

# Achieving Good Glycemic Control: Initiation of New Antihyperglycemic Therapies in Patients With Type 2 Diabetes From the Kaiser Permanente Northern California Diabetes Registry

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**Objective:** To compare the effectiveness of antihyperglycemic therapies in type 2 diabetic patients with poor glycemic control (baseline glycosylated hemoglobin [ $HbA_{1c}$ ] > 8%).

**Study Design:** Longitudinal (cohort) study.

**Methods:** Study patients were 4775 type 2 diabetic patients who initiated new antihyperglycemic therapies and maintained them for up to 1 year. The study setting was Kaiser Permanente Northern California Medical Group, an integrated, prepaid, healthcare delivery organization. Treatment regimens were 1 or more of the following: insulin, thiazolidinediones, sulfonylureas, biguanides (metformin), or other less frequently used options (including meglitinides or  $\alpha$ -glucosidase inhibitors).

**Results:** In this cohort, the mean  $HbA_{1c}$  was 9.9% when therapy was initiated. Within 1 year, there was a drop of 1.3 percentage points in the mean  $HbA_{1c}$  (to 8.6%), and 18% of new initiators achieved  $HbA_{1c}$  values of  $\leq 7\%$ . After adjusting for baseline clinical differences, the proportion of patients treated to goal was greatest among those receiving thiazolidinediones in combination (24.6%-25.7%) or a regimen of metformin and insulin (24.9%), while the least success was experienced by those receiving sulfonylureas alone (12.5%) or insulin-sulfonylureas regimens (10.9%). The probability of achieving the target goal was most strongly predicted by the level of glycemic control before initiation, but patient behaviors (eg, frequent self-monitoring, lower rates of missed appointments) also were strongly associated with greater levels of control.

**Conclusion:** Overall, therapy initiation resulted in an impressive population-level benefit. However, since most new initiators still had not achieved good control within 12 months, careful monitoring and prompt therapy intensification remain important.

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The importance of maintaining tight blood glucose control for the prevention of microvascular complications (eg, retinopathy, nephropathy) is well established.<sup>1,2</sup> For almost half of a century, insulin and sulfonylureas were the only treatment options for diabetes in the United States. In 1959, phenformin, a biguanide, was introduced in the US market but was removed in 1977 because of concerns regarding lactic acidosis.<sup>3</sup> Metformin (another biguanide), while available earlier in other countries, did not reach the US

market until 1995. In the last decade, 3 new therapeutic classes (alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides) have been introduced.<sup>4</sup> Although numerous randomized, placebo-controlled clinical trials have evaluated the efficacy of these medications alone or in combinations,<sup>5</sup> the relative effectiveness of the whole spectrum of pharmacologic options in nonexperimental settings has rarely been assessed. The American Diabetes Association (ADA) recommends treating diabetic patients to achieve a glycemic target of glycosylated hemoglobin ( $HbA_{1c}$ )  $\leq 7\%$ ,<sup>6</sup> but the ability of diabetes therapies to achieve this goal in usual practice is poorly understood. We studied 4775 type 2 diabetic patients with poor glycemic control ( $HbA_{1c}$  > 8%) who initiated new treatment regimens (index therapy) in the Kaiser Permanente Northern California Medical Group (Kaiser Permanente) during 1999-2000. We compared the proportions of patients who achieved good glycemic control ( $HbA_{1c}$   $\leq 7\%$ ) within 3-12 months after initiating the most commonly used therapies.

## RESEARCH METHODS

### Setting

Kaiser Permanente, an integrated, nonprofit, group-practice, prepaid healthcare delivery organization, provides comprehensive medical services to more than 3 million members (as of January 2000) throughout northern California, including the San Francisco Bay and Sacramento metropolitan areas, or ~25% to 30% of the region's population. Care is provided by approximately 4400 physicians of The Permanente Medical Group at 17 hospitals and 152 medical offices. The

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Kaiser Permanente members are predominantly employed or retired individuals and their families, and closely approximate the general population ethnically and socioeconomically except for the extreme tails of the income distribution.<sup>7-9</sup>

### Source Population

In 1993, Kaiser Permanente established the Kaiser Permanente Northern California Diabetes Registry. This registry included 116 344 diabetic patients on January 1, 1999; it has an estimated sensitivity of ~99% and a 2% false-positive rate. The registry is updated annually by identifying all health plan members with diabetes from automated databases for pharmacy, laboratory, hospitalization records, and outpatient diagnoses. The methods used in the Kaiser Permanente diabetes registry have been described previously.<sup>8,10-13</sup>

