Treatment Escalation and Rise in HbA_{1c} Following Successful Initial Metformin Therapy

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OBJECTIVE — To describe secondary failure of initial metformin therapy in patients who achieved initial HbA_{1c} (A1C) <8% and to identify predictors of failure.

RESEARCH DESIGN AND METHODS — We identified 1,288 patients who achieved A1C <8% within 1 year of initiating metformin as their first-ever antihyperglycemic drug. Subjects were followed until they added/switched antihyperglycemics, they terminated health plan membership, or 31 December 2004. We defined secondary failure using two separate but overlapping approaches: *1*) addition/switch to another antihyperglycemic drug or *2*) first A1C measurement >8.0% after at least 6 months on metformin.

RESULTS — The best A1C achieved within 1 year of metformin initiation was the most powerful predictor of avoiding secondary failure. Approximately 50% of subjects whose best A1C was 7–7.9% added/switched antihyperglycemic drugs within 36 months, whereas it took >60 months for those in the 6–6.9% A1C category to reach a 50% failure rate. Those who achieved an A1C <6% did not reach a 50% rate of adding/switching drugs until 84 months. For the alternative secondary failure outcome, about half of those whose best A1C was 7.0–7.9% reached an A1C >8% within 24 months. Only ~25% of subjects in the 6–6.9% category failed by 48 months, and >80% of subjects in the <6% category remained below 8% through 60 months.

CONCLUSIONS — Whether defined by adding/switching to another drug or by reaching an A1C of 8%, secondary failure is inversely associated with the reduction of A1C achieved within the 1st year of metformin monotherapy.

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Although lifestyle modification is often the first step for patients newly diagnosed with type 2 diabetes, ~15% of type 2 diabetic subjects fail to lower their fasting plasma glucose to <15.0 mmol/l within the first 3 months of diet therapy (1). After 3 years, 75% of subjects treated with only dietary intervention fail to maintain an HbA_{1c} (A1C) <7% (2). Thus, pharmacotherapy typically becomes a critical treatment modality to achieve and maintain glycemic goals.

Until recently, sulfonylurea monotherapy was the predominant first choice for treating type 2 diabetes in insured populations in the U.S. (3,4). It has also been previously shown that as a second-line agent, metformin therapy often fails to maintain A1C at optimal levels (5,6). Less is known about the long-term efficacy of metformin as an initial therapy used in routine clinical practice in unselected populations. The U.K. Prospective Diabetes Study reported (2) that similar proportions (44–45%) of newly diagnosed overweight sulfonylurea and metformin patients attained A1C <7% after 3 years of first-line use. Boccuzzi et al. (3) reported secondary failure rates (defined as the addition or switch of antihyperglycemics) of 21.8 and 19.1% for metformin and sulfonylurea, respectively, over a 12-month follow-up, but long-term data were not available. A recent study in Saskatchewan (7) demonstrated that compared with sulfonylurea, metformin was associated with a delay in secondary failure in those who had used it for at least 2 years. However, that study did not evaluate A1C levels, so it is not clear whether the 2-year utilization criterion represented successful treatment or was the result of patient or clinician inertia. To our knowledge, no study to date has described secondary failure of initial metformin in clinical practice in terms of A1C levels. In addition, little is known about the predictors of secondary failure in patients who achieved initial A1C levels <8.0% with metformin monotherapy.

RESEARCH DESIGN AND METHODS

— The current study was conducted within Kaiser Permanente Northwest (KPNW), a long-established, not-for-profit, group-model health maintenance organization. KPNW provides comprehensive, prepaid coverage to ~450,000 members. The organization maintains comprehensive electronic health care utilization data on all its members. The electronic medical record, in use since 1996, allows the attending clinician to record as many as 20 ICD-9-CM–coded diagnoses at each ambulatory patient contact and up to 9 discharge diagnoses for inpatient hospital admissions. An electronic problem list, also coded in ICD-9-CM, is available to the clinician at each contact. In addition, a single regional laboratory performs all KPNW laboratory tests, and the results are stored in a searchable electronic database. A pharmacy is located in each medical office, and most members have a pharmacy benefit, helping to ensure complete capture of pharmaceutical dispenses.

