Glycemic Control Continues to Deteriorate After Sulfonylureas Are Added to Metformin Among Patients With Type 2 Diabetes

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OBJECTIVE — To describe the course and predictors of glycemic control among patients with type 2 diabetes after sulfonylureas (SUs) are added to metformin (MF).

RESEARCH DESIGN AND METHODS — Patients (n = 2,220) treated with MF monotherapy for >90 days before initiating MF plus SU combination therapy between January 1998 and March 2004 were studied in a retrospective analysis of electronic medical records from U.K. primary care practices using the General Practice Research Database. Median glycoslyated hemoglobin A_{1c} (A1C) before and after SU initiation was described, and patient characteristics were evaluated as predictors of time until A1C ≥8.0% or glucose-lowering therapy was intensified (by starting insulin or adding a third oral agent).

RESULTS — At 6 months post-SU initiation, median A1C resumed deteriorating at a somewhat comparable rate to that observed on MF monotherapy. Higher pre-SU A1C, younger age, female sex, shorter diabetes duration, higher serum creatinine, and being an ex-smoker predicted time until A1C ≥8.0% or glucose-lowering therapy was intensified in various analyses. Median A1C was 9.5% when therapy was intensified. A1C ≥8.0% was estimated to occur in 85% of patients 4 years after SU initiation and in 68% 4 years after initially achieving A1C <7% on MF plus SU therapy.

CONCLUSIONS — In this population, glycemic control is improved following the addition of SUs to MF, but deterioration resumes as early as 6 months. The high proportion of patients remaining on MF plus SU therapy despite having A1C ≥8.0% suggests that there are significant barriers to starting insulin or adding a third agent when treatment goals are not achieved with this combination.

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Type 2 diabetes is a chronic progressive disorder, with increasing worldwide prevalence and significant direct and indirect economic costs (1–2). The macrovascular and microvascular complications associated with diabetes are well documented by the U.K. Prospective Diabetes Study (UKPDS) (3) and other studies (4), and current management guidelines have suggested more aggressive goals for glycemic control (5–6). Declining pancreatic β-cell function is thought to underlie the progressive hyperglycemia seen in type 2 diabetes (7). Monotherapy with an oral hypoglycemic agent (OHA) is often initially effective in controlling hyperglycemia, but currently marketed oral therapies are associated with high secondary failure rates (7–13). In the UKPDS, 53% of newly diagnosed diabetic patients treated with a sulfonylurea (SU) required the addition of insulin to maintain adequate glycemic control by 6 years (8). Recent controlled clinical trials (14–20) of 1–2 years duration support these findings. Observational studies (21–24) generally also find a progressive deterioration of glycemic control. For patients not requiring insulin, combination therapy with OHAs, most commonly metformin (MF) and an SU, are being increasingly used to maintain target plasma glucose levels. Early addition of MF to patients on monotherapy with SUs in the UKPDS lowered A1C levels initially, but subsequent values increased at the same rate as on SUs alone (25). Little is known about glycemic control over time with MF plus SU combination therapy among patients previously treated with MF monotherapy. In addition, patient characteristics that predict how long patients can remain on combination therapy before requiring more intensive glucose-lowering interventions have not been well established. We conducted a retrospective population-based observational study using electronic medical records to evaluate combination therapy with MF and SUs in controlling A1C over time among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The General Practice Research Database (GPRD) (26) contains anonymized electronic medical records from primary care for >3 million residents of the U.K. The GPRD includes information on patient demographics, outpatient drug prescriptions, medical diagnoses, specialist referrals, hospital ad-

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Abbreviations: GPRD, General Practice Research Database; IQR, interquartile range; MF, metformin; OHA, oral hypoglycemic agent; SU, sulfonylurea; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

missions, outpatient laboratory test results, and clinical findings (e.g., BMI, smoking, and blood pressure). This study analyzed data from 290 practices deemed to be "up-to-standard" for research purposes as of 31 March 2004 based on data quality criteria (27).

