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# 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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## Abstract

**Objective—**We sought to compare the effectiveness of antihyperglycemic therapies for lowering blood glucose in type 2 diabetic patients with poor glycemic control ($HbA_{1c}$>8%).

**Study Design—**Longitudinal (cohort) study of 4,775 type 2 diabetic patients with baseline $HbA_{1c}$>8% who initiated (1999-2000) new antihyperglycemic therapies and maintained them for up to one year. The study setting was Kaiser Permanente Northern California Medical Group, an integrated, prepaid health care delivery organization. Treatment regimens consisted of any one or a combination of the following prescribed classes of anti-hyperglycemic therapy: insulin, thiazolidinediones, sulfonylureas, biguanides (metformin) or "other" less frequently used options (including meglitinides or alpha-glucosidase inhibitors).

**Methods—**We assessed the proportion of patients who successfully achieved good glycemic control ($HbA_{1c}$ ≤7%) during the follow-up period 3-12 months after initiating and maintaining a new regimen, stratified by therapy and adjusted for pre-initiation $HbA_{1c}$, prior therapy, and demographic, behavioral, clinical, quality of care and provider characteristics.

**Results—**In this new user cohort with poorly-controlled diabetes, the mean $HbA_{1c}$ was 9.9% at the time of initiation of therapy. Within one year, there was a 1.3 point drop in the mean $HbA_{1c}$ (to 8.6%), and 18% of new initiators achieved $HbA_{1c}$ ≤7%. After adjusting for baseline clinical differences, the proportion of patients who were treated to glycemic target 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 target was most strongly predicted by level of glycemic control prior to initiation, but patient behaviors, such as frequent self-monitoring of blood glucose and lower rates of missed appointments were also strongly associated with greater levels of control.

**Conclusions—**Findings suggest the importance of combination therapies including insulin-sensitizing agents and self-management behaviors in helping poorly controlled patients achieve good glycemic control. Overall, therapy initiation resulted in an impressive population-level benefit. However, since most new initiators had still not achieved good control within 12 months, careful follow-up monitoring and prompt therapy intensification remain important.

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### Keywords

treatment effectiveness; treating to target; glycemic control; antihyperglycemic agents

## Introduction

The importance of maintaining tight blood glucose control for the prevention of microvascular complications, such as retinopathy and nephropathy, is well-established.[1,2] For almost half of a century, insulin and sulfonylureas were the only treatment options for diabetes in the U.S. In 1959, Phenformin, a biguanide, was introduced in the United States market but was removed in 1977 because of concerns regarding lactic acidosis.[3] Metformin (another biguanide), while available earlier in other countries, did not reach the U.S. market until 1995. In the last decade, three new therapeutic classes (alpha-glucosidase inhibitors, thiazolidinediones and meglitinides) have been introduced.[4] While numerous randomized, placebo-controlled clinical trials have evaluated the *efficacy* of these medications alone or in combinations,[5] the relative *effectiveness* of the whole spectrum of pharmacologic options in non-experimental settings has rarely been assessed. The American Diabetes Association (ADA) recommends treating diabetic patients to achieve a glycemic target of Hemoglobin $A_{1c}$ ($HbA_{1c}$) ≤ 7%[6], but the ability of diabetes therapies to achieve this goal in usual practice is poorly understood. We studied 4,775 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 proportion of patients that achieved good glycemic control ($HbA_{1c}$ ≤7%) within 3-12 months after initiating the most commonly used therapies.

## Research Methods

### Setting

Kaiser Permanente, an integrated, non-profit, group-practice, prepaid health care delivery organization, provides comprehensive medical services to over 3.0 million members (as of January, 2000) throughout Northern California (including the San Francisco Bay and Sacramento metropolitan areas), or ~25-30% of the region's population. Care is provided by approximately 4,400 physicians of *The Permanente Medical Group* at 17 hospitals and 152 medical offices. The Kaiser Permanente members are predominantly employed or retired individuals and their families, and closely approximates the general population ethnically and socioeconomically except for the extreme tails of the income distribution.[7-9]

### Source population

In 1993, Kaiser Permanente established the *Kaiser Permanente Northern California Diabetes Registry.* The Kaiser Permanente diabetes registry included 116,344 diabetic patients on January 1, 1999; the registry 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.[8,10-13]