We selected all 1,547 members of KPNW with type 2 diabetes whose first-ever antihyperglycemic was metformin, dispensed between 1 January 1996 and 31 December 2003, and who had at least one A1C measured in the year prior and the year following the metformin dis-

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Abbreviations: KPNW, Kaiser Permanente Northwest.

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

Table 1—*Subject characteristics at metformin initiation by whether A1C <8% was achieved within 1 year*

	Achieved A1C <8% within 1 year	Did not achieve A1C <8% within 1 year	*P* value
n	1,288	131	
Proportion of subjects (%)	90.8	9.2	—
Age (years)	57.0 ± 1.8	53.1 ± 11.5	0.001
Women (%)	51.7	53.4	0.706
Months since diabetes diagnosis	16.0 ± 22.5	17.4 ± 19.2	0.437
Cardiovascular disease (%)	12.2	9.2	0.308
Current smoker (%)	22.4	23.7	0.749
Micro- or macroalbuminuria (%)	17.7	26.7	0.011
A1C at initiation (%)	8.6 ± 1.9	9.7 ± 1.8	0.001
Number of A1C measurements in year following initiation	2.1 ± 1.1	1.5 ± 0.7	0.001
Mean BMI (kg/m^2)	36.1 ± 8.2	37.7 ± 8.0	0.045
Mean change in weight (kg) 1 year postinitiation	−4.2 ± 7.9	−1.2 ± 7.5	0.001
Systolic blood pressure (mmHg)	137 ± 15	139 ± 16	0.125
Diastolic blood pressure (mmHg)	81 ± 9	84 ± 8	0.003
Total cholesterol (mg/dl)	209 ± 50	209 ± 41	0.883
HDL cholesterol (mg/dl)	43 ± 12	42 ± 9	0.325
LDL cholesterol (mg/dl)	117 ± 37	122 ± 36	0.157
Triglycerides (mg/dl)	284 ± 321	270 ± 228	0.558
Mean dose, last dispense in 1st year (mg)	1,261 ± 618	1,528 ± 674	0.001

Data are means ± SD unless otherwise indicated.

pense. To ensure that metformin was indeed the first-ever antihyperglycemic, we required subjects to be KPNW members for at least 1 year before the metformin dispense date and to have no other antihyperglycemic medication dispensed in this time period. We also required a minimum of 1 year of membership postdispense. Because we were interested in studying secondary failure, we eliminated 128 subjects who either added or changed to another antihyperglycemic within 6 months of their first metformin dispense (presumably because they did not respond to or could not tolerate metformin). We then divided the population into those who achieved an A1C of <8% (n = 1,288) within 1 year and those who did not (n = 131). The 1,288 successfully treated subjects with A1C <8% constituted the primary analytic sample for the study and were followed until they added or switched antihyperglycemics, had A1C ≥8%, or terminated health plan membership or until 31 December 2004, whichever occurred first.

Study variables

Our primary outcome variable was secondary failure on metformin therapy. We defined secondary failure in two separate but overlapping approaches: *1*) the addition or switch to another antihyperglycemic drug after 6 months of treatment with metformin or *2*) the first A1C measurement ≥8.0% that occurred before the addition/switch of antihyperglycemic therapy. Explanatory factors included A1C at metformin initiation, best A1C achieved in the 1st year after metformin initiation, weight lost in the 1st year after metformin initiation, and metformin adherence. To control for potentially confounding differences in patients who did and did not respond to metformin, we included variables such as patient age, sex, cardiovascular disease status, smoking status, albuminuria, baseline lipid levels, blood pressure, and BMI.