We identified patients with type 2 diabetes in the GPRD whose first evident computer-issued prescription for an antidiabetic agent was for MF and then selected all those with at least one prescription for an SU between 1 January 1998 and 31 March 2004 who continued to receive prescriptions for MF without a concurrent prescription for insulin or a third OHA (acarbose, troglitazone, pioglitazone, rosiglitazone, repaglinide, or nateglinide). Patients were excluded for the following reasons: not registered as a permanent patient of a general practitioner ($n = 11$); registration details incomplete or invalid ($n = 81$); <1 year of registration with a general practitioner ($n = 478$); <1 year of up-to-standard follow-up ($n = 729$); <90 days of prior use of MF monotherapy ($n = 836$); date of first diabetes diagnosis missing or invalid ($n = 119$); recorded history of insulin-dependent diabetes, malnutrition-associated diabetes, drug-induced diabetes, or gestational diabetes ($n = 53$); <30 years of age when diabetes was first diagnosed ($n = 13$); no historical A1C test results recorded ($n = 377$); and no A1C test result recorded within 90 days before SU initiation ($n = 797$). The final study sample consisted of 2,220 patients.

Variable definitions

All patients had complete data on A1C within 90 days of the date of SU initiation (index date), birth year, sex, and date of diabetes diagnoses due to study exclusion criteria. Smoking status, BMI, systolic and diastolic blood pressure, blood glucose, serum creatinine, and total serum cholesterol were obtained from the most recent measurement recorded before the index date (if available). Comorbidities were identified by the presence of a disease-related code in a patient's electronic medical history dated on or before the index date. Past use of specific cardiovascular medications was defined by the presence of at least one computer-issued outpatient prescription dated on or before the index date.

End point definitions

The primary composite end point was defined as time on MF plus SU combination therapy until A1C ≥8.0% or glucose-lowering therapy was intensified. A1C measurements ≥8.0% recorded during the first 90 days of SU treatment were not considered events to allow time for the SU to take effect. The intensification of glucose-lowering therapy was defined as the initiation of insulin or the addition of a third OHA in combination with both MF and an SU agent. The latter required that a patient receive at least one MF and one SU prescription on or after the first prescription for the third OHA to better ensure that the third OHA was not initiated because of intolerances to either MF or SU agents. Otherwise, a patient was censored as a nonevent at the date of the first prescription for a third OHA. Time on MF plus SU combination therapy until therapy intensification (regardless of A1C) and time until first insulin use (regardless of A1C and current OHA treatment regimen) were evaluated as separate end points. Subgroup analyses were conducted for patients who had at least one A1C test result <7% recorded while they were on MF plus SU combination therapy. Increases in A1C of ≥0.5, ≥1.0, and ≥2.0% relative to patients' first A1C measurement 91–180 days after SU initiation also were evaluated as separate end points during the time that patients remained on MF plus SU therapy. Patient follow-up ended at the earliest date of the last A1C test result recorded during the study period (except when evaluating time to therapy intensification and time to insulin use), the first prescription for a third OHA (except when evaluating time to insulin use), the first insulin prescription, death, transferal out of the practice, or the study end date (31 March 2004).

Statistical analysis

The median and interquartile range (IQR) of A1C in the population were estimated using a moving 3-month window that analyzed A1C measurements in cross-sectional samples of the population relative to the dates of patients' first MF prescription (pre-SU period) and first SU prescription (post-SU period). No estimates combined A1C measurements recorded in both the pre- and post-SU periods. Piecewise linear mixed-effects modeling was used to estimate the slope of A1C change per unit time in the population during specific pre- and post-SU periods. Patients were included in these analyses regardless of their adherence to their prescribed drug therapies.

The relationship between patient characteristics and time to each end point was evaluated using Cox proportional hazards regression models. Hazard ratios (HRs) and 95% CIs were estimated using multivariable regression. Subjects with missing data for any predictor variable were excluded from all analyses. Subjects without a subsequent A1C measurement recorded during follow-up were also excluded from analyses of end points defined by A1C. For categorical variables, the HR estimated the ratio of failure rates comparing patients with the characteristic with patients in the reference group. For continuous variables, the HR estimated the change in the failure rate for a one-unit increase in the predictor variable. Kaplan-Meier analyses were used to estimate the proportions of patients over time to have had at least one A1C ≥8.0%, to have been prescribed a new agent (insulin or third OHA), and to have initiated insulin for the overall patient population and for subgroups stratified by pre-SU A1C level.