### Cohort Identification

We identified all diabetes registry members who initiated a new diabetes therapy between June 1, 1999, and May 31, 2000; had been diagnosed with diabetes for at least 1 year before initiation of this therapy; and had a full year of Kaiser membership with pharmacy benefits after initiation. As a group, individuals who initiated new diabetes therapies differed from those who maintained ongoing therapies in terms of glycemic control, disease severity, and patient characteristics and behaviors.<sup>14</sup> Thus, we relied on the “new user” design<sup>15</sup> that restricts the study cohort to individuals who initiated new therapies; we used only those glycemic outcomes that occurred after therapy initiation but before therapy switching or discontinuation, while controlling for patient characteristics present before initiation. By design, type 1 patients were not eligible because they would not switch therapeutic classes once established on insulin. We excluded diabetic patients with end-stage renal disease ( $n = 3177$ ) from our sampling frame because of this disease’s impact on insulin clearance (and thus glycemic control) and clearance of sulfonylureas, and because end-stage renal disease is a contraindication for metformin therapy.<sup>16</sup> All those without continuous health plan membership ( $n = 4752$ ) or without a drug benefit ( $n = 2574$ ) at any time during the study period were excluded to minimize misclassification of subjects who may have filled prescriptions in non-Kaiser pharmacies. Because a single-tiered pharmacy benefit was in place at the time of the study, the out-of-pocket costs were uniform across therapeutic classes regardless of whether medications were branded or generic. Twenty-seven percent ( $n = 23\,501$ ) of diabetic health plan members initiated new diabetes therapies between June 1, 1999, and May 31, 2000, after exclud-

ing those who were diagnosed with diabetes less than 12 months before initiating the new (index) therapy. Of these new users of therapy, 8333 had HbA<sub>1c</sub> measured both during the 12-month window before initiation and the 3- to 12-month period after initiation and before discontinuing or modifying the index therapy. Of these eligible new users, 4775 (57%) had poor glycemic control before initiation, at levels that were above Kaiser’s recommended action level (HbA<sub>1c</sub> > 8%). This group of 4775 poorly controlled new users of therapy formed the basis for this study and all analyses that follow.

### Pharmacotherapeutic Exposure

The exposures of interest were new prescriptions for the 12 most commonly prescribed monotherapy and combination regimens (index therapies): (1) sulfonylurea monotherapy, the reference category; (2) metformin monotherapy; (3) thiazolidinedione monotherapy; (4) insulin monotherapy; (5) metformin plus sulfonylurea; (6) metformin plus insulin; (7) sulfonylurea plus thiazolidinedione; (8) sulfonylurea plus insulin; (9) thiazolidinedione plus insulin; (10) metformin plus sulfonylurea plus insulin; (11) metformin plus sulfonylurea plus thiazolidinedione; and (12) “other” (meglitinides or  $\alpha$ -glucosidase inhibitors as monotherapy or as part of combination therapies). The exposure baseline date (index date) was the date on which the first prescription of the index therapy was dispensed. To ensure that patients were truly starting a new regimen and maintaining that index therapy, we required that there was (1) at least 1 refill after the index date and any time within the follow-up period for each medication in the index therapy; *and* (2) no evidence of utilization of the index therapy during the 12 months before the index date. These restrictions allowed us to minimize misclassification of patients as starting a combination therapy when they were in fact switching from a single therapeutic class to a different class (and thus may have overlapping prescriptions for more than 1 class during the transition).

We ended collection of our outcome (HbA<sub>1c</sub>) values at the first occurrence of any of the following: the end of the study (up to 12 months after initiation of therapy), discontinuation of the index therapy, or modification of the index therapy. Therapy modification included switching from the index therapy to another therapy, adding an additional therapy to the index therapy, or dropping 1 of the components included in the index combination therapy. The date of treatment discontinuation was calculated as the earliest date of the first supply of a new medication or, when medication was discontinued, the date when the last supply plus a 90-day grace period would be used up after the last recorded refill.