The date of metformin initiation was assigned as the index date. We collected all A1C values during the observation period as well as the last A1C measured before the index date. Age and diabetes duration were calculated as of the index date. We ascertained the presence of cardiovascular disease at baseline by searching the electronic medical record for a diagnosis of stroke (ICD-9-CM 430.xx–432.xx, 434.xx–435.xx, 437.1), myocardial infarction (410.xx), angina (413.xx), acute coronary syndrome (411.1, 411.8), and other atherosclerotic cardiovascular disease (414.0, 414.8, 414.9, 429.2). From laboratory data, we identified subjects with baseline microalbuminuria (albumin excretion rate 30–300 mg/day) or macroalbuminuria (albumin excretion rate >300 mg/day, serum creatinine >1.5 mg/dl, or 24-h urine protein >165 mg/day). We also identified baseline lipid values and categorized them using the American Diabetes Association's risk categories (8). Blood pressure and BMI were also ascertained from the medical record as of the index date. As a surrogate for metformin adherence, we used the medication possession ratio, defined as the total days' supply of medication obtained divided by the corresponding number of calendar days. A value of a medication possession ratio >80% was defined as adherence with prescribed medication (9,10).

Statistical analyses

All analyses were performed using SAS statistical software (SAS Institute, Cary, NC). Bivariate associations were tested using Student's *t* test for continuous measures and the χ^2 statistic for dichotomous variables. We used Cox proportional hazards regression models to identify predictors of time to secondary failure (addition/switch to another antihyperglycemic or A1C ≥8%) and used Kaplan-Meier plots to display the proportions of patients over time that reached each outcome. Patients with missing data on any of the explanatory variables were excluded from multivariate analyses.

RESULTS — Most subjects (90.8%) achieved an A1C of <8% within 1 year of initiating metformin (Table 1). Those who failed to reach this level of A1C were, on average, ~4 years younger (53.1 vs. 57.0 years, $P < 0.001$) and were more likely to have microalbuminuria or macroalbuminuria at baseline (26.7 vs. 17.4%, $P = 0.007$). They also had worse A1C levels at initiation (9.7 vs. 8.6%, $P < 0.001$) and averaged fewer A1C measurements over the 1st year of follow-up (1.5 vs. 2.1, $P < 0.001$). Although both groups were obese, those who achieved an A1C <8% had a lower average BMI (36.1 vs. 37.7 kg/m^2, $P = 0.045$) and managed to lose an average of 4.2 kg within the 1st year, compared with a loss of 1.2 kg among those who did not

achieve adequate glycemic control ($P < 0.001$).

Characteristics of the 1,288 subjects who achieved an A1C <8% within 1 year of metformin initiation are displayed in Table 2. Although the 334 (25.9%) subjects who added or switched to a second drug had a mean A1C at metformin initiation similar to the 954 subjects who did not, adders/switchers were more likely to be >8% before initiation than those who maintained metformin monotherapy (59.5 vs. 54.6%, $P < 0.001$). The best A1C achieved within 1 year of initiating metformin was higher for the adders/switchers (6.9 vs. 6.3%, $P < 0.001$), and only 6.3% achieved an A1C <6%, compared with 27.4% who continued metformin monotherapy ($P < 0.001$). Although both groups lost weight on average, adders/switchers lost less than half the weight of those maintained on metformin monotherapy (−1.9 vs. −5.0 kg, $P < 0.001$). The average daily dose of metformin was greater among adders/switchers (1,611 vs. 1,303 mg, $P < 0.001$), and many more adders/switchers reached a dose of ≥2,000 mg (41.8 vs. 22.1%, $P < 0.001$).

Table 2 also compares the 264 (20.5%) subjects who subsequently reached an A1C of ≥8% during follow-up (our second definition of secondary failure) and the 1,024 who maintained an A1C of <8%. Those who later reached 8% were ~3 years younger (54.6 vs. 57.6, $P < 0.001$), had poorer glycemic control at metformin initiation (9.0 vs. 8.5%, $P < 0.001$), and were less likely to have achieved an A1C <7% within the 1st year of follow-up (47.3 vs. 83.5%, $P < 0.001$). They also lost less weight in the 1st year (−1.6 vs. −4.8 kg, $P < 0.001$), were more likely to reach a dose of ≥2,000 mg (45.5 vs. 22.6%, $P < 0.001$), and were less likely to adhere to their medication (53.4 vs. 64.5%, $P < 0.001$).

