

# Secondary Failure of Glycemic Control for Patients Adding Thiazolidinedione or Sulfonylurea Therapy to a Metformin Regimen

Aylin A. Riedel, PhD; Herbert Heien, MS; Jenifer Wogen, MS;  
and Craig A. Plauschinat, PharmD, MPH

Currently, an estimated 10.3 million persons in the United States have diagnosed type 2 diabetes mellitus (DM),<sup>1</sup> and DM causes substantial morbidity and mortality. Consequently, DM represents an enormous burden to US healthcare budgets. Medical expenditures in the United States were estimated at \$132 billion in 2002.<sup>2</sup> The American Diabetes Association<sup>3</sup> has established a target glycosylated hemoglobin (A1C) level of less than 7.0% for patients with type 2 DM overall, with individual patient goal A1C levels as close to normal (<6.0%) as possible because reductions in A1C level in patients with type 2 DM can lower the risk of microvascular and macrovascular complications.<sup>4</sup> Despite more aggressive treatment guidelines and the introduction of several novel oral antihyperglycemic therapies (including thiazolidinediones) during the past few years, glycemic control rates in patients with type 2 DM have not substantially improved from 1988-1994 (42.9%) to 1999-2002 (45.0%).<sup>5</sup>

Metformin is recommended for first-line therapy, in addition to diet and exercise, in patients with type 2 DM<sup>6</sup> primarily because of reduced weight gain and fewer hypoglycemic episodes associated with a metformin regimen compared with sulfonylureas.<sup>7</sup> However, because of the progressive decline of  $\beta$ -cell function and consequent deterioration of glycemic control in type 2 DM, most patients will eventually require combination therapy to maintain goal A1C level.<sup>8</sup> The long-term use of metformin and sulfonylureas, oral antihyperglycemic therapies frequently used in the management of type 2 DM, has been studied in the United Kingdom Prospective Diabetes Study.<sup>8</sup> In addition, recently published findings from ADOPT (A Diabetes Outcome Progression Trial) provided information on the long-term use of rosiglitazone (a thiazolidinedione), in comparison with metformin and glyburide (a sulfonylurea), and the effect on glycemic control when used as monotherapy in patients diagnosed as having type 2 DM for less than 3 years.<sup>9</sup> A common treatment algorithm in the current management of patients with type 2 DM comprises lifestyle modifications, followed by metformin monotherapy after diet and exercise failure, followed by the addition of 1 or more oral antihyperglycemic agents in a combination, with eventual progression to insulin therapy alone or in combination with oral agents.

This study evaluated glycemic control associated with the use of thiazolidinediones or sulfonylureas when

**In this issue**  
Take-away Points / p462  
[www.ajmc.com](http://www.ajmc.com)  
Full text and PDF

**Objective:** To assess glycemic control and secondary failure in patients adding thiazolidinedione or sulfonylurea therapy to a metformin regimen in a managed care setting.

**Study Design:** Retrospective cohort study using administrative claims data.

**Methods:** Participants (mean age, 51.1 years; 55.4% female) were required to have at least 1 prescription claim for a sulfonylurea (n = 300) or a thiazolidinedione (n = 279) between January 1, 2001, and March 31, 2004, as well as metformin use during the prior 6 months and continued metformin use. Secondary failure was measured for patients who initially achieved a glycosylated hemoglobin (A1C) level of less than 7.0% and was defined as a subsequent A1C level of at least 7.0%.

**Results:** The mean baseline A1C level was 8.2% and was higher for the patients receiving a combination of metformin and sulfonylurea (A1C level, 8.4%) compared with patients receiving a combination of metformin and thiazolidinedione (A1C level, 8.0%) ( $P < .05$ ). Overall, 77.7% of patients had a baseline A1C level of at least 7.0%. The mean A1C level decreased by 1.2 (to 7.0%), and 65.1% of patients with a baseline A1C level of at least 7.0% reached goal A1C level. Therapy intensification via addition of another antihyperglycemic agent occurred in 60.7% of study patients. Approximately 2 in 5 patients (41.5%) who initially achieved goal A1C level experienced secondary failure; the mean time to failure was 1.3 years.

