# Achieving further glycemic control in type 2 diabetes mellitus

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ABSTRACT ● **Objectives** To identify patients with type 2 diabetes mellitus who were in poor glycemic control and therapeutic adjustments that might improve control. ● **Design** Using electronic pharmacy data, we assigned subjects to 1 of 4 therapeutic categories. We then identified patients within each category who did not meet the recommended standard of glycemic control (glycosylated hemoglobin [Hb $A_{1c}$] <0.08 [<8.0%]) and studied their therapeutic regimens for possible improvements. ● **Subjects** The subjects were 5,061 members of a large group-model health maintenance organization who had type 2 diabetes and 12 months of 1997 health plan eligibility. ● **Main outcome measures** The dosage of antihyperglycemic agents (sulfonylureas, metformin, and insulin) in relation to glycemic control as measured by the Hb $A_{1c}$. ● **Results** A significant number (n = 1,570 [31.0%]) of persons with type 2 diabetes might improve their glycemic control with simple adjustments to their pharmacologic therapy. ● **Conclusion** Busy clinicians with heavy workloads can improve their management of diabetes by identifying patients whose glycemic control could be improved through a change in medication or simple adjustment in dosage.

## INTRODUCTION

Accumulating evidence demonstrating the benefits of intensive diabetes care[1,2] has put health care plans and clinicians under increasing pressure to improve the glycemic control of patients with diabetes.[3-6] The recent addition of metformin, acarbose, rosiglitazone, and pioglitazone to the therapeutic armamentarium provide more options for patients who have not achieved adequate glycemic control with the use of sulfonylureas or insulin alone. Yet, many patients still do not have satisfactory glycemic control, including patients whose health care organizations meet or exceed national standards of care. Kaiser Permanente Northwest's initiative to provide comprehensive care for patients with type 2 diabetes mellitus, including expanded case management, enhanced health education, and aggressive testing of glycemic control, has been described else-

where.[7] In this report, we identify opportunities for further improvement in glycemic control, with specific focus on the therapeutic regimens currently in use.

## PARTICIPANTS AND METHODS

The subjects of this study were members of a long-established, not-for-profit, group-model health maintenance organization, Kaiser Permanente Northwest Division. Its diabetes registry has been detailed elsewhere.[8] For this study, we selected 6,287 members in the diabetes registry who responded to a 1997 survey and who had 12 months of health plan eligibility in 1997. From these, we excluded 454 members who had type 1 diabetes mellitus and 582 members who did not have an Hb $A_{1c}$ measurement in 1997. We also excluded 173 members who received 3 or more antidiabetic drugs in 1997 (because their therapeutic regimen was likely in flux, proper assignment to a therapeutic category could not be assured). Finally, because of concerns about sample size, we excluded 17 members who received only acarbose or troglitazone. These exclusions yielded a final study population of 5,061.

Using electronic pharmacy data maintained by Kaiser Permanente Northwest, we assigned subjects to 1 of 4 therapy categories: users of insulin, alone or in combination with metformin or sulfonylureas; users of metformin, alone or in combination with sulfonylureas; users of sulfonylureas only; and persons taking no antidiabetic drug. For comparability, prescription fills of sulfonylurea were converted into glyburide equivalents using maximum doses described by Gerich.[9] Within these groups, we divided patients into those who met or exceeded a recommended standard of glycemic control (Hb $A_{1c}$ <0.08 [<8.0%]) and those who did not (≥0.08 [≥8.0%]).

## RESULTS

Glycemic control within the study population was good overall. The mean (SD) Hb $A_{1c}$ level was 0.076 (0.013). Almost two thirds (66.3% [n = 3,356]) of the cohort had a mean Hb $A_{1c}$ level below 0.08, and 87.3% (n = 4,416) were below 0.09.

The mean age of the study population was 65.1 years, 49.9% (n = 2,525) were women, and the average duration of diabetes was 10 years. The mean body mass index (calculated as weight in kilograms divided by the square of height in meters) was 31.1. Users of insulin alone or in combination with sulfonylureas or metformin (n = 1,346) made up 26.6% of the study population. Users of metformin alone or in combination with sulfonylureas were 15.3% of the total population (n = 772). Users of sulfonylureas as monotherapy constituted the largest proportion (40.6% [n = 2,054]) of the study population, and 17.6% of the population was taking no antidiabetic drugs (n = 889).

