


# Adjustments to Diabetes Medications in Response to Increases in Hemoglobin A1c: An Epidemiologic Study

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James Davis, PhD<sup>1</sup>, Benjamin Chavez, PharmD<sup>2,3</sup>,  
and Deborah T. Juarez, ScD<sup>2</sup>

## Abstract

**Objective:** The primary objective was to assess associations between increases in glycosylated hemoglobin (HbA1c) levels and medication adjustments among patients with diabetes. A secondary objective was to measure the effect of adjustments on subsequent HbA1c levels. **Methods:** A retrospective analysis of administrative data from a large health insurer in Hawaii of 7654 patients with diabetes mellitus type II, HbA1c levels greater than 7%, and who were taking oral diabetic medications. Patients were eligible if they had an HbA1c measurement in 2009, a prior measure 30 or more days previously, and at least 30 days of follow-up to identify medication adjustments. Patients were classified into 3 groups based on their extent of change in HbA1c levels. Patients were followed to determine the frequency of medication adjustments and to observe the possible benefit of making adjustments on subsequent HbA1c levels. **Results:** Medication adjustments were the exception, occurring among less than a fourth of patients. Compared with patients without HbA1c increases, patients with <1% HbA1c increases made adjustments 20% more frequently, and patients with increased HbA1c levels of 1% or more made adjustments 60% more frequently. Patients with similar HbA1c increases were more likely to adjust their medications if they had higher baseline HbA1c levels. Medication adjustments were mostly for oral diabetes medications; insulin use was seldom initiated, and then primarily by patients with HbA1c levels of 9% or higher. Patients with medication adjustments averaged about 0.40% lower HbA1c levels when reassessed after 120 days or more. **Conclusion:** The results show limited responsiveness to increases in HbA1c levels and a low initiation rate of insulin use. Patients adjusting their medications, however, had clinically significant improvements in their HbA1c levels. Clinical inertia and patient concerns are discussed as factors possibly limiting the frequency of medication adjustments.

## Keywords

diabetes, medication adjustment, HbA1c, clinical inertia

Diabetes affects 25.8 million Americans or approximately 8% of the US population and is the leading cause of kidney failure, nontraumatic lower limb amputations, and new cases of blindness in the United States, as well as a major cause of heart disease and stroke.<sup>1</sup> Diabetes also takes a large financial toll with direct diabetes-related medical expenditures in 2007 estimated at \$116 billion.<sup>1</sup>

Lowering hemoglobin A1c (HbA1c) levels to below or around 7% has been shown to reduce microvascular complications as well as macrovascular complications in the long term if the reduction occurs shortly after diagnosis.<sup>2-7</sup> Despite widespread knowledge of guidelines that highlight the importance of glycemic control among patients with diabetes, many patients have HbA1c levels outside the recommended range. National population-based estimates suggest that only 56% of patients with diabetes have HbA1c of 7% or lower.<sup>8</sup>

Numerous clinical trials have shown that appropriate medication usage can improve glycemic control. American Diabetes Association Guidelines suggest that if noninsulin monotherapy, usually with metformin, at maximal tolerated dose does not achieve the A1c target over 3 to 6 months, a second oral agent, a GLP-1 receptor agonist, or insulin should be added.<sup>2</sup>

For patients with HbA1c above recommended levels, physicians may try to encourage improved adherence to

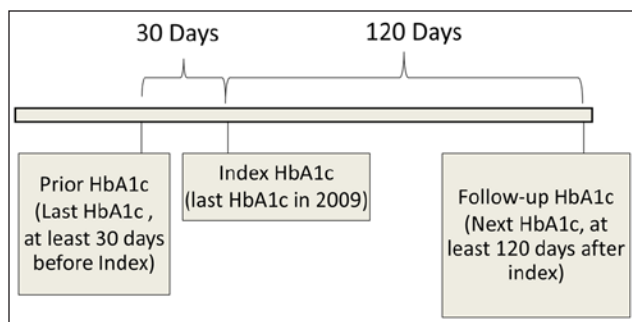
<sup>1</sup>John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA

<sup>2</sup>Daniel K. Inouye College of Pharmacy, University of Hawaii, Hilo, HI, USA