### Cohort identification

We identified all diabetes registry members who initiated a new diabetes therapy during the period between June 1, 1999 and May 31, 2000, had been diagnosed with diabetes for at least one year prior to initiation, 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, patient characteristics and behaviors.[14] Thus we relied on the "new user" type of design[15] restricting the study cohort to individuals who initiated new therapies; we used only glycemic outcomes occurring after initiation but before therapy switching or discontinuation, while controlling for characteristics present prior to initiation. By design, type 1 patients were not eligible because they would not switch therapeutic classes once established on insulin. We excluded diabetic patients (n=3,177) with end-stage renal disease (ESRD) from our sampling frame because of ESRD's impact on insulin clearance (and thus glycemic control), clearance of sulfonylureas, and contraindication for metformin.[16] All those without continuous health plan membership (n=4,752) or lacking a drug benefit (n=2,574) 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 brand 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 excluding those who were diagnosed with diabetes less than 12 months prior to initiating the new (index) therapy. Of these new users, 8,333 had $HbA_{1c}$ measured both during the 12 month window prior to initiation and the 3-12 month period following initiation and before discontinuing or modifying the index therapy. Of these eligible new users, 4,775 (57%) had poor glycemic control prior to initiation, at levels which were above Kaiser's recommended action level ($HbA_{1c}$> 8%). This group of 4,775 poorly controlled new users is the basis for this study and all analyses that follow below.

## Pharmacotherapeutic exposure

The exposures of interest were new prescriptions for the twelve most commonly prescribed monotherapy and combination regimens (index therapies): 1) sulfyonureas monotherapy ("SU"), the reference category, 2) Metformin monotherapy ("MET"), 3) thiazolidinedione monotherapy ("TZD"), 4) insulin monotherapy ("INS"), 5) MET+SU, 6) MET+INS, 7) SU +TZD, 8) SU+INS, 9) TZD+INS, 10) MET+SU+INS, 11) MET+SU+TZD, and 12) "other" (Meglitinides or Alpha-glucosidase inhibitors as mono- or part of combo 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 one refill after the index date and anytime within the data follow-up period for each medication in the index therapy; and 2) no evidence of utilization of the index therapy during the 12 months prior to the index date. These restrictions allowed us to minimize misclassification of patients (as starting a combination therapy) who were in fact switching from a single therapeutic class to a different class (and thus may have overlapping prescriptions for more than one class during the transition). We ended collection of our outcome ($HbA_{1c}$) at the first occurrence of any of the following: the end-of-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, or adding an additional therapy to the index therapy, or dropping one of the components included in the index combination therapy. The date of treatment discontinuation was calculated as the earliest date of the first fill of a new medication or, when medication is discontinued, the date when the "days' 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, as defined by $HbA_{1c} \leq 7\%$, was achieved during the 3-12 month window subsequent to the start of the index therapy using

the last recorded $HbA_{1c}$ in this follow-up period. We did not utilize the $HbA_{1c}$ results during first three-month period following the start 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 after the initiation of the index therapy, we restricted analysis to endpoints ($HbA_{1c}$) collected before that change in therapy occurred. Thus we exclude $HbA_{1c}$ measurements assayed after a new user discontinued their index therapy 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 using high-performance liquid chromatography.

## Case-mix adjustment

We have previously observed that even among new users, there may be substantial variation by initiated diabetes therapy in glycemic control, disease severity, patient characteristics and behaviors.[14] 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; the last previous $HbA_{1c}$ and diabetes regimen (including "no medication taken") prior to initiation of the new therapy. Also included were the following covariates assessed during the calendar year prior to index therapy year: number of outpatient visits, standard diabetes processes of care (occurrence of at least one annual PCP visit, dilated eye exam and LDL-cholesterol test), primary care provider type (endocrinologist vs. other primary care provider), rate of missed scheduled outpatient appointments, prescription co-payment amount, number of emergency room visits, number of ophthalmology exams, and self-monitoring of blood glucose (SMBG) frequency (based on glucose test strip utilization.[8,13]).