We investigated potential surveillance bias in A1C monitoring by evaluating between-group differences in median time to the first A1C test >90 days after the addition of the SU using the log-rank test. The annual frequency of A1C testing during follow-up among different patient subgroups also was compared. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS — The average age of the study population was 62 years (range 31–96 years), 54% were men, and the median time since diabetes diagnosis was 3.8 years (Table 1). Median A1C was 8.8%, and 76% of patients had an A1C >8.0% at the time of SU initiation. The subgroup who achieved A1C <7.0% while on MF plus SU combination therapy had a lower median A1C, higher median age, and longer median duration of diabetes at the time an SU agent was added compared with the overall patient population.

On average, A1C was measured twice a year in this population. Median A1C increased monotonically while patients were on MF monotherapy at an estimated annualized rate of 0.32% (95% CI 0.26–

Table 1—*Patient characteristics and their relationship to shorter time until A1C ≥8% or the intensification of glucose-lowering therapy**

	All patients followed from start of MF plus SU combination therapy (n = 2,220)			Subgroup followed from their first A1C <7% achieved on MF plus SU combination therapy (n = 801)		
	Distribution at SU initiation†	Composite end point of time to A1C ≥8% or therapy intensification‡	End point of time to therapy intensification regardless of A1C	Distribution at SU initiation§	Composite end point of time to A1C ≥8% or therapy intensification	End point of time to therapy intensification regardless of A1C
Characteristic	Median (IQR) or % group	HR (95% CI)	HR (95% CI)	Median (IQR) or % group	HR (95% CI)	HR (95% CI)
A1C (%)	8.8 (8.0–9.9)	1.33 (1.28–1.40)	1.24 (1.13–1.36)	8.3 (7.7–9.2)	1.25 (1.10–1.41)	1.05 (0.80–1.38)
Age (years)	63 (54–70)	0.99 (0.98–1.00)	0.97 (0.96–0.99)	65 (57–72)	1.00 (0.98–1.01)	0.96 (0.92–1.00)
Duration of diabetes (years)	3.8 (1.9–6.9)	0.98 (0.96–1.00)	0.96 (0.92–1.00)	4.0 (1.9–7.2)	1.00 (0.96–1.04)	0.95 (0.86–1.06)
Women (vs. men)	46.4%	1.21 (1.03–1.43)	1.67 (1.19–2.33)	43.8%	0.95 (0.64–1.41)	1.36 (0.61–3.05)
Current smoker (vs. never)	20.0%	0.90 (0.74–1.10)	1.02 (0.68–1.52)	17.5%	1.02 (0.66–1.59)	0.62 (0.20–1.89)
Ex-smoker (vs. never)	34.2%	0.88 (0.74–1.04)	1.03 (0.72–1.47)	35.4%	0.56 (0.38–0.83)	0.59 (0.25–1.41)
BMI (kg/m^2)	31.4 (28.2–35.2)	1.00 (0.99–1.02)	0.99 (0.96–1.02)	31.0 (27.9–34.9)	1.02 (0.99–1.06)	0.98 (0.91–1.05)
Systolic blood pressure (mmHg)	140 (130–154)	1.00 (0.99–1.00)	1.00 (0.99–1.01)	140 (130–155)	1.00 (0.99–1.01)	1.02 (1.00–1.04)
Diastolic blood pressure (mmHg)	80 (77–90)	1.00 (0.99–1.01)	0.99 (0.97–1.01)	80 (77–88)	1.01 (0.99–1.03)	1.00 (0.96–1.05)
Serum creatinine (μmol/l)	86 (74–99)	1.00 (0.99–1.00)	1.01 (1.00–1.02)	88 (76–101)	0.99 (0.99–1.00)	1.01 (1.00–1.03)
Total cholesterol (mmol/l)	5.2 (4.5–6.0)	1.05 (0.98–1.12)	1.02 (0.90–1.16)	5.2 (4.5–5.8)	1.03 (0.88–1.21)	0.95 (0.68–1.33)
Excluded (n)						
No subsequent A1C test	434	434	NA	210	210	NA
Missing data	NA	599	599	NA	200	200
Number followed-up	1,786	1,302	1,621	591	441	601
Person-years of follow-up	1,973.5	1,402.0	2,676.6	703.7	673.2	866.8
Number of events by type						
A1C ≥8%	1,017	723	NA	190	145	NA
Third OHA added	32	19	102	7	4	22
Insulin started	22	14	77	2	0	9
Censored (n)						
Switched to another OHA	42	29	114	14	9	26
Last A1C test	674	518	NA	378	283	NA
Lost to follow-up	NA	NA	1,328	NA	NA	544