### Treatment Response

For each individual, we assessed whether good control ( $HbA_{1c} \leq 7\%$ ) was achieved during the 3- to 12-month window subsequent to the start of the index therapy, based on the last recorded  $HbA_{1c}$  value in this follow-up period. We did not utilize  $HbA_{1c}$  results from the first 3 months of the index therapy to allow for initial dose titration and physiologic adjustments to the new medication. For the new users who discontinued (230 out of 4775 or 5%) or modified (1951 out of 4775 or 41%) the index therapy within 12 months of its initiation, we restricted analysis to end points ( $HbA_{1c}$  values) collected *before* that change in therapy occurred. (In other words, we excluded  $HbA_{1c}$  values assayed after a new user discontinued or modified the index therapy.) Thus, only measures of glycemic control that could be most directly linked with the index therapy were used in analyses.  $HbA_{1c}$  levels were obtained from Kaiser's laboratory database, and all assays were conducted at Kaiser's centralized laboratory with high-performance liquid chromatography.

### Case-mix Adjustment

We previously observed that even among new users, there may be substantial variation in glycemic control, disease severity, and patient characteristics and behaviors, depending on the type of diabetes therapy that was initiated.<sup>14</sup> Such differences may confound crude statistical estimates. We therefore made case-mix adjustments to our statistical models for a wide range of covariates. These included age and sex, and the last previous  $HbA_{1c}$  measurement and diabetes regimen (including no medication taken) before initiation of the new therapy. Also included were the following covariates, assessed during the calendar year before index therapy year: number of outpatient visits, standard diabetes processes of care (at least 1 annual visit to a primary care physician, a dilated eye exam, and measurement of low-density lipoprotein cholesterol); type of primary care provider (endocrinologist vs other primary care provider); rate of missed scheduled outpatient appointments; prescription copayment amount; number of emergency room visits; number of ophthalmology exams; and frequency of self-monitoring of blood glucose (SMBG), based on glucose test strip utilization.<sup>8,13</sup>

For a subanalysis, we used additional covariate data captured by a self-administered questionnaire or a computer-assisted telephone interview in 1994-1997. Eighty-three percent ( $n = 77\,726$ ) of the 94 024 noninstitutionalized health plan members in the diabetes registry (as of 1995) responded to that survey, which asked about the daily number of insulin injections, use of exercise and diet as diabetes treatments, time since dia-

betes diagnosis, body mass index, smoking history, educational attainment, and self-identified race/ethnicity. Neighborhood-level socioeconomic status was assessed by geocoding each member's address, and linking the geocoded address to associated census-block group average annual per capita income and proportion of residents in a working-class profession. To assess whether model estimates based on the full cohort were robust, we compared them with estimates based on subanalyses of survey responders, with further covariate adjustment. In these subanalyses, we included time since diabetes diagnosis, body mass index, smoking history, educational attainment, and self-identified race/ethnicity (58.0% non-Latino white, 12.4% African American, 11.1% Asian, 9.1% Latino, 0.9% Pacific Islander, 0.7% Native American, 0.4% other, and 7.5% multiethnic), in addition to all the covariates included in the full model (see above).

### Analytic Methods

In addition to a crude (unadjusted) assessment, we used multivariate logistic regression models to assess the probability of reaching glycemic control after initiating new therapies. All variables except for 1 (prebaseline  $HbA_{1c}$ ) were specified in their categorical form to conform to model linearity assumptions. Because of the strong, linear relationship between prior  $HbA_{1c}$  values and glycemic control in the follow-up, we included prebaseline  $HbA_{1c}$  in its continuous form. Using data from the subset that returned a detailed health survey during 1994-1997, we conducted additional analyses to assess whether further adjustment for self-reported attributes (time since diabetes diagnosis, body mass index, smoking history, educational attainment, and self-identified race/ethnicity) added important information. Rather than rely on adjusted odds ratios, which would yield biased estimators of effect given the common dependent variables,<sup>17</sup> we derived the adjusted (conditional) probability of achieving good control from the logistic regression model.

## RESULTS

### Study Subject Characteristics

This cohort of poorly controlled new users (Table 1) was typical of the general diabetes patient population in terms of age, sex, and use of health services. Most subjects were cared for by a personal primary care provider, had a relatively low pharmacy copayment, and practiced SMBG. This study cohort had much poorer glycemic control (mean  $HbA_{1c} = 9.9\%$ ; SD = 1.5%) than that observed both in the source population of diabetic patients and in all new users (not just the subjects

with poorly controlled diabetes selected for our cohort). This higher mean HbA<sub>1c</sub> was expected given that we excluded those whose HbA<sub>1c</sub> measurements were below 8% and selected exclusively new initiators (who most likely failed to respond to previous therapy). As a comparison, during this time period, 30.2% of the general Kaiser diabetic population had HbA<sub>1c</sub> ≤ 7% (mean HbA<sub>1c</sub> = 8.2%; SD = 1.9%), and 19.1% of all new users had HbA<sub>1c</sub> ≤ 7% (mean baseline HbA<sub>1c</sub> = 8.8%; SD = 1.9%).