For a sub-analysis, we used additional covariate data that was captured by a self-administered questionnaire or computer-assisted telephone interview conducted in 1994-1997. Eighty-three percent (n = 77,726) of the 94,024 non-institutionalized health plan members in the Registry (as of 1995) responded to that survey which asked about daily number of insulin injections, use of exercise and diet as diabetes treatments, time since diabetes 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 to associated census block group average annual per capita income and proportion in a working class profession. To assess whether model estimates based on the full cohort were robust, we compared them to estimates based on sub-analyses in survey responders with further covariate adjustment. In these sub-analysis 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% multi-ethnic), 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 one (pre-baseline $HbA_{1c}$) were specified in their categorical form to conform to model linearity assumptions. Because of the strong, linear relationship between prior $HbA_{1c}$ and glycemic control in the follow-up, we included pre-baseline $HbA_{1c}$ 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[17], we derived the adjusted (conditional) probability of achieving good control from the logistic regression model (see Appendix for algorithm).

## Results

### Study subject characteristics

This cohort of poorly-controlled, new users (Table l) was not atypical 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 co-payment, and practiced self-monitoring of blood glucose (SMBG). This study cohort had much poorer glycemic control ($HbA_{1c}$ = 9.9; SD=1.5) than the background levels in the source population of diabetic patients and in all new users (not just poorly-controlled subjects selected for our cohort). This higher mean $HbA_{1c}$ is expected given we excluded those with $HbA_{1c}$ below 8% and selected exclusively new initiators (who most likely failed previous therapy). As a comparison, during this time period, 30.2% of the general Kaiser diabetic population had $HbA_{1c}$ ≤7% (mean $HbA_{1c}$ = 8.2; SD=1.9) and 19.1% of all new users had $HbA_{1c}$ ≤7% (mean baseline $HbA_{1c}$ = 8.8; SD = 1.9).

Most new users were treated with monotherapies (52.6%) or no medication (11.9%) prior to initiation; the majority (69.0%) of this new user cohort initiated combination therapies (Table 2). The most common therapy prior to initiation was SU monotherapy (41.1%), while the most commonly initiated therapy was SU+MET combination therapy (38.7%). Ninety-one percent of cohort subjects treated with monotherapy oral agents transitioned onto 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 switching off of insulin completely (i.e., onto oral agents only). Most patients who were originally on oral agent plus insulin combinations 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 poorly controlled diabetic patients ($HbA_{1c}$ >8%) who initiated new therapies, 18.4% (95% C.I.: 17.3-19.4) achieved good glycemic control ($HbA_{1c}$≤7%) during the 3-12 months following initiation and maintenance of their index therapy. Their mean $HbA_{1c}$ went from 9.9 (SD = 1.5) prior to initiation to 8.6 (SD=1.7) after initiation, an ~1.3 point drop in the sample means. Post-initiation levels of glycemic control brought these poorly controlled new users closer to the overall source population mean ($HbA_{1c}$ = 8.2; SD = 1.9); 30.2% of the source population had $HbA_{1c}$ ≤7%. In this cohort of 4,775 poorly-controlled new users, 41% of the cohort had modified the index therapy within one year after initiation and 5% had discontinued the index therapy.

In unadjusted analyses, patients initiating SU, MET, and TZD monotherapy and SU+TZD combination were the most successful at achieving good glycemic control (Table 3). Because the choice of initiated therapy should be indicated 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 $HbA_{1c}$, previous diabetes therapy, primary care physician specialty, outpatient visit attendance, frequency of self-monitoring of blood glucose (based on test strip consumption), drug

benefit co-payment amount, number of annual outpatient visits, antihypertensive and antilipemic therapies, and indicators for emergency room visits and dilated eye exams in the prior year. SU was specified as the reference group index therapy.

The effect of adjustment was substantial and consistent with prescribing patterns. The two first line therapies (SU and MET), prescribed commonly to patients with milder diabetes, had high levels of 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"[18] and the magnitude of the effect illustrates the importance of careful model adjustment for assessing pharmacotherapeutic effectiveness.

Achieving good control varied by index therapy. Of the monotherapies, only initiators of MET monotherapy had significantly greater adjusted probability of achieving achieving good control than the reference group, SU initiators (17% vs. 12%). TZD monotherapy initiators also had elevated adjusted probability of achieving good control (32%), however this estimate was not statistically significant, likely due to insufficient power since TZD is rarely prescribed as a monotherapy. Of the combination therapies, initiators of the MET +INS combination and all combinations including TZD as one of the components had significantly higher adjusted probability (often exceeding two-fold increase) of achieving good glycemic control relative to initiators of SU monotherapy.