*Therapy intensification defined as the initiation of insulin or the addition of a third OHA in combination with both MF and an SU agent. †Initial SU agent prescribed in combination with MF was gliclazide (74.8%), glimepiride (11.8%), glibenclamide (6.1%), glipizide (4.1%), and tolbutamide (3.2%). Prevalence of comorbidities: hypertension (54.2%), dyslipidemia (24.7%), coronary heart disease (24.4%), heart failure (5.3%), peripheral vascular disease (5.0%), venous thromboembolism (4.9%), and proteinuria (3.2%). Prevalence of cardiovascular medication use: diuretics (44.9%), ACE inhibitors (44.3%), statins (38.8%), low-dose aspirin (36.2%), β-blockers (35.6%), calcium channel blockers (33.2%), nitrates (19.5%), and antiarrythmia drugs (16.8%). ‡A1C test results ≥8% recorded during the first 90 days of SU treatment were ignored as events to allow time for the SU to take effect. Results were comparable when event times for A1C ≥8% were shifted to after the date of the patients' last recorded A1C <8% while they were still on MF plus SU therapy. §Initial SU agent prescribed in combination with MF was gliclazide (77.7%), glimepiride (9.5%), glibenclamide (5.6%), glipizide (4.1%), tolbutamide (3.1%). Prevalence of comorbidities and cardiovascular medication use in this subgroup was similar to the overall population reported above.

0.38) from 3 years to 6 months before an SU agent was added to MF (Fig. 1). In the 6-month period immediately preceding SU initiation, loss of glycemic control appeared to accelerate sharply at an estimated annualized rate of 1.21% (0.96–1.46). Median A1C dropped from 8.8% to an observed population nadir of 7.3% at 6 months post-SU. After the 6th month of MF plus SU treatment, median A1C resumed its pre-SU pattern of deterioration, with an estimated annualized rate of change of 0.61% (0.28–0.94) between 6 and 12 months after SU initiation when the use of other glucose-lowering therapies was still limited (<9%). As increasing numbers of patients were censored due to starting insulin or other OHAs, the rate of A1C change in the population appeared to become fairly flat, and median A1C remained ~8.0% between 1 and 3 years after SU initiation.

Higher pre-SU A1C ($P < 0.001$), younger age ($P = 0.016$), and female sex ($P = 0.021$) predicted shorter time to A1C ≥8.0% or therapy intensification after the addition of an SU to MF (Table 1). Higher pre-SU A1C ($P < 0.001$) and being an ex-smoker ($P = 0.004$) were predictive in the subgroup who achieved