Most new users were treated with monotherapies (52.6%) or no medication (11.9%) before initiation of the new therapy; the majority (69.0%) of this new-user cohort initiated combination therapies (Table 2). The most common therapy before initiation was sulfonylurea monotherapy (41.1%), while the most commonly initiated therapy was sulfonylurea plus metformin (38.7%). Ninety-one percent of cohort subjects treated with 1 oral agent transitioned into combination therapies with 2 or more oral agents. Similarly, 98.3% of the patients utilizing insulin monotherapy added an oral agent to their insulin regimen rather than discontinuing insulin completely for oral agents. Most patients who originally were taking an oral agent plus insulin were switched to other combination therapies including insulin, or dropped oral agents and relied on insulin monotherapy; however, relatively few discontinued the use of insulin.

**Proportion Achieving Good Control**

Among patients with poorly controlled diabetes (HbA<sub>1c</sub> > 8%) who initiated new therapies, 18.4% (95% confidence interval [CI] = 17.3%, 19.4%) achieved good glycemic control (HbA<sub>1c</sub> ≤ 7%) during the 3 to 12 months after initiation and maintenance of their index therapy. Their mean HbA<sub>1c</sub> went from 9.9% (SD = 1.5%) before initiation to 8.6% (SD = 1.7%) after initiation, a drop of ~1.3 percentage points in the sample means. Post-initiation levels of glycemic control brought these poorly controlled new users closer to the overall source population mean (HbA<sub>1c</sub> = 8.2%; SD = 1.9%); 30.2% of the source population had HbA<sub>1c</sub> values of ≤7%. In this cohort of

**Table 1.** Subject Characteristics Before Initiation of New Diabetes Therapy (n = 4775)\*

Characteristic	Value
Age, mean ± SD	60.0 y (11.5 y)
Female	49.2%
HbA <sub>1c</sub> , mean (SD)	9.9% (1.5%)
LDL cholesterol, mean (SD)	122.0 mg/dL (37.1 mg/dL)
Hypertension	77.3%
Has personal primary care provider	87.6%
Pharmacy copayment ≤ \$5	71.8%
Number of times per day of SMBG, mean (SD)	0.9 (1.0)
Number of primary care visits in prior year, mean (SD)	2.0 (2.0)
Proportion of scheduled outpatient visits missed in prior year, mean (SD)	0.1 (0.2)

\*HbA<sub>1c</sub> indicates glycosylated hemoglobin; LDL, low-density lipoprotein; SMBG, self-monitoring of blood glucose.

**Table 2.** Diabetes Pharmacotherapy Utilization Before and After Initiating New Diabetes Therapies (n = 4775)

Diabetes Therapy	Percentage	
	Preinitiation	Postinitiation
No medication	11.9	0
Sulfonylureas	41.1	15.0
Metformin	1.7	5.1
Thiazolidinediones	0.2	0.2
Insulin	9.6	7.5
Sulfonylureas + metformin	17.8	38.7
Sulfonylureas + thiazolidinediones	0.7	2.2
Sulfonylureas + insulin	4.3	4.7
Sulfonylureas + metformin + thiazolidinediones	0.8	4.5
Sulfonylureas + metformin + insulin	3.1	6.0
Metformin + insulin	2.9	9.7
Thiazolidinediones + insulin	1.7	2.6
All others*	4.3	3.8

\*Monotherapy or combination therapy with meglitinides or α-glucosidase inhibitors.

4775 poorly controlled new users, 41% of the cohort had the index therapy modified within 1 year after initiation, and 5% had discontinued the index therapy.

In unadjusted analyses, patients initiating sulfonylurea, metformin, or thiazolidinedione monotherapy or combination therapy with sulfonylurea plus thiazolidinedione were the most successful at achieving good glycemic control (Table 3). Because the choice of initial therapy should be dictated by a patient's condition, we assessed differences in the probability of achieving good control across the various diabetes regimens after adjusting for patients' prior glycemic control in addition to other relevant attributes. These case mix-adjusted logistic models included age, sex, pre-initiation HbA<sub>1c</sub> value, previous diabetes therapy, primary care physician specialty, outpatient visit attendance, frequency of SMBG (based on test strip consumption), amount of drug benefit copayment, number of annual outpatient visits, antihypertensive and antilipemic therapies, and indicators for emergency room visits and dilated eye exams in the prior year. Sulfonylurea was specified as the reference group index therapy.