Behavioral factors also were predictive of achieving good glycemic control. More frequent self-monitoring of blood glucose (SMBG) and satisfactory appointment keeping behavior (low rate of missing scheduled outpatient appointments) were both 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 (95% C.I.) achieving good control ranged from 13.4% (reference, 11.3-15.8%) with no practice of SMBG, 15.5% (14.0-17.2%; p=0.13) with some but less than daily SMBG practice, and 18.8% (16.9-20.9%; p=0.0008) 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%) achieved good control among those missing <30% of appointments vs. 11.2% (8.7-14.2%; p=0.0009) among those missing ≥30% of outpatient appointments.

A further analysis among the subset of the 67% (n=3190) of the study cohort that 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 sub-analysis resulted in no substantive differences and yielded the same conclusions suggested by analysis of the full cohort.

## Comment

We studied the probability of achieving good glycemic control ($HbA_{1c} \leq 7\%$) within 3-12 months after initiating and maintaining a new diabetes regimen. This study was conducted in a cohort of poorly-controlled type 2 diabetes patients who initiated a new therapy during 1999-2000. Prior to initiating therapy, these new users had a mean $HbA_{1c}$ of 9.9%. Initiation of new therapy was associated with a 1.3 point drop in the population mean $HbA_{1c}$ (from 9.9% pre-initiation to 8.6% post-initiation) although only 18.4% of these new users achieved $HbA_{1c} \leq 7\%$. There were substantive differences in the proportion brought into good control across index therapies. Of the 11 most commonly used therapeutic regimens, those treated

with the insulin-sensitizers (thiazolidinediones and metformin) were most likely to achieve good control, particularly when used in combination with insulin or another oral agent. The treatments that had significantly greater proportions achieving good control than the first line therapy (SU monotherapy: 12.46% achieved good control) were MET monotherapy (17.1% achieved good control; p=0.04), SU+TZD (24.6%; p=0.002), MET+INS (24.9%; p=0.0008), TZD+INS (25.7%; p=0.007), and the triple combination TZD+MET+SU (25.1%; p=0.0007). No therapy was significantly poorer than SU monotherapy.

Despite the impressive response to initiated therapy, 82% failed to achieve good control and 54% percent of the new users still had $HbA_{1c}$ that exceeded 8% (ADA recommended action level) 3-12 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 following therapy initiation, suggesting 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 is one of the few assessments of “real world” effectiveness comparing 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 criteria. In the United Kingdom Prospective Diabetes Study (UKPDS), a randomized, controlled trial 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 three years, but the proportion declined progressively to 20-28% after nine years.[19] It is unclear how much of the efficacy in the UKPDS is attributable to the additional clinical attention common in clinical trials. A UKPDS sub-study of patients allocated to treatment with sulfonylurea monotherapy, reported that sulfonylurea inadequacy contributed to the progressive failure; 53% required additional insulin therapy within 6 years of follow-up.[20]

Randomized controlled trials (RCT) are considered the gold standard measure for evidence of efficacy, but have limitations. RCTs include highly selected populations receiving special clinical attention and usually evaluate a single medication rather than multiple medication therapies.[21,22] While these are necessary constraints in experimental settings, they limit generalizability.[23] Moreover, low levels of medication adherence may explain why the effectiveness observed in clinical practice[24] 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.[25] Thus real-world effectiveness studies provide important complementary information.[26,27]

The observed proportion of patients achieving good glycemic control is lower than those achieving recommended level of control for other chronic conditions, such as hypertension or hyperlipidemia. Estimates of the proportion of hypertensive patients that achieved well-controlled blood pressure (≤ 140/90) ranged from 27%-61% (U.S. NHANES III, 1991-94, 27%, New York managed care sample, 1998, 35%,[28] Metropolitan New York City sample, 1999, 61% [29]), although 74% has been achieved in randomized controlled trials.[30] Estimates of good lipid control (LDL-C ≤ 100 mg/dL) range from 41.7% [31] to 88.5%.[32] This suggests the currently available pharmacotherapies for hypertension and dyslipidemia may have greater relative effectiveness than antihyperglycemic 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.[26]