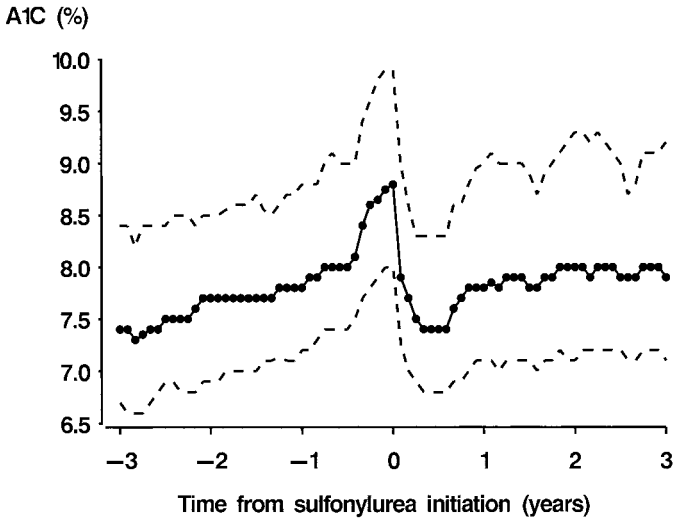

Figure 1—*Rolling 3-month median (●) and upper and lower quartiles (broken lines) of A1C before and after the addition of SUs to MF monotherapy (cross-sectional data, number of patients contributing an A1C measurement was 210, 402, 695, 2,220, 810, 441, and 269 at −3, −2, −1, 0, 1, 2, and 3 years from the initiation of the SU agent, respectively).*

A1C <7% while on MF plus SU combination therapy (Table 1). Disregarding therapy intensifications in the composite end point did not materially change these results.

Over 3,810 person-years of follow-up, while patients were treated with MF plus SU combination therapy (n = 2,220), 278 patients intensified their glucose-lowering regimen (123 started insulin and 155 added a third OHA in combination with both MF and an SU agent), while 155 patients switched to a third OHA and discontinued either MF or the SU agent. Median (IQR) A1C at the time of therapy intensification was 9.5% (8.7–10.5), and median (IQR) time from patients' first post-SU A1C ≥8.0% (n = 218) to therapy intensification was 331 days (143–582). Median (IQR) A1C at the time of an OHA switch was 8.7% (7.8–10.0), which was similar to the distribution of A1C in the overall population at the time of SU initiation. Higher pre-SU A1C ($P < 0.001$), younger age ($P < 0.001$), female sex ($P = 0.003$), shorter diabetes duration ($P = 0.040$), and higher serum creatinine ($P = 0.032$) predicted shorter time until therapy was intensified among the overall patient population, while younger age ($P = 0.047$) was predictive of this end point among the subgroup who initially achieved A1C <7% while on MF plus SU therapy (Table 1).

Over 4,207 person-years of follow-up, 188 patients initiated insulin, of whom 65 had previously tried a third OHA. Median (IQR) A1C at the time of patients' first insulin prescription was 9.9% (9.0–11.0). Higher pre-SU A1C ($P < 0.001$), younger age ($P = 0.004$), female sex ($P = 0.001$), and being an ex-smoker ($P = 0.033$) predicted shorter time to the initiation of insulin (n = 1,621 patients, events = 122). Among patients with an A1C measurement recorded 91–180 days post-SU, pre-SU A1C ($P = 0.005$) was the only factor predictive of shorter time to a ≥1% increase in A1C (n = 730, events = 278). No variable was predictive of time to either a ≥0.5 or ≥2.0% increase in A1C.

Kaplan-Meier estimates of the proportion of patients with at least one A1C ≥8.0% >90 days after initiating an SU agent were 44, 68, 79, and 85% at 1, 2, 3, and 4 years of follow-up, respectively, with median times to this end point occurring sooner for those with higher pre-SU A1C levels (Fig. 2). The proportion of patients estimated to be prescribed a new glucose-lowering agent (including OHA switches) at 1, 2, 3, and 4 years after SU initiation was 8, 20, 32, and 42%, respectively, while the corresponding proportions estimated to be using insulin were 2, 8, 14, and 20%, respectively. In the subgroup who initially achieved A1C <7% after the addition of an SU to MF, the proportion estimated to have had an A1C ≥8.0% was 19, 43, 60, and 68% at 1, 2, 3, and 4 years follow-up, respectively, with median times to this end point occurring sooner for patients with higher pre-SU A1C levels (Fig. 2).

Median time to the first A1C test after the 90th day of SU treatment was 83 days in the overall population (n = 1,786), and it was significantly longer for younger compared with older patients ($P < 0.01$) and significantly longer for patients with higher compared with lower levels of pre-SU A1C ($P = 0.02$). Median time to the first A1C test after 90 days of SU treatment was materially shorter for women than for men ($P = 0.06$). No material differences in median times to A1C testing were observed across levels of smoking, diabetes duration, and serum creatinine. Frequency of A1C testing during each year of follow-up was similar across these patient subgroups.