**Conclusion:** Although most patients failing metformin monotherapy reached goal A1C level after addition of a sulfonylurea or a thiazolidinedione, 41.5% of patients observed for up to 4 years who initially attained goal A1C level experienced secondary failure.

(*Am J Manag Care.* 2007;13:457-463)

**For author information and disclosures, see end of text.**

added to existing metformin therapy in a managed care setting. Patients were observed longitudinally for up to 4 years after the addition of a thiazolidinedione or a sulfonylurea to metformin therapy to determine the proportion attaining goal A1C level in a usual care setting. We also evaluated the ability of thiazolidinediones and sulfonylureas to maintain glycemic control in combination with metformin therapy by assessing rates of secondary failure following initial goal A1C level achievement.

## METHODS

This longitudinal retrospective cohort study used an administrative medical and pharmacy claims database with integrated laboratory data from a large, geographically diverse US managed care plan. The index date was defined as the date of a patient's first prescription for a thiazolidinedione or a sulfonylurea during the study identification period, January 1, 2001, through March 31, 2004. Patients who received at least 1 new prescription for a thiazolidinedione (rosiglitazone or pioglitazone hydrochloride) or a sulfonylurea during the identification period who also received at least 90 days of metformin therapy during the 6 months preceding the index date were identified for cohort inclusion. To ensure that patients were receiving combination therapy and were not switching to a different oral antidiabetic medication, at least 1 prescription fill of metformin on or after the study index date was required. Patients were required to be continuously eligible for benefits for at least 6 months before and 75 days after the index date and were required to have no other oral antidiabetic medication or insulin prescriptions during the 6 months before the index date. Patients using fixed combination tablets (metformin-glyburide or metformin-glipizide) were also included, provided that other study entry criteria were met. Patients were observed for up to 48 months after the index date and were required to have at least 1 A1C laboratory result during a baseline window of 3 months before and 7 days after the study index date, as well as at least 1 A1C laboratory result following a stabilization period of 76 days following the study index date. For patients with more than 1 test result during the baseline period, the most recent test result was used. We used a study design that evaluated the study cohort until the end of the observation period or until the end of patient health plan benefit eligibility.

The primary study outcome variable was the progressive loss of glycemic control, evaluated as the rate of secondary therapy failure. Secondary outcome variables related to glycemic control included change in A1C level, percentage change in A1C level, goal A1C level attainment, and thera-

py intensification. Secondary failure was evaluated for study patients whose A1C level was at least 7.0% at study baseline and who achieved goal A1C level at some time during the study follow-up period; secondary failure was defined in this subset of patients as the presence of a subsequent A1C test result of at least 7.0%. Change in A1C level was calculated as the last available A1C test result during the follow-up period minus the baseline A1C level. Percentage change in A1C level was also calculated as the percentage change from the baseline A1C test result to the last available A1C test result (change in A1C level/baseline A1C level). Goal A1C level was defined according to American Diabetes Association<sup>3</sup> recommendations as less than 7.0%. The percentage of patients with secondary failure was calculated as the number of patients who experienced failure divided by the number of patients who were not at goal A1C level at baseline who subsequently met goal A1C level and who also had at least 1 A1C test result available for analysis following goal A1C level achievement. Time to secondary failure was defined as the number of days elapsed from the index prescription date until occurrence of goal A1C level failure. Therapy intensification was defined as the addition of a nonindex antidiabetic drug (oral agent or insulin) to the index drug regimen after the index prescription date, with at least 1 refill of the index drug following the date of the addition of the second agent. Patient A1C level before therapy intensification was assessed using A1C test results during the period between the A1C level stabilization period and 7 days following the therapy intensification date and was only calculated for patients who experienced an intensification of antidiabetic therapy.

To assess and control for other patient comorbid conditions, the Charlson index was used.<sup>10</sup> The Charlson index was calculated based on medical claims during the 6 months before the study index period that corresponded to specific *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes to identify the presence of specific comorbid conditions. A single numeric index was calculated for each patient that represented that patient's total comorbid status on a numeric scale. In addition to using this index, specific comorbid conditions were identified, including DM with complications, hypertension, hyperlipidemia, cardiovascular disease, and retinopathy.