Table 3 shows the results of the Cox regression models predicting the time to adding/switching to a second drug and time to reaching an A1C of ≥8%. In the model predicting adding/switching to a second drug, the best A1C achieved within the 1st year was by far the strongest predictor of the outcome. Compared with the reference group of <6.0%, those who achieved an A1C of 6.0–6.9% had a 3.29-times greater risk of adding/switching (95% CI 1.84–5.88), and those who achieved 7.0–7.9% had a 6.54 (3.58–12.0)-times greater risk ($P < 0.0001$ for both comparisons). One-year weight change was also highly predictive of adding/switching (1.04 per kg, 95% CI 1.02–1.06, $P = 0.0007$). Higher metformin dose, baseline microalbuminuria or macroalbuminuria, and having an A1C of 7–7.9% at initiation were also significant predictors of adding/switching to another antihyperglycemic drug.

The "best A1C achieved in the 1st year" categories were also the strongest predictors in the model of subsequently reaching an A1C of ≥8%. Compared with the reference group of <6%, those in the 7.0–7.9% range had a 8.08-times greater risk (95% CI 4.30–15.2, $P < 0.0001$), whereas those achieving the 6.0–6.9% range had 2.21-times the risk (1.19–4.11) of A1C of ≥8%. In addition, poorer A1C at initiation was predictive; compared with the reference group of <7%, the risk of subsequently reaching 8% was more than triple for all three A1C initiation categories. Younger age was also predictive, with each additional 10 years of age reducing risk by 17% (hazard ratio 0.83 [95% CI 0.72–0.96], $P = 0.013$). One-year weight change was again highly predictive of failure (1.06 per kg [1.03–1.09], $P = 0.002$). Higher metformin dose was protective of reaching 8% (0.95 per 100 mg [0.93–0.98], $P = 0.001$).

Kaplan-Meier estimates of time to adding/switching to a second drug stratified by categories of the best A1C achieved in the 1st year of metformin monotherapy are graphed in Fig. 1*A*. By 24 months, ~40% of those whose best A1C was 7.0–7.9% had added/switched drugs and 50% had failed within 36 months. However, it took >60 months for those in the 6–6.9% category to reach a 50% failure rate, and <50% of those who achieved an A1C <6% failed by the end of follow-up.

About half of those whose best A1C was 7.0–7.9% reached an A1C of ≥8% within 24 months (Fig. 1*B*). Only about one-quarter of subjects in the 6–6.9% category had failed by 48 months, and >80% of subjects in the <6% category remained <8% through 60 months of follow-up.

CONCLUSIONS — Diabetes is a progressive disease that typically requires a succession of antihyperglycemic therapy adjustments, often leading to multiple simultaneous therapies (2). Although pharmacologic options are increasing, maximizing the effectiveness at each stage should increase therapeutic flexibility and reduce glycemic burden in the long term. Metformin is a commonly prescribed first-line agent for treating hyperglycemia with proven efficacy (11). Our results indicate that it succeeds in reducing A1C to <8% in >90% of patients who take it for at least 6 months. However, the duration of that success, whether subsequent failure is defined by adding or switching to another drug or by reaching an A1C of ≥8%, largely depends upon the reduction of A1C achieved within the 1st year of metformin monotherapy. This finding has important ramifications.

The benefits of lower A1C levels were well documented in the U.K. Prospective Diabetes Study (1,12). Recently, the Epidemiology of Diabetes Intervention study, the follow-up to the Diabetes Control and Complications Trial, reported that patients who achieved mean A1C values of 7% had better outcomes after 20 years of follow-up than the control group (mean A1C ~9%) irrespective of subsequent glycemic levels (13,14). Thus, lowering A1C levels is likely to have positive long-term health effects. Our results indicate that if glycemic control is achieved initially with metformin monotherapy, it can be successfully maintained for several years. The A1C level achieved, and little else, best predicts secondary failure of metformin monotherapy, however it is defined.

