623 (50.0)
Race, *N* (%)				
Caucasian	74,900 (46.3)	56,656 (46.1)	57,373 (47.8)	58,832 (48.5)
African American	15,905 (9.8)	11,683 (9.5)	11,530 (9.6)	13,071 (10.8)
Asian	22,722 (14.1)	18,647 (15.2)	17,942 (15.0)	16,849 (13.9)
Pacific Islander	166 (0.1)	116 (0.1)	131 (0.1)	129 (0.1)
Hispanic/Latino	17,750 (11.0)	13,837 (11.3)	13,134 (10.9)	13,548 (11.2)
Other	9,724 (6.0)	7,279 (6.9)	7,152 (6.0)	7,727 (6.4)
Missing	20,530 (12.7)	14,749 (12.0)	12,768 (10.6)	11,050 (9.1)
Hypertension, *n* (%)	130,821 (80.9)	102,433 (83.3)	102,619 (85.5)	na
Dyslipidemia, *n* (%)	137,302 (84.9)	108,062 (87.9)	na	107,867 (89.0)

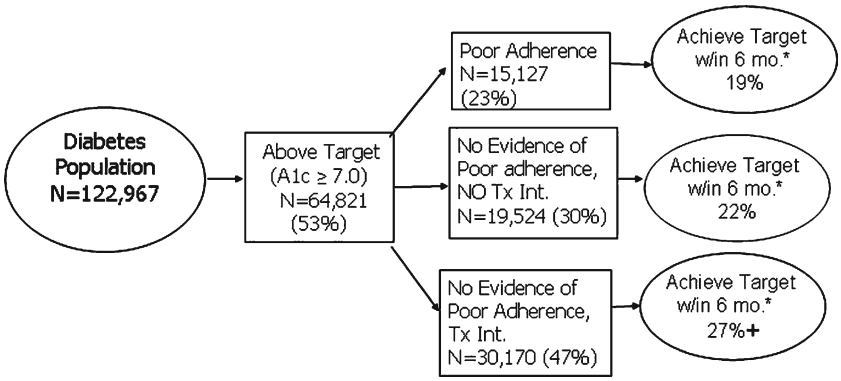

Figure 1. Medication adherence and intensification for glycemic control in patients not on insulin at baseline. *Among patients who had a follow-up laboratory value within 6 months (44%). +$p<.001$ difference between treatment intensification group and other 2 groups.

were already at MMT, and only 16% of those who did receive treatment intensification were moved to MMT (data not shown).

To see if the relative importance of adherence versus clinical inertia observed at these risk factor target cut points was similar at less stringent cut points, we performed the same stratification using A1c ≥8, LDL-c ≥130 mg/dL, and SBP ≥140 mm Hg. At these cut points, we found 29%, 20%, and 22% of patients to be above target, respectively. For patients above these higher cut points, the proportions with poor adherence to their therapies were slightly higher but quite similar, ranging from 22–27% across conditions compared to 20–23% when lower cut points were used. Treatment intensification occurred somewhat more frequently at these higher levels (as noted in previous studies),[44] from 36–54% across conditions compared to 32–47% at the lower cut points (data not shown). As seen in the strict cut point analysis for both hypertension and hyperlipidemia, the proportions of these patients who had no evidence of poor adherence but had not recently received treatment intensification exceeded the proportion that had poor adherence to their current medications.

Rates of Achieving Target CVD Risk Factor Levels within 6 months

Across the conditions, Figures 1, 2, and 3 show that patients with no evidence of poor adherence who received treatment intensification were more likely to achieve target risk factor levels during the following 6 months than those who were either poorly adherent or who did not receive treatment intensification ($p<.001$). This was most dramatic for hyperlipidemia where almost half of patients with treatment intensification achieved good control within 6 months, whereas only a quarter of those not intensified did so.

DISCUSSION

In this diabetes population, approximately 50% of patients experienced at least a transient period of being above target for A1c, LDL-c, and SBP levels during 2005. Together, poor adherence or lack of treatment intensification was found for 53–68% of all patients above target, depending on the condition. This pattern persisted even when less stringent cut points were examined: poor adherence or lack of treatment intensification was evident in 46–65% of patients with above target risk factor levels. Only a small proportion of lack of therapy intensification could be explained by patients already at MMT levels.

Rates of patient nonadherence to medications found in this study are similar to those found in other recent studies of adherence in diabetes patients enrolled in managed care settings, usually ranging from 20% to 30% across condi-

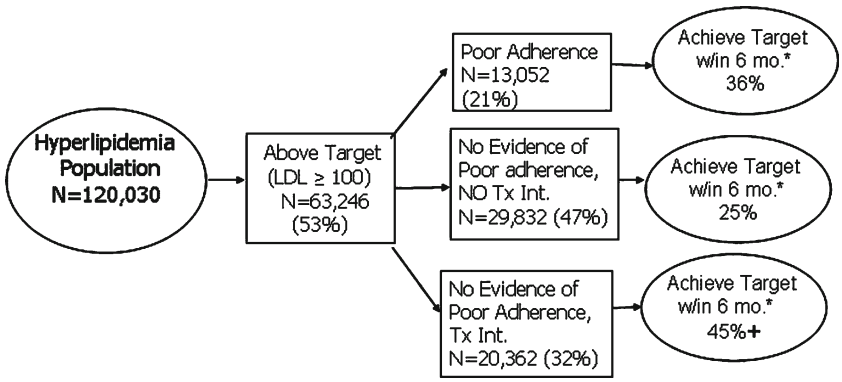

Figure 2. Medication adherence and intensification for hyperlipidemia among diabetes patients. *Among patients who had a follow-up laboratory value within 6 months (46%). +$p<.001$ difference between treatment intensification group and other 2 groups.