In table 1, we divide the sulfonylurea-only users into 2 levels of control (±0.08) and compare them with subjects using no drugs. Of the 2,054 sulfonylurea-only users, 1,385 (67.4%) had mean Hb $A_{1c}$ values below 0.08. Compared with sulfonylurea-only users with Hb $A_{1c}$ levels of 0.08 or above (n = 669), these better-controlled sulfonylurea-only users were older ($P$<0.001), more obese ($P$<0.01), and more likely to be women ($P$<0.001). The sulfonylurea-only users with Hb $A_{1c}$ levels below 0.08 also

Table 1 *Patient characteristics, sulfonylurea-only users, and patients receiving no drug therapy**

| Characteristics | No drug therapy | Sulfonylureas only | | Total |
|---|---|---|---|---|
| | | Hb $A_{1c}$ ≥0.08 | Hb $A_{1c}$ <0.08 | |
| Study subjects, no. | 889 | 669 | 1,385 | 2,054 |
| Mean Hb $A_{1c}$ level† | 0.07 | 0.09 | 0.069 | 0.076 |
| Age, yr‡ | 65.1 | 63.8 | 66.0 | 65.3 |
| Sex, female, No. (%) | 459 (51.6) | 306 (45.7) | 669 (48.3) | 975 (47.5) |
| Race, white, No. (%) | 834 (93.8) | 593 (88.6) | 1,285 (92.8) | 1,878 (91.4) |
| BMI§ | 30.2 | 30.5 | 31.3 | 31.0 |
| Years since diabetes mellitus recognized | 7.8 | 7.8 | 7.2 | 7.4 |
| 1997 daily glyburide equivalents, mg‡ | — | 13.0 | 9.7 | 10.8 |
| Years taking drug§ | — | 4.2 | 3.8 | 3.9 |
| 1997 prescription fills of sulfonylurea† | — | 5.8 | 4.6 | 5.0 |

BMI = body mass index.
*Except as otherwise noted, data are mean values. Statistical comparisons are made between sulfonylurea users with glycosylated hemoglobin (Hb $A_{1c}$) levels of 0.08 or higher (≥8.0%) and those with Hb $A_{1c}$ levels below 0.08 only.
†Expressed as a proportion of 1. For conventional units, multiply by 100 to obtain percentage.
‡$P$< 0.001.
§$P$< 0.01.

had had diabetes for a slightly shorter time ($P<0.1$). The mean daily dose of sulfonylureas (in glyburide equivalents) for those with Hb $A_{1c}$ levels below 0.08 was much lower than for those above this threshold ($P<0.001$). Well-controlled sulfonylurea-only users had been taking sulfonylureas for a shorter time and received fewer prescription fills of sulfonylureas than those with Hb $A_{1c}$ levels of 0.08 or above ($P<0.001$ for both).

Table 2 displays similarly organized statistics for insulin users with Hb $A_{1c}$ values below 0.08 (n = 783 [58.2% of insulin users]), those with values of 0.08 or above taking less than 100 units of insulin per day (n = 393 [29.2%]), and those with Hb $A_{1c}$ values of 0.08 or above taking 100 units or more of insulin per day (n = 170 [12.6%]). Users of insulin with Hb $A_{1c}$ levels below 0.08 were much more likely to be women ($P<0.001$) than were either of the groups with Hb $A_{1c}$ levels of 0.08 or above. Users of insulin who had Hb $A_{1c}$ levels above 0.08 and who were receiving more than 100 units of insulin per day were more than 4 years younger ($P<0.001$). Finally, those with Hb $A_{1c}$ levels of 0.08 or above receiving fewer than 100 units of insulin per day had had diabetes significantly longer ($P<0.001$) than those receiving more than 100 units or those with Hb $A_{1c}$ levels below 0.08.