A potential limitation of the present study is that our definitions of secondary failure might have been overly strict. For example, among subjects who added/switched drugs, the median A1C before the therapy change was 7.7%, and 59% of these subjects had an A1C <8% (data not shown). It is possible that some of these patients could have continued to have A1C <8% with metformin monotherapy for several months or even years. In addition, a previous study demonstrated that an A1C following a measurement >8% was, about half the time, <8% (15). Thus, by defining secondary failure as the "first" time an A1C reached ≥8%, our second definition of failure might have also been too strict. On the other hand, that previous study also estimated that substantial glycemic burden accumulated by using an A1C of 8% as an action point for therapeutic adjustments. Moreover, the American Diabetes Association recommends an A1C treatment goal of 7%, not 8% (16). Thus, the selection of 8% as the cut point for defining failure might, in fact, be considered too liberal from the standpoint of optimal control.

The mean metformin doses that we

Table 2—*Subject characteristics at metformin initiation of those who achieved A1C <8% within 1 year* (n = *1,288) by study outcomes*

	Added/switched to second drug	No second drug	*P* value	A1C ≥8%	A1C never ≥8%	*P* value
n	334	954		264	1,024	
Proportion of subjects (%)	25.9	74.1	—	20.5	79.5	—
Age (years)	57.2 ± 11.7	57.0 ± 11.9	0.817	54.6 ± 12.0	57.6 ± 11.8	0.001
Women (%)	54.8	50.6	0.190	50.8	52.0	0.729
Months since diabetes diagnosis	16.1 ± 21.1	16.0 ± 23.0	0.937	15.6 ± 19.5	16.1 ± 23.2	0.700
Months of follow-up	27.5 ± 16.9	32.8 ± 17.3	0.001	21.6 ± 13.6	30.5 ± 16.8	0.001
CVD	15.0	11.2	0.071	11.0	12.5	0.502
Current smoker	18.6	23.8	0.049	18.6	23.4	0.090
Micro- or macroalbuminuria	24.6	15.3	0.001	24.2	16.0	0.002
A1C at metformin initiation (%)						
<7.0	7.8	18.7	0.001	5.3	18.5	0.001
7.0–7.9	32.9	26.7		26.5	28.8	
8.0–8.9	26.7	22.8		29.2	22.5	
≥9.0%	32.6	31.8		39.0	30.2	