<sup>3</sup>Pacific University School of Pharmacy, Hillsboro, OR, USA

## Corresponding Author:

James Davis, PhD, John A. Burns School of Medicine, University of Hawaii, MEB 401B, 651 Ilalo Street, Honolulu, HI 96813, USA.  
Email: jamesdav@hawaii.edu



**Figure 1.** Timeline of assessments of HbA1c.

existing medications or prescribe additional medications. This study examines how frequently patients adjust their medications following HbA1c increases, and the extent that HbA1c levels and recent changes in levels are associated with medication adjustments. This study also investigates the effect of medication adjustments on subsequent HbA1c levels.

## Methods

### Study Design and Patient Population

The patients were members of the largest insurer in Hawaii who were identified as having diabetes by the insurer and who lived on one of the four major islands in the state. In addition, patients were required to have been prescribed an oral diabetes medication in 2009, had a serum HbA1c measurement during the year, and had a prior HbA1c measurement a minimum of 30 days before the last HbA1c measurement in 2009. Patients were required to remain enrolled for at least 30 days after the start of follow-up to identify medication adjustments. The last HbA1c measure of 2009 was considered the “index” HbA1c measure and the medication prescription date was used as the start of follow-up. The most recent HbA1c measure prior to the index one, that was a minimum of 30 days before, was labeled the “prior HbA1c.” The first HbA1c following the index HbA1c measurement, and a minimum of 120 days afterward, was identified as the “follow-up HbA1c.” Figure 1 illustrates the timeline of assessments of HbA1c measurements.

This study only included de-identified data and was granted an exemption from institutional review board review by the University of Hawaii Institutional Review Board.

The predictor of primary interest to the study was the change in HbA1c levels prior to the baseline measurement. Patients were classified into 3 groups based on the extent of change: no increase in HbA1c levels, an increase of less than 1%, or an increase of 1% or more. The primary outcome was making a medication adjustment during the first 30 days of follow-up. Medication adjustments included increased dosage of an oral medication, addition of a new

medication for diabetes, and initiated insulin use. A new medication was defined as the addition of an oral diabetes medication of a specific therapeutic class not used by the patient in the past 90 days. To assess the possible benefit of medication adjustments, changes in HbA1c levels were examined between the baseline HbA1c measurement and the next subsequent measure obtained after 120 days or more of follow-up.

### Data Analysis

The study population was characterized initially by examining frequencies of patient characteristics and other study variables. Subsequently, stratified analyses using the Cochran-Mantel-Haenszel method examined associations between increases in HbA1c levels and making a medication adjustment. Fisher’s exact test was used to test for significance when there were 5 people or fewer in individual strata in a cross-classified category. Trends of increasing medication adjustments with increasing changes in HbA1c levels were tested using the Cochran-Armitage trend test. The stratified analyses were extended by employing multivariable logistic regression models. Having made a medication adjustment (yes or no) was the outcome for these models. Other analyses examined if medication adjustments were associated with improvements in HbA1c levels using multiple linear regression models. All regression models were adjusted for age, sex, living on Oahu or a neighboring Hawaiian island, years with diabetes, time between HbA1c measurements, high or low morbidity, use of insulin (yes or no), number of oral diabetes medications in the past 90 days, and HbA1c level at the start of follow-up. Patient morbidity level was determined by using *ICD-9-CM* codes according to the Johns Hopkins Adjusted Clinical Group methodology; patients with levels of 4 or 5 on the 5-point scale were categorized as high morbidity.<sup>9</sup> Data were analyzed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, NC).