Descriptive statistics were used for patient demographic and clinical characteristics. For continuous variables such as age, means or medians were compared using *t* test or Mann-Whitney test. For categorical variables,  $\chi^2$  test was used for statistical comparisons. Time-to-event variables such as time to therapy failure are presented using Kaplan-Meier curves. All study analyses were performed using SAS version 8.2

## Adding Thiazolidinedione or Sulfonylurea Therapy to a Metformin Regimen

(SAS Institute, Cary, NC) and STATA version 9 (StataCorp LP, College Station, Tex).

### RESULTS

The final study cohort consisted of 579 patients who added a sulfonylurea (n = 300) or a thiazolidinedione (n = 279) to existing metformin therapy. Study cohort characteristics are given in **Table 1**. The mean ± standard deviation (SD) age of the cohort was 51.1 ± 8.7 years, and 55.4% were female. The mean age was similar for patients receiving a combination of metformin and a sulfonylurea (metformin-sulfonylurea) compared with patients receiving a combination of metformin and a thiazolidinedione (metformin-thiazolidinedione). The mean duration of patient follow-up was 1.8 years and did not differ for patients receiving metformin-sulfonylurea compared with patients receiving metformin-thiazolidinedione. The Charlson index was similar for patients receiving metformin-sulfonylurea (mean, 1.3) compared with patients receiving metformin-thiazolidinedione (mean, 1.4), indicating that study patients had a similar number of comorbid conditions at study baseline; 59.2% of the study cohort had hypertension, 59.8% had hyperlipidemia, and 20.7% had a claims history of eye disease or retinopathy.

Baseline A1C levels are given in **Table 2**. The mean ± SD baseline A1C level for the study cohort was 8.2% ± 1.9%. The patients receiving metformin-sulfonylurea had slightly higher baseline A1C levels (mean A1C level, 8.4%) compared with patients receiving metformin-thiazolidinedione (mean A1C level, 8.0%) (*P* < .05). At the start of the study, 22.3% of the study cohort had a baseline A1C level of less than 7.0%; patients receiving metformin-thiazolidinedione (27.6%) were more likely to be at or below goal A1C level at study baseline compared with patients receiving metformin-sulfonylurea (17.3%) (*P* < .01).

The mean A1C level of the cohort at follow-up was 7.0%, corresponding to a mean decrease of 1.2. The mean decrease in A1C level was similar for patients receiving metformin-sulfonylurea and for patients receiving metformin-thiazolidinedione (Table 2). Overall, 71.7% of the entire study cohort achieved goal A1C level at some point during the study follow-up period. In the subset of patients whose baseline A1C level was greater than or equal to 7.0%, 67.8% of patients receiving metformin-sulfonylurea and 62.9% of patients receiving metformin-thiazolidinedione achieved goal A1C level during the follow-up period. Among this subset of patients with a baseline A1C level greater than or equal to 7.0%, the mean ± SD A1C level at follow-up was 7.3% ± 1.3% for patients receiving metformin-sulfonylurea and 7.2% ± 1.3% for patients receiving metformin-thiazolidinedione. Patients with a higher baseline A1C level had lower odds of ever achieving goal A1C level (odds ratio, 0.68; 95% confidence interval, 0.59-0.79), and patients with hyperlipidemia had higher odds of ever achieving goal A1C level (odds ratio, 1.56; 95% confidence interval, 1.05-2.33).

Overall, 60.6% of the study cohort experienced therapy intensification; 67.4% of patients receiving metformin-thiazolidinedione and 57.0% of patients receiving metformin-sulfonylurea intensified the initial therapeutic regimen (Table 2). The rates of therapy intensification among the subset of patients with a baseline A1C level greater than or equal to 7.0% were 69.3% for patients receiving metformin-thiazolidinedione and 57.3% for patients receiving metformin-sulfonylurea. The mean duration from the study index date until the date of therapy intensification was 59.7 days overall, 48.0 days for patients receiving metformin-thiazolidinedione, and 72.6 days for patients receiving metformin-sulfonylurea. Only 21.4% of cohort patients who experienced therapy intensification had an available A1C test result before intensification.