In this study population, ~27% of the diabetic patients initiated new therapy regimens during the one year observation period. In the cohort we studied (poorly controlled, new users), 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 insulin.[19] UKPDS findings also suggested that most patients fail sulfonylureas therapy as beta cell dysfunction increases, and suggested the need to add insulin or other therapies long before maximal doses become inadequate.[20] We observed a dramatic shift from monotherapy-dominated regimens used in the pre-baseline period to the use of combination therapies. This trend towards diabetes polypharmacy, particularly with inclusion of insulin sensitizers to address insulin resistance, has been noted in other populations.[4,33]

Some limitations are worth noting. We were unable to assess differences in effectiveness among patients who had not completed a $HbA_{1c}$ test during the 3-12 month window following 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 is not an “intent-to-treat analysis” that includes all initiators. Therefore our study slightly underestimates 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 $HbA_{1c}$ test. The mean “post-initiation” $HbA_{1c}$ would have been slightly higher (8.7% rather than 8.6%) if we had included these few subjects that discontinued therapy before having a post-initiation $HbA_{1c}$ 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.

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

Between-therapy comparisons of the proportions achieving good glycemic control are not interpretable as causal therapy effects as in the case of clinical trial results. We assume 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 for the preceding therapy; or 2) the patient discontinued the preceding therapy of their own accord. We are unable to distinguish between these causes. Case mix differences due to association between diabetes severity and choice of treatment distort findings (“confounding by indication”[34]) so that more intense therapy is associated with poorer glycemic control. Although controlling for pre-initiation $HbA_{1c}$, previous therapy and duration of diabetes did alter our findings, in some cases dramatically, additional residual confounding is 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 (over 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 not unlike those in other published studies and thus findings are likely generalizable to insured individuals with diabetes. The proportion in good control in the whole Kaiser diabetes population (30%) is consistent with a previously published study[35] from the *Type 2 Diabetes Patient Outcomes Research Team (PORT) Study* (32% in control) and NHANES III, where 26.5% of insulin-treated and 37.7% of oral agent treated patients achieved good control.[36]

If, as we observed, the majority of patients need to achieve better control, this suggests new pharmacotherapeutic modalities with greater efficacy 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.[37] 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,[13] despite being associated with better glucose control.[8] We also noted that frequently missed medical appointments was associated with poorer control in this and a previous study in this population,[11] 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 have been demonstrated previously,[38,3940-43]although the effectiveness is frequently limited by low levels of adherence. Exploration of novel behavioral approaches, such as stress management[44] may also prove useful.

*Clinical inertia*, i.e., the failure of health care providers to initiate or intensify therapy when indicated, has been identified as a significant obstacle to effective disease management.[2545,46] A previous study based on a population with a similar form of integrated care[47] showed that, before new therapies were initiated, levels of $HbA_{1c}$ were typically closer to 9% rather than 8%, which was the action threshold recommended by the American Diabetes Association (ADA) Clinical Practice Recommendations up until 2003. We had similar findings. After expanding the analysis to the whole diabetic population (not just those new users with poor control we selected for this study), the mean baseline $HbA_{1c}$ was 8.7% prior to initiating new therapy. An earlier initiation of new therapy (i.e., before control greatly exceeded 7%) would have likely resulted in a larger proportion of patients being brought into good control. Prior to 2003, the ADA guidelines stipulated an “action level” ($HbA_{1c}$ = 8%), above which therapy intensification was recommended. This action level was one point higher than the “glycemic target” ($HbA_{1c}$ = 7%) recommended also 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 $HbA_{1c}$ 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 $HbA_{1c}$ (7% - 8%). Moreover, in addition to specifying the glycemic target of $HbA_{1c} \leq 7\%$, 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 lower limit below which further lowering doesn't confer clinical benefits. The *American Association of Clinical Endocrinologists (AACE)* and the *American College of Endocrinology (ACE)* recommends a goal of “$HbA_{1c}$ 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 is currently 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 over 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 poorly controlled diabetic patients, initiation of combination therapies that included thiazolidinedione or a regimen of metformin and 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 sub-optimal glycemic control 3-12 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[47,48]

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## Appendix

Conditional (adjusted) probability of achieving good control derived from the logistic regression model using the following algorithm.