## Results

In preliminary analyses, medication adjustments were analyzed separately for patients with normal and elevated HbA1c levels. Among patients with HbA1c levels of 7% or less at the start of follow-up, a new medication was used by 4.1% of 5291 patients who did not have an HbA1c increase, 5.3% of 2987 patients with an increase of less than 1%, and 3.0% of 33 patients with a 1% or greater increase. These percentages were only marginally significantly different ( $P = .04$ ), and the frequency of adjustments did not consistently increase with greater changes in HbA1c levels. In contrast, patients with HbA1c levels greater than 7%, increases in HbA1c levels were highly significantly associated with beginning a new medication ( $P < .001$ ). A total of

**Table 1.** Baseline Characteristics of the Study Participants.<sup>a</sup>

Characteristic	
Age in years, mean $\pm$ SD	59.8 $\pm$ 13.9
Initial HbA1c level, mean $\pm$ SD	8.5 $\pm$ 1.4
Years with diabetes, mean $\pm$ SD	7.6 $\pm$ 3.7
Gender, n (%)	
Female	3944 (51.5)
Male	3715 (48.5)
Morbidity, n (%)	
Low	4558 (59.5)
High	3101 (40.5)
Island, n (%)	
Oahu	5559 (72.3)
Neighboring island	2120 (27.7)
Number of oral diabetes medications, n (%)	
0	1264 (16.5)
1	2,969 (39.0)
2	2330 (30.4)
$\geq 3$	1096 (14.3)
Percentage change in HbA1c levels, n (%)	
$\leq 0\%$	3457 (45.1)
$>0\%$ , $<1\%$	2999 (39.2)
$\geq 1\%$	1203 (15.7)
Insulin use, n (%)	
Yes	1938 (25.3)
No	5721 (74.7)

<sup>a</sup>Restricted to patients with HbA1c levels at baseline of greater than 7%.

11.0% of 3452 patients without an HbA1c increase, 13.9% of 2999 patients with an increase of less than 1%, and 24.6% of 1203 patients with an increase of 1% or higher had medication adjustments. Medication changes were also examined among patients with HbA1c levels greater than 7% between 30 and 60 days of follow-up to determine if the effect of an increase in HbA1c levels was prolonged beyond 30 days. A statistically significant ( $P < .001$ ) but smaller effect was observed in the second 30 days as compared with the first 30 days. The percentages of patients adding medications between 30 and 60 days were 3.3% among patients without HbA1c increases, 4.7% among patients with less than a 1% increase, and 5.9% among patients with 1% or greater increases in HbA1c levels.

Because substantial changes in medication usage occurred primarily among patients with HbA1c levels higher than 7%, and the importance of improving glycemic control for these patients, the results presented are restricted to this population. Table 1 presents the baseline characteristics of these patients. They averaged about 60 years of age, had mean HbA1c levels of 8.5%, and were about equal in percentages by sex and morbidity level. The patients averaged over 7 years since first being identified as having diabetes. About two thirds of the patients were taking either 1 or 2 oral medications and one fourth of the patients were using insulin.

As a first step to understand medication adjustments, patients were cross-classified by baseline HbA1c levels and the extent of increase in examining medication adjustments (Table 2). Most adjustments had been the result of adding a new medication; only 4.3% resulted from dose increases to a medication already being taken. Within similar ranges of baseline HbA1c, patients with greater increases were more likely to adjust their medications. Among patients with similar increases in HbA1c, medication adjustments were more frequent at higher baseline HbA1c levels. Patients with baseline levels of 9% or higher were especially likely to have begun new medications. However, adjustments were made less than 30% of the time even among the subgroup of these patients with 1% or greater HbA1c increases.

Patients not initially on insulin could either initiate insulin use or adjust their oral hypoglycemic medications. Table 3 summarizes the choices observed. Adjustment to oral medications was by far more common, a practice that increased with higher baseline HbA1c levels and with greater increases in HbA1c levels prior to the start of follow-up. Adding insulin was infrequent for patients with baseline HbA1c levels less than 9%, and the percentage of patients beginning insulin use remained less than 7% regardless of baseline level or the extent of HbA1c increase.

Subsequent analyses examined the relation between increases in HbA1c levels and medication additions using logistic regression models. These analyses were adjusted for age, sex, years with diabetes, time between HbA1c measurements, high or low morbidity, use of insulin, number of oral diabetes medications, and HbA1c level at the start of follow-up. Figure 2 presents these results. The adjusted analyses confirmed that new medication use became more frequent among patients with greater increases in their HbA1c levels. Compared with patients without an increase in HbA1c levels, patients with increases of less than 1% were 20% more likely (odds ratio = 1.20, 95% confidence interval = 1.03% to 1.40%,  $P = .02$ ) and patients with increases of 1% or greater were 60% more likely to add new diabetes medications (odds ratio = 1.58, 95% confidence interval = 1.29-1.92,  $P < .001$ ).