The effect of adjustment was substantial and consistent with prescribing patterns. The 2 first-line therapies (sulfonylurea and metformin), prescribed commonly to patients with milder diabetes, were strongly associated with achieving good control in unadjusted models. However, their performance was greatly attenuated after adjusting for prior glycemic levels and disease severity. Similarly, most of the combination therapies, which are presumably reserved for more advanced diabetes, had relatively low unadjusted but higher adjusted probability of achieving good control. This pattern of "confounding by indication"<sup>18</sup> and the magnitude of the effect illustrate the importance of careful model adjustment when assessing pharmacotherapeutic effectiveness.

Different index therapies produced different levels of glycemic control. Among subjects initiating monotherapy, only metformin users had a significantly greater adjusted probability of achieving good control than users of the reference therapy, sulfonylurea (17% vs 12%). Initiators of thiazolidinedione monotherapy also were more likely to achieve good control (32%); however, this estimate was not statistically significant, probably due to insufficient power because thiazolidinedione is rarely prescribed as a monotherapy. Among subjects initiating combination therapy, users of the metformin-plus-insulin combination and all combinations including thiazolidinedione were significantly more likely (often exceeding a 2-fold increase) to achieve good glycemic control compared with users of sulfonylurea monotherapy.

Behavioral factors also were predictive of achieving good glycemic control. More frequent SMBG and satisfactory appointment-keeping behavior (low rate of missing scheduled outpatient appointments) both were associated with a significant and graded increase in good control after adjusting for initiated therapies and all of the covariates in the full model discussed above. The adjusted proportions of subjects (95% CI) achieving good control ranged from 13.4% (reference, 11.3%, 15.8%) with no practice of SMBG, 15.5% (14.0%, 17.2%;  $P = .13$ ) with some but less than daily practice of SMBG, and 18.8% (16.9%, 20.9%;  $P = .0008$ ) with daily SMBG practice. The likelihood of achieving good control was greatest among those missing fewer scheduled outpatient appointments. In adjusted models, 17.0% (15.8%, 18.2%) of those who missed fewer than 30% of their outpatient appointments achieved good control compared with 11.2% (8.7%, 14.2%;  $P = .0009$ ) of those who missed 30% or more of their outpatient appointments.

A further analysis among the subset of the 67% ( $n = 3190$ ) of the study cohort who responded to a previous health survey (1994-1997) allowed us to further adjust for self-reported case mix and severity-indicating variables including time since diabetes diagnosis, body mass index, smoking history, educational attainment, and self-identified race/ethnicity. This subanalysis resulted in no substantive differences and yielded the same conclusions suggested by analysis of the full cohort.

## DISCUSSION

Of subjects treated with the 11 most commonly used therapeutic regimens, those who received the insulin sensitizers (thiazolidinediones and metformin) were most likely to achieve good control, particularly when these agents were used in combination with insulin or another oral agent. Treatments that were significantly more effective than the first-line therapy, sulfonylurea monotherapy (12.46% achieved good control), were metformin monotherapy (17.1% achieved good control;  $P = .04$ ), sulfonylurea plus thiazolidinedione (24.6% achieved good control;  $P = .002$ ), metformin plus insulin (24.9% achieved good control;  $P = .0008$ ), thiazolidinedione plus insulin (25.7% achieved good control;  $P = .007$ ), and the triple combination thiazolidinedione plus metformin plus sulfonylurea (25.1% achieved good control;  $P = .0007$ ). No therapy was significantly less effective than sulfonylurea monotherapy.

Despite the impressive response to initiated therapy, 82% of the new users failed to achieve good control and 54% percent still had HbA<sub>1c</sub> measurements that exceed-

**Table 3.** Probability of Achieving Good Glycemic Control (HbA<sub>1c</sub> ≤7%) Within 3 to 12 Months After Initiation of a New Diabetes Therapy and Adjusted Odds Ratios Comparing Initiated Therapies\*