CONCLUSIONS — Based on this retrospective analysis of a large database of electronic medical records from U.K. primary care practices, we found that the progressive deterioration in A1C observed while patients were treated with MF monotherapy resumes after the initial 6 months of MF plus SU combination therapy. This observation is consistent with UKPDS findings for oral monotherapy among newly diagnosed patients with diabetes. In this interventional study, median A1C rose from 6.0 to ~8.5% for intensive therapy with MF or SUs at 6 years (12,25). The annualized rate of A1C change in the 6–12 months after SU initiation in our population (0.6%) was comparable to the rate observed >6 months before an SU was added (0.3%) while our population was still on MF monotherapy, and it was also similar to the annualized rate of A1C change observed among patients treated with glibenclamide (0.5%) in the UKPDS (8). The accelerated deterioration of glycemic control observed during the 6 months leading up to the addition of the

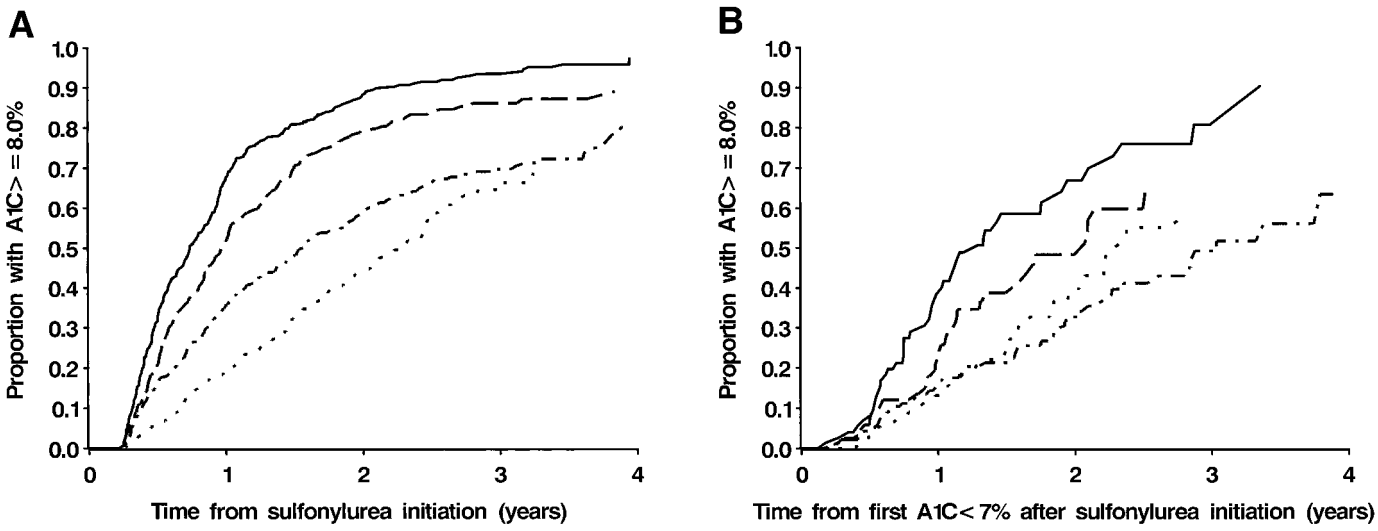

Figure 2—*Kaplan-Meier estimates of the proportion of patients who have had at least one A1C test result ≥8.0% recorded >90 days after the addition of an SU agent to MF* (n = *1,786, 717, 251, 92, and 22 at 0, 1, 2, 3, and 4 years, respectively)* (A) *and after initially achieving A1C <7% following the addition of an SU agent to MF* (n = *591, 307, 120, 40, and 8 at 0, 1, 2, 3, and 4 years, respectively)* (B) *stratified by pre-SU A1C level ≥10% (———), 9.0–9.9% (— — —), 8.0–8.9% (— - —), or 4.0–7.9% (- - - -). Median (IQR) time from SU initiation to patients' first A1C test result <7% was 160 days (92–287) for the data presented in* B.