To understand the possible benefits of medication adjustments, changes between the index and follow-up HbA1c levels were examined comparing patients that did and did not adjust their medications (Table 4). Changes in levels were assessed after a minimum of 120 days, varying with the availability of an HbA1c measurement. Ninety percent of the study participants had both HbA1c values and were included in this analysis. The mean time ( $\pm$  standard deviation) between measurements was 0.46  $\pm$  0.35 years. In adjusted, multivariable regression models patients making medication adjustments averaged 0.40% lower HbA1c levels than those that had not adjusted their medications. When examined by whether the adjustment was adding insulin or altering oral medication usage, adding insulin was associated with

**Table 2.** Number and Percentage of Patients Adjusting Their Diabetes Medications Within 30 Days by Baseline HbA1c Level and by the Percentage Increase in HbA1c Before the Start of Follow-up.<sup>a</sup>

Baseline HbA1c Level	% Increase in HbA1c Level	No. of Patients	No. (%) Making Adjustments
≤7%	≤0	5291	216 (4.1)
≤7%	>0, <1	2987	157 (5.3)
≤7%	≥1	33	1 (3.0)
>7%, <8%	≤0	1966	170 (8.7)
>7%, <8%	>0, <1	1769	209 (11.8)
>7%, <8%	≥1	181	34 (18.6)
≥8%, <9%	≤0	797	103 (12.9)
≥8%, <9%	>0, <1	685	104 (15.2)
≥8%, <9%	≥1	279	59 (21.0)
≥9%	≤0	692	108 (15.6)
≥9%	>0, <1	546	104 (19.1)
≥9%	≥1	739	203 (27.5)

<sup>a</sup>For all baseline HbA1c levels, the proportions of added medications differed significantly by the percentage increase in HbA1c ( $P < .05$ ). For the 3 baseline HbA1c levels greater than 7%, trends in increasing percentages of medication adjustments with increasing increases in HbA1c levels were statistically significant ( $P < .01$ ). In all, 17.6% of patients with baseline HbA1c levels of >7% and <8% were taking insulin as were 30.7% of those with HbA1c levels ≥8% and <9%, and 35.0% of patients with HbA1c levels ≥9%.

**Table 3.** Adjustments to Oral Medications or Addition of Insulin by HbA1c Level and by the Percentage Increase in HbA1c Level Before the Start of Follow-up.<sup>a</sup>

HbA1c Level	% Change in HbA1c Level	No. of Patients	No. (%) by Type of Adjustment	
			Oral Medication	Insulin
>7%, <8%	≤0	1563	139 (8.9)	13 (0.8)
>7%, <8%	>0, <1	1511	191 (12.6)	11 (0.7)
>7%, <8%	≥1	153	29 (19.0)	2 (1.3)
≥8%, <9%	≤0	508	82 (16.1)	11 (2.2)
≥8%, <9%	>0, <1	493	94 (19.1)	5 (1.0)
≥8%, <9%	≥1	222	51 (23.0)	3 (1.4)
≥9%	≤0	409	80 (19.6)	15 (3.7)
≥9%	>0, <1	328	76 (23.2)	10 (3.1)
≥9%	≥1	534	147 (27.5)	33 (6.2)

<sup>a</sup>Analyses were restricted to patients not on insulin at the start of follow-up.

improvements in HbA1c levels of 0.71% and other medication adjustments showed improvements of 0.36%.