Diabetes Therapy	No. of Patients	Crude (Unadjusted) Percentage (95% CI)	Adjusted Percentage <sup>†</sup> (Conditional Probability) (95% CI)	Adjusted Odds Ratios <sup>†</sup> (95% CI)	P From Adjusted Model <sup>†</sup>
Sulfonylureas	617	23.60 (20.49, 26.71)	12.46 (9.86, 15.62)	1.00	Reference
Metformin	241	26.56 (20.98, 32.13)	17.10 (12.88, 22.36)	1.45 (1.01, 2.09)	.0449
Thiazolidinedione	9	22.22 (0.00, 49.38)	32.26 (6.40, 76.84)	3.35 (0.48, 23.56)	.2249
Insulin	359	15.04 (11.34, 18.74)	16.57 (12.26, 22.02)	1.40 (0.91, 2.14)	.1275
Sulfonylureas + metformin	1848	18.56 (16.79, 20.33)	14.61 (12.43, 17.09)	1.20 (0.86, 1.68)	.2768
Sulfonylureas + thiazolidinediones	106	28.30 (19.73, 36.88)	24.61 (17.18, 33.93)	2.30 (1.35, 3.90)	.0021
Sulfonylureas + insulin	224	10.71 (6.66, 14.76)	10.87 (7.24, 16.02)	0.86 (0.54, 1.46)	.5697
Sulfonylureas + metformin + thiazolidinediones	214	18.22 (13.05, 24.06)	25.13 (18.06, 33.83)	2.36 (1.44, 3.87)	.0007
Sulfonylureas + metformin + insulin	287	12.89 (9.01, 16.77)	16.95 (12.00, 23.40)	1.43 (0.88, 2.33)	.1456
Metformin + insulin	465	15.05 (11.8, 18.3)	24.86 (18.54, 32.47)	2.33 (1.42, 3.80)	.0008
Thiazolidinediones + insulin	125	16.80 (10.25, 23.35)	25.65 (16.41, 37.74)	2.42 (1.27, 4.64)	.0074
Other <sup>§</sup>	181	12.71 (7.86, 17.56)	16.55 (11.10, 23.94)	1.39 (0.81, 2.39)	.2270

\*CI indicates confidence interval; HbA<sub>1c</sub> glycosylated hemoglobin.

<sup>†</sup>Adjusted for sex, age, baseline HbA<sub>1c</sub>, prebaseline therapy, frequency of self-monitoring of blood glucose, specialty of primary care physician, outpatient primary care utilization and appointment-keeping behavior, pharmacy copayment amount, and eye examination and emergency room visits in the past year.

<sup>‡</sup>Relative to reference.

<sup>§</sup>Monotherapy or combination therapy with meglitinides or  $\alpha$ -glucosidase inhibitors.

ed 8% (the level at which ADA recommends action) 3 to 12 months after initiation, and before subsequent therapy changes. This suggests the importance of intensive follow-up after initiating new therapy and prompt therapy intensification when needed. Forty percent of this new-user cohort had additional therapy modifications within the year after therapy initiation, suggesting that providers are tracking therapy response and taking rapid action. Additionally, behavioral factors, including SMBG frequency and outpatient appointment attendance, were strongly predictive of good control.

Our study, one of the few assessments of real-world effectiveness, compared all currently available diabetes pharmacotherapies within a single population. In this observational study, patients did not achieve the level of control reported in randomized clinical trials. However, it is important to note that our study stipulated poor baseline control as an eligibility criterion. In the United Kingdom Prospective Diabetes Study (UKPDS), a randomized, controlled trial (RCT) with arms including intensive regimens of behavioral, pharmacological, and diet therapy, ~50% (47%-52% for any medication) of patients randomized to either insulin or sulfonylurea monotherapy maintained good

control after 3 years, but the proportion declined progressively to 20% to 28% after 9 years.<sup>19</sup> It is unclear how much of the efficacy in the UKPDS was attributable to the additional clinical attention common in clinical trials. A UKPDS substudy of patients allocated to treatment with sulfonylurea monotherapy reported that inadequacy of this therapy contributed to the progressive failure; 53% required additional insulin therapy within 6 years of follow-up.<sup>20</sup>

Randomized, controlled trials are considered the gold standard for evidence of efficacy, but they have limitations. These trials include highly selected populations receiving special clinical attention and usually evaluate a single medication rather than multiple medication therapies.<sup>21,22</sup> Although these are necessary constraints in experimental settings, they limit generalizability.<sup>23</sup> Moreover, low levels of medication adherence may explain why the effectiveness observed in clinical practice<sup>24</sup> usually falls short of the efficacy demonstrated in RCTs. For this reason, there is a growing skepticism regarding RCT results, creating a barrier to early adoption of new evidence-based recommendations.<sup>25</sup> Thus, real-world effectiveness studies provide important complementary information.<sup>26,27</sup>