Mean A1C at initiation (%)	8.7 ± 1.8	8.5 ± 1.9	0.112	9.0 ± 1.8	8.5 ± 1.9	0.001
Best A1C achieved in 1st year (%)						
<6.0	6.3	27.4	0.001	6.8	25.8	0.001
6.0–6.9	47.9	56.4		40.5	57.7	
7.0–7.9	45.8	16.2		52.7	16.5	
Mean best A1C achieved in 1st year (%)	6.9 ± 0.6	6.3 ± 0.6	0.001	7.0 ± 0.6	6.4 ± 0.6	0.001
Annual A1C measurements	2.4 ± 1.0	1.8 ± 0.7	0.001	2.7 ± 1.8	1.9 ± 0.8	0.001
BMI (kg/m^2)						
<25	6.4	4.0	0.036	5.4	4.5	0.182
25–29.9	13.2	20.3		13.8	19.6	
30–34.9	30.6	27.7		28.9	28.3	
≥35	49.8	48.0		51.9	47.6	
Mean BMI (kg/m^2)	36.5 ± 8.5	36.0 ± 8.1	0.345	36.6 ± 8.3	36.0 ± 8.2	0.300
Mean change in weight (kg) 1 year postinitiation	−1.9 ± 5.7	−5.0 ± 8.5	0.001	−1.6 ± 5.9	−4.8 ± 8.3	0.001
Systolic blood pressure (mmHg)	138 ± 15	136 ± 15	0.089	137 ± 15	136 ± 15	0.618
Systolic blood pressure ≥135 mmHg (%)	56.1	50.6	0.087	53.1	51.8	0.713
Diastolic blood pressure (mmHg)	82 ± 8	81 ± 9	0.066	83 ± 9	81 ± 8	0.001
Diastolic blood pressure ≥85 mmHg (%)	35.6	34.2	0.648	39.6	33.2	0.054
HDL cholesterol risk of CVD (%)						
Low (men >60 and women >70 mg/dl)	4.7	3.5	0.038	3.2	4.0	0.473
Borderline (men 40–59 and women 50–69 mg/dl)	29.4	37.1		32.4	35.7	
High (men <40 and women <50 mg/dl)	65.9	59.4		64.4	60.3	
Mean HDL cholesterol (mg/dl)	42 ± 13	43 ± 11	0.370	42 ± 11	43 ± 12	0.047
LDL cholesterol risk of CVD (%)						
Low (< 100 mg/dl)	32.5	32.7	0.366	32.3	32.8	0.728
Borderline (100–129 mg/dl)	31.2	35.0		32.3	34.4	
High (≥130 mg/dl)	36.3	32.3		35.4	32.8	
Mean LDL cholesterol (mg/dl)	118 ± 37	117 ± 37	0.532	118 ± 37	117 ± 37	0.618
Triglyceride risk of CVD (%)						
Low (<150 mg/dl)	25.4	27.9	0.640	30.3	26.5	0.044
Borderline (150–399 mg/dl)	58.3	57.3		50.8	59.3	
High (≥400 mg/dl)	16.3	14.8		18.9	14.2	
Mean triglycerides (mg/dl)	306 ± 418	276 ± 279	0.237	312 ± 454	277 ± 276	0.247
Mean metformin dose, last dispense before outcome (mg)	1,611 ± 715	1,303 ± 585	0.001	1,313 ± 615	1,306 ± 621	0.871
Mean dose ≥2,000 mg/day (%)	41.9	22.1	0.001	45.5	22.6	0.001
Metformin adherence (MPR ≥80%) (%)	61.1	62.5	0.651	53.4	64.5	0.001