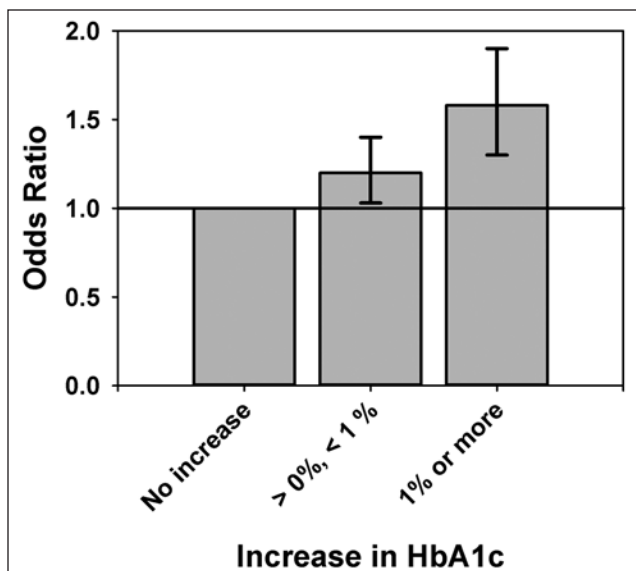
## Discussion

Our analyses reflect, in some ways, what we expect to happen in clinical practice. Patients, whose diabetes is uncontrolled, demonstrated here as having an increase in HbA1c, are more likely to have a dose increase or a new medication added to their regimen. However, it is also striking that the percentage of patients having medications added, although statistically significant, is low. For example, only 21% of patients who had a baseline HbA1c between 8% and 9%, and had an increase greater than 1%, had a medication added to their regimen. Of these same patients, only 1.4% had insulin added to their regimen. Even in the group with a baseline HbA1c >9%, insulin was added only to 6.2% of

these patients. These numbers are relatively low despite our knowledge that insulin has the best glucose-lowering properties of the treatment options in our armament. The same is true at baseline, as only 35% of patients with an HbA1c >9% were receiving insulin.

There could be several reasons for this low number of patients being prescribed insulin. Many patients have a hesitation, or fear, of injecting themselves. Some patients may have a needle phobia, or simply believe that they will not be able to inject themselves every day.<sup>10</sup> However, if patients are taught how to use insulin devices appropriately, particularly insulin pen delivery devices, these concerns can be alleviated. Patients are often surprised at the ease of insulin administration once they are shown proper technique.<sup>11</sup>

Patients may also feel that they have failed in their treatment if they have to take insulin. It is a misconception among patients that insulin is a last resort for diabetes, when



**Figure 2.** Odds ratios of making a medication adjustment within 30 days by the percent increase in HbA1c level at the start of follow-up. The odds ratios are adjusted for age, sex, island, years with diabetes, time between HbA1c measurements, high or low morbidity, use of insulin, number of oral diabetes medications, and HbA1c level at the start of follow-up.

in fact national guidelines are recommending basal insulin to be used as a second step in treatment after metformin. Prescribers could help in this matter by educating patients about the role of insulin in the treatment of diabetes.<sup>10,12</sup> Patients may also have misconceptions of insulin, such as believing that it may cause blindness, renal failure, severe hypoglycemia, and have an inadequate understanding of the risks/benefits.<sup>13</sup>

Another possible reason for low insulin prescribing is prescriber apprehension. Prescribers may feel that patients cannot handle the monitoring required with insulin and therefore may be more prone to hypoglycemia.<sup>14</sup> However, most patients already monitor their blood glucose at home from the time they are diagnosed with diabetes. Addition of

basal insulin, which is the recommended initial insulin choice, does not require any additional monitoring than patients who receive oral hypoglycemic agents. In fact, the risk of hypoglycemia with basal insulin is lower than with some oral hypoglycemics, such as sulfonylureas. Insulin glargine and NPH (neutral protamine Hagedorn) insulin have an incidence of hypoglycemia of 1.7% and 1.1%, respectively, when combined with oral agents.<sup>15</sup>

Prescribers also may not be educated themselves on how to use insulin delivery devices, and therefore, may not feel comfortable prescribing them to their patients. More education of healthcare professionals may help increase the use of insulin.<sup>12,14</sup>

A failure of some health care providers to appropriately intensify therapy was recognized and named “clinical inertia” by Phillips et al.<sup>16</sup> They noted that physicians have less training in treating to target than in relieving symptoms, and cited diabetes studies documenting clinical inertia. Phillips and his collaborators also reviewed evidence showing improvements when reminders are available to prompt providers to take immediate action when the patient is present. A more recent study by Phillips’s group reported that face-to-face feedback to physicians coupled with reminders led to significant improvements in patient HbA1c levels.<sup>17</sup>