The observed proportion of patients achieving good glycemic control is lower than the proportion achieving the recommended level of control for other chronic conditions (eg, hypertension, hyperlipidemia). Estimates of the proportion of hypertensive patients who achieved well-controlled blood pressure ( $\leq 140/90$ ) ranged from 27% to 61% (27% in the US National Health and Nutrition Examination Survey III, 1991-1994; 35% in the New York managed care sample, 1998<sup>28</sup>; 61% in the metropolitan New York City sample, 1999<sup>29</sup>), although a rate of 74% has been achieved in RCTs.<sup>30</sup> Estimates of good lipid control (low-density lipoprotein cholesterol  $\leq 100$  mg/dL) range from 41.7%<sup>31</sup> to 88.5%.<sup>32</sup> This suggests the currently available pharmacotherapies for hypertension and dyslipidemia may have greater relative effectiveness than antihypertensive agents.

Previous studies have shown that initiation of new diabetes therapies (switching or augmenting) occurs frequently, perhaps driven by the need for intensification of therapy.<sup>26</sup> In this study population, ~27% of the diabetic patients initiated new therapy regimens during the 1-year observation period. In the cohort we studied (new users with poorly controlled type 2 diabetes), 5% discontinued therapy and 41% modified therapy (switched or augmented the index therapy) within 12 months. The UKPDS demonstrated that diabetes is a progressive disorder, requiring a stepwise therapy intensification, with transitions from diet to monotherapy, to combination therapy, and eventually to insulin.<sup>19</sup> UKPDS findings also suggested that most patients fail to respond to sulfonylurea therapy as beta cell dysfunction increases, and suggested the need to add insulin or other therapies long before maximal doses become inadequate.<sup>20</sup> We observed a dramatic shift from monotherapy-dominated regimens used in the prebaseline period to the use of combination therapies. This trend toward diabetes polypharmacy, particularly with inclusion of insulin sensitizers to address insulin resistance, has been noted in other populations.<sup>4,33</sup>

Some limitations are worth noting. We were unable to assess differences in effectiveness among patients who had not completed a HbA<sub>1c</sub> test during the 3- to 12-month window after initiation. Among subjects who discontinued the initiated therapy within 12 months, we only included measures of glycemic control assayed before the point of therapy modification or discontinuation. Thus, this was not an intent-to-treat analysis that included all initiators. Therefore, our study slightly underestimated the proportion of subjects failing to achieve control relative to a cohort that would have included the ~5% of subjects who discontinued their index therapies before having a

HbA<sub>1c</sub> test. The mean post-initiation HbA<sub>1c</sub> value would have been slightly higher (8.7% rather than 8.6%) if we had included those few subjects who discontinued therapy before having a post-initiation HbA<sub>1c</sub> test. The percentage failing to achieve good control observed in this study thus may be viewed as conservative, further reinforcing the public health message suggesting the importance of intensive post-initiation follow-up. Additionally, we were unable to assess adherence to diet and exercise recommendations, both of which could play a role in achieving glycemic goals.

Thiazolidinedione use was low (9.5% of our new users) during the study observation period, but has increased steadily since its introduction to the Kaiser formulary in April 1997. This low usage was not because of a patient financial barrier associated with branded therapies. All patients included in this study had single-tier drug benefits; thus, there was no out-of-pocket cost difference between initiating therapy with one versus another of the therapeutic classes.

Between-therapy comparisons of the proportions achieving good glycemic control are not interpretable as causal effects of therapy, as in the case of clinical trial results. We assumed that observed therapy initiations occurred for a variety of reasons, including (1) the provider decided to prescribe a new therapy because of low effectiveness, side effects, or lack of medication-taking compliance with the preceding therapy; or (2) the patient discontinued the preceding therapy of his or her own accord. We were unable to distinguish between these causes. Case-mix differences due to association between diabetes severity and choice of treatment distort findings (confounding by indication<sup>34</sup>), so that more intense therapy is associated with poorer glycemic control. Although controlling for pre-initiation HbA<sub>1c</sub> values, previous therapy, and duration of diabetes did alter our findings, in some cases dramatically, additional residual confounding was expected. Nonetheless, both unadjusted and adjusted estimates of real-world effectiveness associated with pharmacotherapy in a clinical setting provide an important benchmark for evaluation, given the daunting array of therapies and their combinations available for patients with diabetes.