The conditional probability of achieving good control = e($U$) = pr($Z$=1|$U$) where we assume:

$Z_i$ = 0 if subject $i$ has $HbA_{1c} > 7\%$

1 if subject $i$ has $HbA_{1c} \leq 7\%$

$U_i$ = The vector of observed covariates (both continuous and categorical)

$i$ = 1, …., $n$ = total number of subjects

$$Pr\left(Z_i,\ldots,Z_n \middle| U_1,\ldots,U_n\right)=\prod_{i=1}^{n}\left\{e(U_i)^{Zi}\right\}\left\{1-e(U_i)^{Zi}\right\}^{1-Zi}$$

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## Table 1

Subject characteristics prior to initiation of new diabetes therapy (n=4774).

| Characteristic | Percentage or Mean (SD) |
|---|---|
| Age, years | 60.0 (11.5) |
| Female | 49.2% |
| $HbA_{1c}$ | 9.9 (1.5) |
| Low-density lipoprotein (LDL) cholesterol mg/dl | 122.0 (37.1) |
| Hypertension | 77.3% |
| Has personal primary care provider | 87.6% |
| Pharmacy co-payment ≤$5 | 71.8% |
| Self-monitoring of blood glucose (times per day) | 0.9 (1.0) |
| Number of primary care visits in prior year | 2.0 (2.0) |
| Proportion of scheduled outpatient visits missed in prior year | 0.1 (0.2) |

## Table 2

Diabetes pharmacotherapy utilization before and after initiating new diabetes therapies (n=4,775)

| Diabetes therapies | Percentage | |
|---|---|---|
| | Pre-initiation | Post-initiation |
| 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 |

*Mono- or combination therapy with Meglitinides or Alpha-glucosidase inhibitors.

**Table 3**

Probability of achieving good glycemic control ($HbA_{1c} \leq 7\%$) within 3-12 months after initiation of a new diabetes therapy and adjusted odds ratios comparing initiated therapies.

| | N | Crude (unadjusted) percentage (95% CI) | Adjusted* percentage (conditional probability) (95% CI) | Adjusted odds ratios* (95% CI) | p-value from adjusted model (relative to reference) |
|---|---|---|---|---|---|
| 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) | 0.0449 |
| Thiazolidinedione | 9 | 22.22 (0.00-49.38) | 32.26 (6.40-76.84) | 3.35 (0.48-23.56) | 0.2249 |
| Insulin | 359 | 15.04 (11.34-18.74) | 16.57 (12.26-22.02) | 1.40 (0.91-2.14) | 0.1275 |
| Sulfonylureas + Metformin | 1848 | 18.56 (16.79-20.33) | 14.61 (12.43-17.09) | 1.20 (0.86-1.68) | 0.2768 |
| Sulfonylureas + Thiazolidinediones | 106 | 28.30 (19.73-36.88) | 24.61 (17.18-33.93) | 2.30(1.35-3.90) | 0.0021 |
| Sulfonylureas + Insulin | 224 | 10.71 (6.66-14.76) | 10.87 (7.24-16.02) | 0.86 (0.54-1.46) | 0.5697 |
| Sulfonylureas + Metformin + Thiazolidinediones | 214 | 18.22 (13.05-24.06) | 25.13 (18.06-33.83) | 2.36 (1.44-3.87) | 0.0007 |
| Sulfonylureas + Metformin + Insulin | 287 | 12.89 (9.01-16.77) | 16.95 (12.00-23.40) | 1.43 (0.88-2.33) | 0.1456 |
| Metformin + Insulin | 465 | 15.05 (11.8-18.3) | 24.86 (18.54-32.47) | 2.33 (1.42-3.80) | 0.0008 |
| Thiazolidinediones + Insulin | 125 | 16.80 (10.25-23.35) | 25.65 (16.41-37.74) | 2.42 (1.27-4.64) | 0.0074 |
| Other** | 181 | 12.71 (7.86-17.56) | 16.55 (11.10-23.94) | 1.39 (0.81-2.39) | 0.2270 |

*Adjusted for sex, age, baseline $HbA_{1c}$, pre-baseline therapy, self-monitoring of blood glucose frequency, specialty of primary care physician, outpatient primary care utilization and appointment-keeping behavior, pharmacy co-payment amount, eye examination and emergency room visits in the past year.

**Mono- or combination therapy with Meglitinides or Alpha-glucosidase inhibitors.