Another study showed that having a rapid turnaround of HbA1c values to providers led to more frequent intensification, especially among patients with levels higher than 8%.<sup>18</sup> This result suggests that in part clinical inertia may result from lack of timely information available to providers. A further study identified more frequent intensification among patients having specialists’ care.<sup>19</sup> Most of the difference was attributed to initiation of insulin by specialists in response to elevated HbA1c levels. Patient factors may also be important. One study, for example, reported that low medication adherence was negatively associated with intensification.<sup>20</sup>

Medication adjustment among patients not at goal has been suggested as a novel target for quality improvement measures.<sup>21</sup> The feasibility of monitoring tightly linked measures such as HbA1c and medication adjustment was

**Table 4.** Percentage Decrease in HbA1c Levels Following the Addition of a New Medication for Diabetes Among Patients With Increased HbA1c Levels at Baseline.<sup>a</sup>

Comparison	Number	Medication Adjustment	% Decrease in HbA1c Level (95% Confidence Interval)	P
Any medication adjustment	3133	No adjustment	Reference	—
	592	Some medication adjustment	0.40 (0.29-0.52)	<.001
Insulin or an oral medication adjustment	3133	No adjustment	Reference	—
	45	Addition of insulin	0.71 (0.36-1.07)	<.001
	547	Adjustment to oral medication	0.38 (0.26-0.49)	<.001

<sup>a</sup>Separate regression models were fit for the 2 comparisons. The outcome for both was the change in HbA1c levels between baseline and the first subsequent measure after 120 days or more. Both models adjusted for age, sex, island, morbidity, years with diabetes, baseline HbA1c level, number of oral medications, and whether or not the patients were on insulin at the start of follow-up.

demonstrated in a large patient population using an electronic database.<sup>22</sup> Others note, however, that decisions should be patient centered, analyzing the clinical situation within its psychosocial context.<sup>23</sup> Lack of medication intensification may reflect issues not apparent in databases such as a choice to reassess the need for intensification at the next office visit, or after dietary efforts.

Pharmacists are in a unique position to monitor patient medication usage and potentially to intervene to encourage appropriate therapy.<sup>24</sup> Office-based clinical pharmacists have been suggested as having the ability in particular to collaboratively intensify therapy.<sup>25-28</sup> A meta-analysis in 2006, however, reported that only 8 of 18 studies showed improved medication adherence from interventions delivered by community pharmacists.<sup>29</sup> More recent studies have also reported mixed results.<sup>30-32</sup> The type and intensity of the intervention may substantially influence the effectiveness. A recent large study matched patients with diabetes in a controlled comparison. Pharmacists using timely information from a pharmacy benefit management company increased physicians' initiation rates of diabetes medications by 38%.<sup>24</sup> After the program ended, however, the intervention group quickly became similar to the control group.

Our study results have a number of limitations that need to be considered in interpreting the results. The study population constitutes members of a single health plan and results cannot be directly generalized to other settings. The study uses administrative and laboratory data, sources that do not include the reasons for medication additions or for maintaining the prescribed medications even with a clinically meaningful HbA1c increase. As a consequence, this study describes the pattern of care but lacks the detail to explore the underlying causes. A strength of the study is having longitudinal data and sufficiently complete follow-up to examine changes in HbA1c levels following medication adjustments. This study does document practice in a real-world setting and reflects a practice that would be of concern in other communities.

## Conclusion

The results reflect expectations in that medication changes were minimal in well managed patients, those with HbA1c levels of 7% or less, whereas changes became proportionally more frequent with higher HbA1c levels and greater increases in HbA1c levels. The response to a 1% or greater increase in HbA1c, however, was less than 1 patient in 4. Initiation rates of insulin were low even among patients with HbA1c levels of 9% or greater. Our study extends others in demonstrating inertia to making medication adjustments, and specifically in the face of recent, clinically significant increases in HbA1c levels. The results reinforce, however, that patients who make medication adjustments can obtain meaningful clinical benefit.

## Authors' Note

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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