Several unique strengths of this study are worth mentioning. These findings come from a large source population (more than 3 million patients), which is almost one third of the population of Northern California. The rich data available in the Kaiser electronic records facilitated statistical adjustment for confounding variables usually unavailable in claims databases. Levels of control in our diabetes population

are like those in other published studies, which likely makes our findings generalizable to insured individuals with diabetes. The proportion in good control in the whole Kaiser diabetes population (30%) is consistent with that reported by other studies: 32% of patients were reported in good control in the Type 2 Diabetes Patient Outcomes Research Team study,<sup>35</sup> and 26.5% of insulin-treated and 37.7% of oral agent-treated patients were reported in good control in the US National Health and Nutrition Examination Survey III.<sup>36</sup>

If, as we observed, the majority of patients need to achieve better control, this suggests that new pharmacotherapeutic modalities with greater effectiveness are needed, but also points out the existence of provider- and patient-related barriers to achieving control. A multifactorial approach that integrates pharmacologic options with patient self-management, clinical initiative, and social support has been shown to provide optimum management of diabetes.<sup>37</sup> We found evidence of the importance of patient behaviors: significantly better glycemic control was associated with frequent SMBG. Previous studies in this same population indicated that this self-management practice was underutilized,<sup>13</sup> despite being associated with better glucose control.<sup>8</sup> We also noted that frequently missed medical appointments were associated with poorer control in this and a previous study in this population,<sup>11</sup> highlighting the importance of continuity of care and patient adherence factors. The efficacy of behavioral interventions focusing on diet and exercise for patients with diabetes has been demonstrated previously,<sup>38,39,40-43</sup> although the effectiveness is frequently limited by low levels of adherence. Exploration of novel behavioral approaches (eg, stress management<sup>44</sup>) also may prove useful.

Clinical inertia (ie, failure of healthcare providers to initiate or intensify therapy when indicated) has been identified as a significant obstacle to effective disease management.<sup>25,45,46</sup> A previous study based on a population with a similar form of integrated care<sup>47</sup> showed that before new therapies were initiated, levels of HbA<sub>1c</sub> were typically closer to 9% rather than 8%. We had similar findings. After expanding the analysis to the whole diabetic population (not just the new users with poor control we selected for this study), the mean baseline HbA<sub>1c</sub> was 8.7% before initiating new therapy. Earlier initiation of new therapy (ie, before HbA<sub>1c</sub> greatly exceeded 7%) likely would have resulted in a larger proportion of patients being brought into good control.

Before 2003, the ADA guidelines stipulated an action level (HbA<sub>1c</sub> = 8%), above which therapy intensification was recommended. This action level was 1 percentage point higher than the glycemic target (HbA<sub>1c</sub> = 7%) also

recommended by the ADA. This gap between target and action level created a gray zone that could have potentially reduced the clinical attention given to patients with HbA<sub>1c</sub> between 7% and 8%. The elimination of the action level from the ADA recommendations (2003 and after) may stimulate prompter intensification of therapy for patients with borderline HbA<sub>1c</sub> (7%-8%). Moreover, in addition to specifying the glycemic target of HbA<sub>1c</sub> ≤ 7%, ADA now further recommends that even more stringent goals (<6%) should be considered on an individual basis, given that epidemiologic evidence has failed to detect a limit below which further lowering doesn't confer clinical benefits. The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology recommend a goal of "HbA<sub>1c</sub> level of 6.5% or less" in their Medical Guidelines for the Management of Diabetes Mellitus: The AACE System of Intensive Diabetes Self-Management. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study currently is evaluating the risks and benefits of such near-normalization of blood sugars.

It is worth noting that, since the time of this study, the proportion of patients achieving good glycemic control has increased steadily in the source population for this study (Kaiser Permanente Northern California Diabetes Registry) from around 30% during the study (1999-2000) to more than 50% in 2004 (unpublished data). This favorable trend is likely attributable to more aggressive therapy intensification and increased use of combination therapy and insulin-sensitizing agents.

## CONCLUSIONS

Among patients with poorly controlled diabetes, initiation of combination therapies that included thiazolidinedione or a regimen of metformin plus insulin resulted in the highest proportion of patients achieving good glycemic control, while monotherapy sulfonylureas resulted in the lowest proportion. Patient self-management, particularly SMBG and appointment-keeping behavior, also played an important role. However, the majority of patients still had suboptimal glycemic control 3 to 12 months after initiating even the most effective treatment options. This suggests the need for increased vigilance among providers to promptly identify failures to achieve good control after initiating new therapies and aggressive stepwise therapy intensification when initial treatments fail.<sup>47,48</sup>

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