We also divided the subjects receiving metformin into 3 groups (table 3): those with Hb $A_{1c}$ values below 0.08 (n = 434 [56.2%]), those with Hb $A_{1c}$ values of 0.08 or above receiving 1,500 mg or more of metformin per day (n = 233 [30.2%]), and those with Hb $A_{1c}$ values of 0.08 or above receiving less than 1,500 mg per day (n = 105 [13.6%]). Well-controlled users were somewhat more likely to be women than were users with Hb $A_{1c}$ levels of 0.08 or above who were receiving low doses of metformin (46.7%) and those with Hb $A_{1c}$ levels of 0.08 or above who were high-dose users (36.9%), and they were more likely than either of the other 2 groups to be white ($P<0.05$). High-dose users with Hb $A_{1c}$ values of 0.08 or above also were significantly younger ($P<0.01$) than those with values below 0.08 and had had diabetes longer ($P<0.01$). Low-dose users with Hb $A_{1c}$ levels of 0.08 or above had been taking metformin for less time ($P<0.001$) and received fewer prescription fills of the drug ($P<0.05$).

## DISCUSSION

Some demographic patterns emerged that may assist health plans and physicians in identifying at-risk patients. Most notably, younger patients who had type 2 diabetes longer were in poorer control than older patients who had type 2 diabetes for shorter duration. This finding, and the finding that women were in better control than men, holds across all drug therapy categories.

Despite the good overall level of glycemic control in this health plan, we found room for improvement. Of 5,061 members in this study, 1,570 (31%) had Hb $A_{1c}$ values that exceeded the American Diabetes Association's recommended threshold for action (0.08).[10] Many of these members could benefit from relatively simple adjustments to their therapeutic regimens.

First, almost a third (n = 669) of the 2,054 patients (32.6%) receiving sulfonylurea monotherapy had an Hb $A_{1c}$ of 0.08 or above. They had been taking sulfonylureas somewhat longer and were receiving higher doses and

Table 2 *Patient characteristics, users of insulin alone or with any oral agent**

| Characteristics | Hb $A_{1c}$ ≥0.08 Insulin, ≥100 U/day | Hb $A_{1c}$ ≥0.08 Insulin, <100 U/day | Hb $A_{1c}$ < 0.08 | Total |
|---|---|---|---|---|
| Study subjects, no. | 170 | 393 | 783 | 1,346 |
| Mean Hb $A_{1c}$ level† | 9.0† | 9.0† | 6.9‡ | 7.8 |
| Age, yr | 62.2† | 66.1‡ | 66.9‡ | 66.1 |
| Sex, female, no. (%) | 83 (48.8)† | 190 (48.3)† | 456 (58.2)‡ | 729 (54.2) |
| Race, white, no. (%) | 160 (94.1) | 337 (85.7) | 730 (93.2) | 1,255 (93.2) |
| BMI | 33.1† | 28.9‡ | 32.2§ | 31.4 |
| Years since diabetes mellitus recognized | 15.0† | 17.9‡ | 15.2† | 16.0 |
| 1997 average daily insulin dose, units | 164† | 60‡ | 99§ | 96 |
| Years taking drug | 5.2 | 5.4 | 5.3 | 5.3 |
| 1997 prescription fills of insulin | 9.7 | 10.3 | 10.2 | 10.2 |

Hb $A_{1c}$ = glycosylated hemoglobin (hemoglobin $A_{1c}$); BMI = body mass index.
*Except where otherwise noted, data are mean values. Figures with different symbols (†, ‡, and §) are significantly different from each other ($P< 0.05$).
†Expressed as a proportion of 1. For conventional units, multiply by 100 to obtain percentage.

Table 3 *Patient characteristics and users of metformin alone or with sulfonylureas**