Overall, 60.6% of the study cohort experienced therapy intensification; 67.4% of patients receiving metformin-thiazolidinedione and 57.0% of patients receiving metformin-sulfonylurea intensified the initial therapeutic regimen (Table 2). The rates of therapy intensification among the subset of patients with a baseline A1C level greater than or equal to 7.0% were 69.3% for patients receiving metformin-thiazolidinedione and 57.3% for patients receiving metformin-sulfonylurea. The mean duration from the study index date until the date of therapy intensification was 59.7 days overall, 48.0 days for patients receiving metformin-thiazolidinedione, and 72.6 days for patients receiving metformin-sulfonylurea. Only 21.4% of cohort patients who experienced therapy intensification had an available A1C test result before intensification.

**Table 1. Study Cohort Demographic and Clinical Characteristics\***

Variable	Metformin-Sulfonylurea (n = 300)	Metformin-Thiazolidinedione (n = 279)	Total (N = 579)
Mean age, y	51.0 ± 8.5	51.2 ± 9.0	51.1 ± 8.7
Female sex	53.0	58.1	55.4
Mean follow-up, y	1.8	1.7	1.8
Charlson Index	1.3 ± 0.7	1.4 ± 0.8	1.4 ± 0.7
<b>Comorbid condition</b>			
Diabetes mellitus with complications	8.7	7.5	8.1
Hypertension	60.3	58.1	59.2
Hyperlipidemia	60.7	58.8	59.8
Cardiovascular disease	17.0	10.4	13.8
Eye disease or retinopathy	21.7	19.7	20.7

\*Data are given as percentage or as mean ± SD unless otherwise indicated. SD indicates standard deviation.

## ■ CLINICAL ■

tion. For this patient subset, the mean A1C level preceding therapy intensification was 7.9% overall, 7.8% for patients receiving metformin-sulfonylurea, and 7.9% for patients receiving metformin-thiazolidinedione. As seen in Table 2, intensification with insulin therapy was infrequent in this cohort, as fewer than 5% of study patients used insulin during the follow-up period.

Overall, 104 patients receiving metformin-sulfonylurea and 89 patients receiving metformin-thiazolidinedione met the eligibility criteria for assessment of secondary failure, and 41.5% of cohort patients experienced secondary failure. Fifty percent of patients receiving metformin-sulfonylurea and 31.5% of patients receiving metformin-thiazolidinedione experienced secondary failure. The mean  $\pm$  SD time from the index date to secondary failure was  $489.5 \pm 239.2$  days for patients receiving metformin-sulfonylurea and  $480.1 \pm 207.1$  days for patients receiving metformin-thiazolidinedione and is depicted using Kaplan-Meier techniques in the **Figure**.

## DISCUSSION

This usual care study of a type 2 DM managed care population who added a sulfonylurea or a thiazolidinedione to metformin therapy found that 2 of every 5 patients who initially achieved goal A1C level experienced secondary treatment failure during the follow-up period, although 65.1% of patients

with a baseline A1C level greater than or equal to 7.0% reached goal A1C level at some point during the follow-up period. Overall, the mean time to secondary failure after the addition of a sulfonylurea or a thiazolidinedione was 1.3 years. Approximately 1 in 4 patients in this managed care setting had a second agent added to their initial metformin monotherapy regimen, despite having a baseline A1C level of less than 7.0%. Although an intensified therapeutic regimen at an A1C level of less than 7.0% is more aggressive than the American Diabetes Association guidelines<sup>11</sup> in place at the time of the study, this finding is consistent with the American College of Endocrinology<sup>12</sup> 2001 consensus guidelines recommending the treatment of patients with DM to an A1C level of less than 6.5%.

The recent publication of the results of ADOPT<sup>9</sup> demonstrated the differences between initial monotherapy regimens of metformin, glyburide, and rosiglitazone. ADOPT found that at 5 years the cumulative incidence of monotherapy failure was 21% with metformin and 34% with glyburide, compared with 15% with rosiglitazone. However, the study had a high rate of discontinuation, and patients receiving rosiglitazone gained substantially more weight during the study follow-up period than patients receiving glyburide or metformin. Another recent investigation of combination regimens, a randomized trial of pioglitazone or gliclazide added to metformin therapy, found that at 1 year and at 2 years after study initiation patients