Data are means ± SD unless otherwise indicated. CVD, cardiovascular disease; MPR, medication possession ratio.

Table 3—*Cox regression models of time to secondary failure, defined alternatively as adding/switching antihyperglycemic agents and reaching an A1C of ≥8%*

	Model of adding/switching			Model of A1C ≥8%		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age per 10 years	1.01	0.89–1.15	0.892	0.83	0.72–0.96	0.013
Male sex	0.82	0.64–1.06	0.134	1.08	0.80–1.45	0.626
Months since diabetes diagnosis	1.00	0.99–1.01	0.909	1.00	0.99–1.01	0.774
Cardiovascular disease	1.24	0.88–1.75	0.216	1.24	0.79–1.94	0.352
Current smoker	1.00	0.73–1.37	0.984	0.95	0.65–1.39	0.786
Micro- or macroalbuminuria	1.49	1.11–2.00	0.008	1.37	0.96–1.94	0.084
A1C at initiation (%)*						
7.0–7.9	1.79	1.09–2.93	0.021	3.09	1.51–6.31	0.002
8.0–8.9	1.30	0.77–2.18	0.333	3.26	1.57–6.78	0.002
≥9.0	1.33	0.79–2.24	0.282	3.19	1.54–6.61	0.002
Best A1C achieved in 1st year (%)†						
6.0–6.9	3.29	1.84–5.88	0.0001	2.21	1.19–4.11	0.012
7.0–7.9	6.54	3.58–12.0	0.0001	8.08	4.30–15.2	0.0001
BMI (kg/m^2)‡						
25–29.9	0.59	0.33–1.05	0.072	0.67	0.32–1.37	0.269
30–34.9	1.02	0.60–1.74	0.938	0.98	0.50–1.94	0.960
≥35	1.06	0.62–1.80	0.838	1.12	0.57–2.20	0.744
One-year weight change (per kg)	1.04	1.02–1.06	0.0007	1.06	1.03–1.09	0.0001
Systolic blood pressure ≥135 mmHg	1.09	0.82–1.44	0.559	0.92	0.66–1.29	0.641
Diastolic blood pressure ≥85 mmHg	0.88	0.66–1.19	0.409	1.10	0.78–1.56	0.596
HDL cholesterol§						
Men 40–59 and women 50–69 mg/dl	0.69	0.37–1.26	0.227	0.77	0.34–1.74	0.525
Men <40 and women <50 mg/dl	0.76	0.42–1.37	0.353	0.86	0.38–1.91	0.855
LDL cholesterol (mg/dl)‖						
100–129	0.73	0.54–0.99	0.041	0.79	0.55–1.14	0.199
≥130	0.71	0.52–0.96	0.024	0.98	0.69–1.40	0.926
Triglycerides (mg/dl)¶						
150–399	1.12	0.83–1.50	0.467	0.87	0.63–1.22	0.417
≥400	1.32	0.85–2.04	0.218	1.01	0.62–1.62	0.982
Mean metformin dose of last dispense before outcome (per 100 mg)	1.03	1.01–1.05	0.0004	0.95	0.93–0.98	0.0006
Poor metformin adherence (MPR <80%)	1.09	0.84–1.42	0.525	1.40	1.04–1.90	0.029

Reference groups: *initial A1C <7%; †best A1C <6%; ‡BMI <25 kg/m^2; §HDL cholesterol, men ≥60 and women ≥70 mg/dl; ‖LDL cholesterol <100 mg/dl; ¶triglycerides <150 mg/dl. MPR, medication possession ratio.

observed were somewhat lower than the maximum recommended dose. It is possible that subjects whose best A1C was between 7 and 8% did not achieve better control because they were not titrated to maximum doses. This is supported by the Cox model of the A1C ≥8% outcome, where higher doses reduced the risk of exceeding 8%. Conversely, higher metformin doses also predicted the initiation of new antihyperglycemic therapy. Whether patients could not tolerate the higher doses or they and their clinicians merely became impatient with monotherapy could not be determined from our data. It is also possible that patients who failed metformin monotherapy were not adequately adhering to their prescribed doses. Although actual adherence could not be ascertained, we calculated the medication possession ratio as a surrogate. This measure was not associated with adding/switching a drug, but poorer adherence was significantly associated ($P = 0.029$) with reaching an A1C of ≥8%.

Our multivariate analyses were conducted on the two-thirds of subjects ($n = 772$) who had complete data for all independent variables, perhaps limiting the generalizability of our findings. However, reestimation of models excluding the lipid, blood pressure, BMI, and weight change variables (the only predictors with missing values) did not substantively change our results (data not shown); the best A1C achieved in the 1st year remained the strongest predictor of failure, with hazard ratios similar to those reported in the full model.

The generalizability of our results might also be limited by the nature of our study setting. KPNW has a somewhat unique organizational structure, and members with diabetes receive more guideline-adherent care and achieve lower-than-average levels of risk factors (17). We note, however, that risk factors other than A1C did not predict failure in our models. In addition, our analyses included patients with less-than-optimal follow-up (mean number of annual A1Cs approximately two). Although this could possibly bias our conclusions, the data we report are representative of a population-based clinical practice.