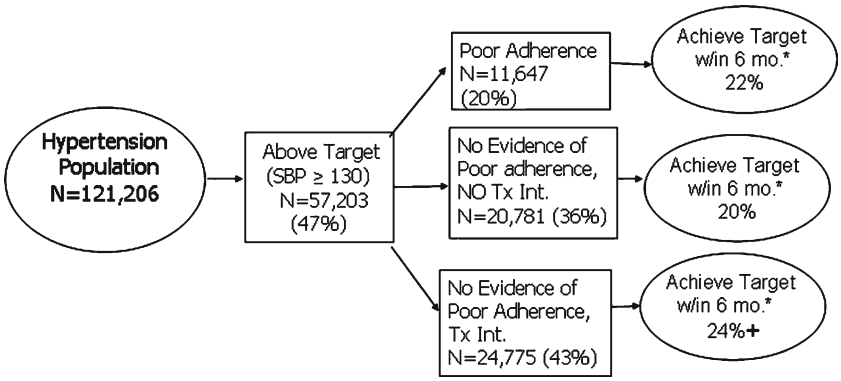

Figure 3. Medication adherence and intensification for hypertension among diabetes patients. *Among patients who had a follow-up laboratory value within 6 months (49%). +$p<.001$ difference between treatment intensification group and other 2 groups.

tions.[41,42,51] While methodologies differ, it appears that the rates of treatment intensification for KP diabetes patients may be somewhat higher than those previously reported.[51–53] However, this is the first study we are aware of that examines both medication adherence and treatment intensification rates in a single diabetes population that is above target for CVD risk factor levels. While treatment intensification is most appropriate in patients who are adhering well to their current treatment regimens, providers often also intensify treatments when patients are poorly adherent to current treatment regimens.[51] It is important to distinguish whether patients have good or poor medication adherence in assessing appropriate rates of treatment intensification.

It is important to note that these findings suggest that clinical inertia, or failure to intensify pharmacotherapy appropriately, may be as great a problem as poor patient compliance and point to important opportunities for interventions to improve risk factor control by working through clinicians,[54] their teams, or their delivery systems. Our findings of relatively high levels of patient adherence to chronic medications should also further dispel any misperceptions among clinicians that patients simply are not or will not take prescribed medications.

This analysis has a few limitations worth noting. We did not identify and exclude persons with contraindications to some medication classes or with comorbidities such as terminal conditions that would make intensification inappropriate; it is possible that small numbers of poorly controlled patients with no evidence of poor adherence and no treatment intensification may not have been appropriate candidates for further intensification. System level interventions aiming to improve treatment intensification for CVD risk factor medications would ideally be designed to identify and remove such patients from consideration for intensification.

These results were obtained from a large, integrated delivery system where convenient pharmacy services are provided to the vast majority of patients with chronic illnesses. It is possible that adherence and intensification rates as defined through our classification system are even lower in other health care settings. Our finding that 53–68% of diabetes patients above target levels for CVD risk factors are in need of interventions to improve adherence or intensify treatments may be a conservative estimate of the need for such interventions nationally.

Because we were unable to track adherence to or intensification of insulin use in this study, it is possible that we underestimated patient adherence and provider clinical inertia in hyperglycemia control. Whereas these estimates may be conservative, our analysis still demonstrates that more than half of patients with above target hyperglycemia levels could potentially benefit from either treatment intensification or improved adherence.

Finally, comparison of patient characteristics of individuals in the 3 categories described in this paper was outside the scope of this analysis. Previous studies have shown that adherence to medications is related to factors such as regimen complexity, comorbidities, race, health literacy, and length of time on regimens.[39,55,56] Other studies of treatment intensification have shown a relationship between treatment intensification rates and age, race, current levels of control, and presence of comorbidities.[44,51–53] A comparison of patients as stratified in this analysis may provide further insights to health plans and clinicians hoping to address issues of nonadherence and clinical inertia.

In conclusion, poor medication adherence and lack of treatment intensification each frequently occur in diabetes patients who are above target levels for CVD risk factors; however, lack of clinician treatment intensification appears more common than patient nonadherence. Quality improvement efforts that focus on these modifiable barriers to clinical risk factor control could potentially improve risk factor levels and reduce longer-term complications.

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Conflict of Interest: *None disclosed.*

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APPENDIX

Diagnostic Criteria for Diabetes Mellitus, Hypertension, and Dyslipidemia

Diabetes mellitus (one of the following):

1. at least 1 prescription of insulin or an oral hypoglycemic agent; or
2. at least 2 outpatient diagnoses of diabetes mellitus; or
3. 1 outpatient diagnosis of diabetes mellitus plus ≥1 Hb A1c ≥7%; or
4. at least 1 hospital discharge with a primary DM-related diagnosis (ICD-9 code 250.X).

Hypertension (one of the following):

1. at least 1 prescription for an antihypertensive medication plus an outpatient diagnosis of hypertension; or
2. at least 2 outpatient diagnoses of hypertension; or
3. at least 1 prescription for an antihypertensive medication plus 1 or more elevated outpatient blood pressure readings (≥140 mm Hg systolic or ≥90 mm Hg diastolic); or
4. at least 1 outpatient diagnosis of hypertension plus at least 1 blood pressure reading of ≥140 mm Hg systolic or ≥90 mm Hg diastolic.

Dyslipidemia (one of the following):

1) at least 1 prescription for an antilipemic agent; or
2) outpatient diagnosis of hyperlipidemia/hypercholesterolemia with an LDL-cholesterol value greater than or equal to the risk-appropriate cut point value; or
3) Outpatient diagnosis of hyperlipidemia/hypercholesterolemia with a prior LDL-cholesterol value greater than or equal to the risk-appropriate cut point value.