■ **Table 2.** Baseline Glycosylated Hemoglobin (A1C) Level and Change During the Follow-up Period\*

Variable	Total (N = 579)		A1C Level of $\geq 7.0\%$ at Baseline (n = 450)	
	Metformin-Sulfonylurea (n = 300)	Metformin-Thiazolidinedione (n = 279)	Metformin-Sulfonylurea (n = 248)	Metformin-Thiazolidinedione (n = 202)
Baseline A1C (%) level	8.4 $\pm$ 1.9	8.0 $\pm$ 1.8	8.9 $\pm$ 1.8	8.8 $\pm$ 2.0
A1C level of $<7.0\%$ at baseline, %	52 (17.3)	77 (27.6)	—	—
A1C level (%) at follow-up	7.1 $\pm$ 1.3	7.0 $\pm$ 1.3	7.3 $\pm$ 1.3	7.2 $\pm$ 1.3
Change in A1C level from baseline	-1.2 $\pm$ 1.9	-1.2 $\pm$ 1.7	-1.4 $\pm$ 2.0	-1.6 $\pm$ 1.7
Change in A1C level from baseline, %	-12.3 $\pm$ 18.3	-12.1 $\pm$ 16.5	-14.2 $\pm$ 18.9	-17.2 $\pm$ 15.0
Achieved goal A1C level during the follow-up period	207 (69.0)	208 (74.6)	156 (62.9)	137 (67.8)
Therapy intensification	171 (57.0)	188 (67.4)	142 (57.3)	140 (69.3)
Insulin use after index date	14 (4.7)	11 (3.9)	13 (5.2)	9 (4.5)
<b>Secondary failure</b>				
Patients meeting eligibility criteria, no. <sup>†</sup>	—	—	104	89
Patients who experienced secondary failure	—	—	52 (50.0)	28 (31.5)

\*Data are given as mean  $\pm$  SD or as number (percentage) unless otherwise indicated.

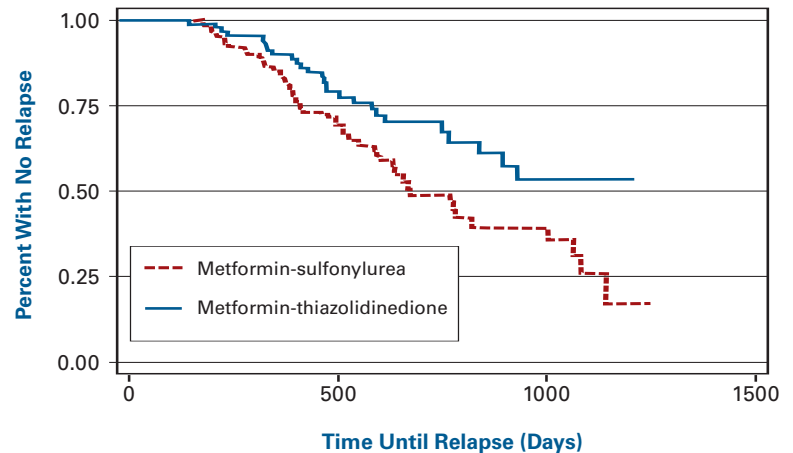
<sup>†</sup>To be eligible for assessment of secondary failure, patients were required to have a baseline A1C greater than or equal to 7.0%, have a follow-up A1C test result during the study period that was less than 7.0%, and have a subsequent A1C test result available for assessment. SD indicates standard deviation.