SU in our study is likely due to the selection of patients at the time of a recent spike in their A1C (which had prompted their physicians to add an SU agent). A sharp rise in mean A1C manifesting in the year preceding the addition of MF to SU monotherapy was also noted in another observational study that used similar methods (21). The apparent lack of A1C deterioration observed in our data 12 months after SU initiation may be largely due to survivor bias, where patients with higher A1C levels were disproportionately censored at earlier time points due to starting other agents, leaving patients with better glycemic control in the analysis at later time points.

Few observational studies have evaluated predictors of A1C deterioration over time among patients with type 2 diabetes treated with OHAs, particularly MF plus SU combination therapy. A study (24) of patients with type 2 diabetes treated in a health maintenance organization in the Pacific Northwest found that higher A1C, older age, and poorer medication adherence predicted a >0.10% increase in the next A1C measurement for patients treated with the combination of MF plus SU, with no significant association found with sex or the number of months of therapy. A Scottish study (22) found that higher pretreatment A1C, younger age, lower BMI, but not duration of diabetes were associated with a higher rate of switching to insulin among new users of OHAs. These results agreed with those of the UKPDS, which found a faster rate of progression to additional therapy among subjects with higher pretreatment A1C, younger age at diagnosis, low BMI (<25 kg/m^2), lower β-cell function, and white race (12). Our study population included predominantly overweight patients previously treated with MF, which may partially explain why BMI was not a significant predictor. The observation that a higher baseline A1C is predictive of inadequate glycemic control after the start of combination therapy is to be expected because patients with more severe baseline hyperglycemia likely have less residual β-cell function and, hence, may be more susceptible to disease progression. Patients with higher serum creatinine, younger age, and shorter duration of disease at the time that a second agent is initiated may also have disease marked by more rapid progression, which would predict a subsequent rapid deterioration in A1C. The biological relevance of quitting smoking to diabetes progression is unclear but may be related to weight gain. The sex difference in A1C deterioration observed in our data should be interpreted with caution in light of the shorter time to A1C testing found among women compared with men in our study.

Our data suggest that half of all patients had A1C ≥8.0% 1 year after starting MF plus SU combination therapy. Physicians typically waited several months after patients' first post-SU A1C test result ≥8.0% before prescribing a new agent, with most therapy changes occurring only after A1C was well >9.0%. American physicians practicing in a health maintenance organization in the Pacific Northwest also waited until A1C was >9.0% before initiating therapy changes, possibly because of the short-term unpredictability of A1C (21,24). Alternatively, this delay in initiating new agents may be due to a general reluctance by patients or physicians to try insulin or a more complex regimen of multiple oral agents when combination therapy fails to provide adequate glycemic control. The high median A1C that preceded the initiation of insulin in our population is particularly troubling and suggests that there are substantial barriers to its initiation. Given the established value of good glycemic control in preventing the complications of diabetes, educational programs that promote earlier and more aggressive treatment to glycemic targets may improve health outcomes in patients with type 2 diabetes.

Several considerations should be taken into account in interpreting our results. The timing of A1C measurements during follow-up may have been dependent on patients' pre-SU A1C level. We attempted to minimize this potential bias

by using a moving 3-month interval and by using mixed-effects modeling. Our analyses were also unable to control for dosage changes or account for patient adherence to their prescribed drug therapies. In view of our use of electronic medical records, there was considerable variability in the timing and frequency of laboratory measurements, and some patients were excluded from some analyses due to missing data.

The availability of A1C values in electronic medical records provided a unique opportunity to study the deterioration of glycemic control over time in patients treated with MF plus SU combination therapy under conditions of routine primary care in the U.K. Our findings suggest that the progressive deterioration of A1C observed while patients are treated with MF monotherapy resumes within 6 months after an SU agent is added and highlights the importance of aggressive monitoring and prompt intervention to improve glycemic control in patients with type 2 diabetes.

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