A key finding in our study was the importance of weight loss, and the avoidance of weight gain, in slowing the progression of hyperglycemia and delaying

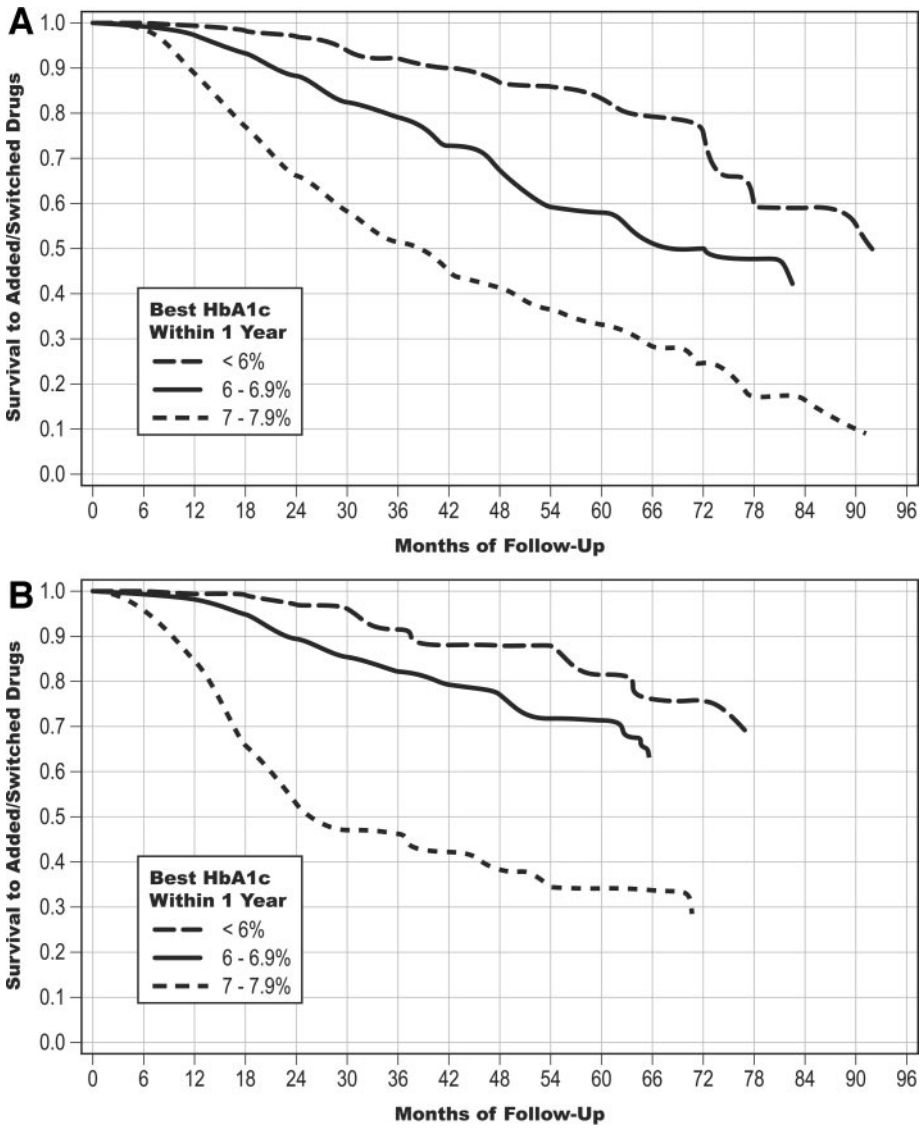

Figure 1—A*: Unadjusted Kaplan-Meier analysis of added or switched drugs.* B*: Unadjusted Kaplan-Meier analysis of A1C ≥8%.*

the need for additional drugs. Weight reduction is often associated with metformin therapy (11,18), and in our data, most patients lost weight following initiation. Nevertheless, average weight loss was significantly greater among patients who avoided secondary failure, however it is defined. A mere 1-kg weight gain was associated with an increase in the risk of failure of 4–6%. These results confirm the importance of ongoing reduction in total caloric intake and increased physical activity concurrent with pharmacologic treatment in patients with diabetes.

Whether secondary failure to initial metformin therapy is defined by adding/switching to another oral antihyperglycemic agent or by reaching an A1C of 8%, it is inversely associated with the reduction of A1C achieved within the 1st year.

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