## Adding Thiazolidinedione or Sulfonylurea Therapy to a Metformin Regimen

receiving pioglitazone and gliclazide, when added to metformin, had similar reductions in A1C level and were equally as likely to achieve target A1C level.<sup>13,14</sup> However, few studies have evaluated these second-line therapy regimens in usual care, nonclinical trial settings. Bell and Ovalle,<sup>15</sup> in a retrospective study of 100 patients, found that after monotherapy failure (A1C level,  $\geq 8.0\%$ ), combination therapy with metformin plus a sulfonylurea maintained glycemic control (A1C level,  $\leq 7.9\%$ ) for a mean of 7.9 years. Another study<sup>16</sup> of patients who added a sulfonylurea to existing metformin therapy in primary care practices in the United Kingdom found that, although glycemia improved initially, within 4 years 85% of all patients and 68% of patients who initially achieved an A1C level of less than 7.0% had A1C levels that exceeded 8.0%. An analysis of thiazolidinediones used in “triple therapy” demonstrated that the addition of a thiazolidinedione to metformin-sulfonylurea resulted in maintenance of glycemic control (A1C level,  $< 7.0\%$ ) and delay of insulin therapy initiation for a median duration of 6 years.<sup>17</sup> Finally, Karter et al<sup>18</sup> conducted a study among poorly controlled (A1C level,  $> 8.0\%$ ) patients with type 2 DM from Kaiser Permanente in Northern California that included 329 patients using thiazolidinediones as monotherapy and in combination with other oral antidiabetic medications and found that the presence of thiazolidinediones in the therapeutic regimen was associated with greater odds of achieving glycemic control than the odds of controlled A1C for patients using a metformin-sulfonylurea regimen. In the Kaiser Permanente cohort of poorly controlled (A1C level,  $> 8.0\%$ ) patients with type 2 DM with a change in treatment regimen, despite an overall mean reduction in A1C level of 1.3%, only 18% of patients studied achieved A1C levels of 7.0% or lower within a year.<sup>18</sup> This is in contrast to the present study, in which 65.1% of patients who were poorly controlled (A1C level,  $\geq 7.0\%$ ) at study baseline achieved glycemic control during the study period. However, the differences in the patient populations studied, in addition to the threshold used to define “poorly controlled” patients may explain these apparent discrepancies, as the mean baseline A1C level in the present study was 8.3% compared with a mean baseline A1C level of 9.9% in the Kaiser Permanente study cohort.<sup>18</sup>

Other investigators have evaluated patients transitioning from oral antihyperglycemic monotherapy to dual combination therapy and have reported mean A1C levels of approximately 9% to 10% at the time of therapy intensification.<sup>16,18-21</sup> The mean baseline A1C level reported in the pres-

■ **Figure.** Time Elapsed From Initiation of Combination Therapy to Secondary Failure (Kaplan-Meier Curves)



ent study at the point of dual combination therapy initiation was 8.3%, which is somewhat lower than what has been reported for patients transitioning from monotherapy to dual therapy in the other studies. Therefore, our managed care population may have better glycemic control than populations studied elsewhere. One potential reason for this may be that 96.5% of our study population was younger than 65 years, as the database used for our study was primarily limited to patients before eligibility for Medicare benefits. By contrast, other observational studies<sup>16,18-20</sup> included a greater proportion of patients 65 years or older. Another possibility may be that our data are slightly more current and may reflect more recent changes in provider practice patterns than what has been reported in the earlier studies.

A recent retrospective, population-based study by Brown et al,<sup>21</sup> conducted at Kaiser Permanente Northwest, underscores the implications of our study findings. They calculated glycemic burden, defined as months of A1C level that exceeded 8.0% or 7.0%, and used multivariate analysis to predict future deterioration of glycemic control. Patients on average accumulated 10 years of glycemic burden greater than 7.0% and 5 years of glycemic burden greater than 8.0%. Furthermore, the authors found that a change in therapeutic regimen at an A1C level of 7.0% or lower was more likely to prevent future additional deterioration of glycemic control than an action point of 8.0%. On average, patients in our study had a second therapeutic agent added at an A1C level of 8.2% and had dual therapy intensified at an A1C level of 7.9%. The importance of earlier interventions aimed at more aggressive patient management to improve glycemic control over time and to delay the onset of complications cannot be overstated.

The present analysis provides insight to the real-world effectiveness of dual-combination oral antihyperglycemic

### Take-away Points

Type 2 diabetes mellitus treatment guidelines recommend initial therapy with metformin, followed by addition of a sulfonylurea or thiazolidinedione when metformin therapy alone fails to achieve or maintain a glycosylated hemoglobin level of less than 7.0%.