| Characteristics | Hb $A_{1c}$ ≥0.08 Metformin dose ≥1,500 mg/day | Metformin dose <1,500 mg/day | Hb $A_{1c}$ <0.08 | Total |
|---|---|---|---|---|
| Study subjects, No. | 233 | 105 | 434 | 772 |
| Mean Hb $A_{1c}$ level† | 9.0‡ | 9.0‡ | 7.2§ | 8.0 |
| Age, yr | 61.2‡ | 62.2§ | 63.6§ | 62.7 |
| Sex, female, No. (%) | 86 (36.9)‡ | 49 (46.7)§ | 225 (51.8)‖ | 360 (46.6) |
| Race, white, No. (%) | 217 (93.1)‡ | 95 (90.5)§ | 411 (94.7)‡ | 723 (93.7) |
| BMI | 31.7 | 32.0 | 31.6 | 31.7 |
| Years since diabetes mellitus recognized | 9.7‡ | 9.1§ | 8.1§ | 8.7 |
| 1997 average daily metformin dose, mg | 2,223‡ | 955§ | 1,864‖ | 1,849 |
| Years taking drug | 1.1‡ | 0.7§ | 1.1‡ | 1.0 |
| 1997 prescription fills of metformin | 7.1‡ | 5.5§ | 7.3‡ | 7.0 |

Hb $A_{1c}$ = glycosylated hemoglobin (hemoglobin $A_{1c}$); BMI = body mass index.
*Except as otherwise noted, data are mean values. Figures with different symbols (‡, §, and ‖) are significantly different from each other ($P$<0.05).
†Expressed as a proportion of 1. For conventional units, multiply by 100 to obtain percentage.

more prescription fills than those who were well controlled. By definition, these patients are in secondary sulfonylurea failure[11] and are candidates for the addition or substitution of insulin, metformin, rosiglitazone, or pioglitazone.

Second, of the 1,346 patients using insulin alone or in combination with sulfonylureas or metformin, 563 (41.8%) failed to achieve glycemic control below the recommended threshold. Most (n = 393 [29.2%]) were taking an average of 60 units of insulin daily, suggesting that they were not administering enough insulin to achieve adequate control. By comparison, insulin users with Hb $A_{1c}$ values of less than 0.08 averaged 90 units per day.

Third, 170 insulin users (12.6%) who had an Hb $A_{1c}$ of 0.08 or above were receiving high doses of insulin—averaging 164 units per day—reflecting the insulin-resistant character of type 2 diabetes mellitus. These patients may benefit from increases in their insulin dose. However, only 26 (15.3%) of these 170 relatively younger patients were supplementing their insulin with metformin. Adding newer oral agents such as metformin, rosiglitazone, or pioglitazone might improve their glycemic control.

Fourth, of those using metformin alone or in combination with sulfonylureas, nearly half (43.8% [n = 338]) had not achieved glycemic control (Hb $A_{1c}$ level <0.08). Most of these metformin users (30.2% [n = 233]) received sufficient doses of their drug, averaging more than 2,200 mg per day. Failure to achieve good control at this level of metformin dosing suggests that insulin therapy should be started for these patients. Another 105 of those metformin users whose Hb $A_{1c}$ values remained above the recommended glycemic goals (13.6%) received an average dose of less than 1,500 mg per day, which may reflect subtherapeutic dosing. These patients had been receiving metformin for a much shorter period (about 8 months) and received fewer prescription fills of metformin than all other metformin users, so some of this subtherapeutic dosing may reflect the initiation of therapy with low doses. On average, however, their mean duration of therapy (8.4 months) was sufficient to titrate to full therapeutic dosing.

A limitation of the current study was the exclusion of 13% of the potential study population because the subject did not have an Hb $A_{1c}$ measurement (9%) or because the therapeutic regimen of the subject could not be assessed (4%). Whether these subjects differ from those included with respect to glycemic control or pharmacotherapy cannot be determined, but the "take-home messages" of the results presented here are not biased by the exclusion of these subjects.

In summary, a substantial number of persons (1,570 [31.0%]) with type 2 diabetes mellitus might improve their glycemic control with simple adjustments to their pharmacologic therapy. Of the 901 users of either insulin or metformin who had not achieved glycemic control, 498 (55.3%) might achieve better glycemic control merely by increasing their doses. Many patients manifesting secondary failure of sulfonylurea therapy, nevertheless, were continued on this therapy, rather than being switched to combination therapy or having insulin added to their regimen.

Busy clinicians with heavy workloads can enhance their management of diabetes by identifying patients whose glycemic control could be increased through a change in medication or simple adjustment in dosage. Even within clinician practices and health care organizations performing well by recommended standards, there may still be room for improvements—improvements that are affordable and within reach.

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