- By demonstrating a high rate of failure of glycemic control with a thiazolidinedione or a sulfonylurea added to metformin therapy during a 4-year period in a managed care setting, this study highlights the need for continual patient monitoring, more aggressive patient management, and earlier initiation of combination therapy regimens.
- The availability of multiple antidiabetic therapeutic options is important to effectively treat patients with type 2 diabetes mellitus in the long term.

therapy during 4 years, but a few limitations must be considered. Secondary failure refers to the concept of the failure of oral antihyperglycemic medications to control blood glucose level after a period of initial success.<sup>22</sup> Our study used pharmacy claims and laboratory results data to examine the frequency of secondary failure, defined in a subset of patients not at goal A1C level at baseline who during the study initially achieved goal A1C level but subsequently had their A1C level increase greater or equal to 7.0%. Other studies<sup>22-25</sup> examined this concept using different data sources or definitions of secondary failure, often using the criterion of elevated A1C level (>7.0% or >8.0%) or fasting glucose level after a period of initial medication efficacy. Comparisons of rates of secondary failure in the literature should consider the data source and the criteria used to identify secondary failure specific to each study. We used a stabilization period of more than 76 days after the index prescription to assess follow-up A1C level; this may have been disadvantageous to thiazolidinediones because they may take up to 12 weeks to reach A1C stabilization. Because we conducted a retrospective study using claims data, the duration of DM, body mass index, and patient racial/ethnic background information was unavailable for analysis. We studied patients from a large US managed care plan; therefore, findings may not be applicable to patients without health insurance. Also, few patients (3.5%) 65 years or older were included because the study database was primarily limited to persons younger than 65 years. This study also did not assess concomitant use of medications to treat other related cardiovascular conditions such as hyperlipidemia. Nevertheless, although retrospective studies cannot facilitate comparisons of drug efficacy that are evaluated in prospective clinical trials, they provide valuable information about real-world treatment effectiveness outside of the controlled clinical trial setting. Therefore, this study provides important information that reflects the usual care of patients with type 2 DM.

### CONCLUSIONS

We used a retrospective design to analyze a unique managed care database with integrated A1C level, medical, and pharmacy claims data. We evaluated commonly used second-line oral antihyperglycemic therapies added to the regimen of patients with type 2 DM receiving metformin monotherapy for up to 4 years following dual-combination therapy initiation. Despite initial decreases in A1C level, the proportion of patients who experienced goal A1C level failure after initially achieving goal A1C level after adding a thiazolidinedione or a sulfonylurea to metformin therapy was 41.5%, and the mean time elapsed from addition of a thiazolidinedione or a sulfonylurea to existing metformin therapy was only 1.3 years. Furthermore, 60.7% of study patients had another antihyperglycemic agent added to their initial combination therapy regimen during the study period. Our study highlights the need for continual patient follow-up and monitoring and for more aggressive management of type 2 DM in usual practice. Earlier initiation of combination therapy may delay the onset of secondary failure and may have a beneficial effect on the course of type 2 DM by preventing or delaying the onset of microvascular and macrovascular complications.

**Author Affiliations:** From Health Economics and Outcomes, i3 Innovus, an Ingenix Company, Eden Prairie, Minn (AAR, HH); and MedMentis Consulting, LLC, Towaco (JW), and Novartis Pharmaceuticals Corporation, East Hanover (CAP), NJ.

**Funding Source:** This study was funded by Novartis Pharmaceuticals Corporation.

A portion of this study was presented at the 66th Scientific Sessions of the American Diabetes Association; Washington, DC; June 10, 2006.

**Author Disclosure:** Ms Wogen reports receiving compensation from Novartis for assistance with manuscript preparation. Dr Plauschinat is an employee of Novartis and holds stock in the company.

The authors (AAR, HH) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter discussed in this manuscript.

**Authorship Information:** Concept and design (AAR, JW, CAP); acquisition of data (AAR); analysis and interpretation of data (AAR, HH); drafting of the manuscript (AAR, JW, CAP); critical revision of the manuscript for important intellectual content (AAR, HH, JW, CAP); statistical analysis (AAR, HH); administrative, technical, or logistic support (HH); supervision (AAR, CAP).

**Address correspondence to:** Jenifer Wogen, MS, MedMentis Consulting, LLC, 145 Waughaw Rd, Towaco, NJ 07082. E-mail: jen@medmentis.com.

### REFERENCES

1. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care*. 2004;27:17-20.
2. Hogan P, Dall T, Nikolov P; American Diabetes Association. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26:917-932.
3. American Diabetes Association. Standards of medical care in diabetes: 2007. *Diabetes Care*. 2007;30(suppl 1):S4-S41.

## Adding Thiazolidinedione or Sulfonylurea Therapy to a Metformin Regimen

- 4. United Kingdom Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837-853.
- 5. Fan T, Koro CE, Fedder DO, Bowlin SJ.** Ethnic disparities and trends in glycemic control among adults with type 2 diabetes in the U.S. from 1988 to 2002. *Diabetes Care*. 2006;29:1924-1925.
- 6. Nathan DM, Buse JB, Davidson MB, et al.** Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2006;29:1963-1972.
- 7. United Kingdom Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.
- 8. Turner RC, Cull CA, Frighi V, Holman RR; UK Prospective Diabetes Study (UKPDS) Group.** Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281:2005-2012.
- 9. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group.** Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443.
- 10. Charlson ME, Pompei P, Ales KL, MacKenzie CR.** A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-378.
- 11. American Diabetes Association.** Standards of medical care for patients with diabetes mellitus. *Diabetes Care*. 2002;25:213-229.
- 12. ACE Consensus Development Conference on Guidelines for Glycemic Control.** Available at: <http://www.aace.com/meetings/consensus/dcc/pdf/dccwhitepaper.pdf>. Accessed July 26, 2007.
- 13. Charbonnel B, Scherthamer G, Brunetti P, et al.** Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of glimepiride or metformin in patients with type 2 diabetes. *Diabetologia*. 2005;48:1093-1104.
- 14. Matthews DR, Charbonnel BH, Hanefeld M, Brunetti P, Scherthamer G.** Long-term therapy with addition of pioglitazone to metformin compared with the addition of glimepiride to metformin in patients with type 2 diabetes: a randomized, comparative study. *Diabetes Metab Res Rev*. 2005;21:167-174.
- 15. Bell DSH, Ovalle F.** How long can insulin therapy be avoided in the patient with type 2 diabetes mellitus by use of a combination of metformin and a sulfonylurea? *Endocr Pract*. 2000;6:293-295.
- 16. Cook MN, Girman CJ, Stein PP, Alexander CM, Holman RR.** Glycemic control continues to deteriorate after sulfonylureas are added to metformin among patients with type 2 diabetes. *Diabetes Care*. 2005;28:995-1000.
- 17. Bell DSH, Ovalle F.** Long-term glycaemic efficacy and weight changes associated with thiazolidinediones when added at an advanced stage of type 2 diabetes. *Diabetes Obes Metab*. 2006;8:110-115.
- 18. Karter AJ, Moffet HH, Liu J, et al.** Achieving good glycemic control: initiation of new antihyperglycemic therapies in patients with type 2 diabetes from the Kaiser Permanente Northern California Diabetes Registry. *Am J Manag Care*. 2005;11:262-270.
- 19. Blonde L, Wogen J, Kreilick C, Seymour AA.** Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. *Diabetes Obes Metab*. 2003;5:424-431.
- 20. Brown JB, Nichols GA.** Slow response to loss of glycemic control in type 2 diabetes mellitus. *Am J Manag Care*. 2003;9:213-217.
- 21. Brown JB, Nichols GA, Perry A.** The burden of treatment failure in type 2 diabetes. *Diabetes Care*. 2004;27:1535-1540.
- 22. Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D.** Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. *Diabetes Care*. 1986;9:129-133.
- 23. Lopez-Alvarenga JC, Aguilar-Salinas CA, Velasco-Perez ML, et al.** Acarbose vs bedtime NPH insulin in the treatment of secondary failures to sulphonylurea-metformin therapy in type 2 diabetes mellitus. *Diabetes Obes Metab*. 1999;1:29-35.
- 24. Nichols GA, Alexander CM, Girman CJ, Kamal-Bahl SJ, Brown JB.** Treatment escalation and rise in HbA1c following successful initial metformin therapy. *Diabetes Care*. 2006;29:504-509.
- 25. Nichols GA, Alexander CM, Girman CJ, Kamal-Bahl SJ, Brown JB.** Contemporary analysis of secondary failure of successful sulfonylurea therapy. *Endocr Pract*. 2007;13:37-44. ■