The Burden of Treatment Failure in Type 2 Diabetes

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OBJECTIVE — In type 2 diabetes, therapies to maintain blood glucose control usually fail after several years. We estimated the glycemic burden that accumulates from treatment failure and describe the time course and predictors of failure.

RESEARCH DESIGN AND METHODS — A prospective, population-based study using retrospective observational data. We identified all 7,208 complete courses of treatment with nondrug therapy, sulfonylurea monotherapy, metformin monotherapy, and combination oral antihyperglycemic therapy between 1994 and 2002, inclusive, among members of the Kaiser Permanente Northwest Region. We calculated mean cumulative glycemic burden, defined as HbA_{1c}-months >8.0 or 7.0% for each treatment. We then measured the likelihood that the next HbA_{1c} would exceed 8.0 and 7.0% after HbA_{1c} exceeded each of ten hypothetical treatment thresholds. Finally, we estimated multivariate logistic regression models to predict when HbA_{1c} would continue to deteriorate.

RESULTS — In this well-controlled population, the average patient accumulated nearly 5 HbA_{1c}-years of excess glycemic burden >8.0% from diagnosis until starting insulin and about 10 HbA_{1c}-years of burden >7.0%. Whenever patients crossed the American Diabetes Association–recommended treatment threshold of 8.0%, their next HbA_{1c} result was as likely to be <8.0 as >8.0%. Multivariate prediction models had highly statistically significant coefficients, but predicted <10% of the variation in future HbA_{1c} results.

CONCLUSIONS — Clinicians should change glucose-lowering treatments in type 2 diabetes much sooner or use treatments that are less likely to fail. An action point at 7.0% or lower is more likely to prevent additional deterioration than the traditional action point of 8.0%.

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Glycemic control reduces the risk of blindness, renal failure, neuropathy, and other microvascular complications in type 2 diabetes (1–3). Good glycemic control has become even more important with earlier diagnosis and more aggressive cardiovascular prevention and treatment. Recently diagnosed patients can expect to live several years longer than patients diagnosed only a decade or two ago (4,5). An extended lifespan provides more time to develop blindness, renal failure, and other microvascular complications. Therefore, the level of cumulative glycemic burden that was considered manageable in the past may no longer protect the patients of today. Before 2004, the American Diabetes Association (ADA) recommended that HbA_{1c} not be allowed to exceed 8.0% and that patients be treated to a goal of 7.0% (6). In its 2004 Standards of Medical Care in Diabetes (7), the ADA dropped the 8.0% "action threshold" in favor of a general recommendation to treat most patients to <7.0%.

A major but perhaps not widely appreciated contributor to glycemic burden is the response of clinicians to antihyperglycemic treatment failure. In most patients, diet and exercise and most oral agents eventually lose their effectiveness. Brown and Nichols (8) recently reported that even in a population with very low average levels of HbA_{1c} (7.6%), HbA_{1c} averaged 9.4% before metformin was added to sulfonylurea therapy. We decided to use a retrospective database to conduct a prospective analysis of secondary treatment failure in type 2 diabetes. Our goals were to quantify the amount of glycemic burden that accumulates when treatment fails, identify the causes and predictors of failure, and identify methods to possibly reduce the burden caused by failure.

RESEARCH DESIGN AND METHODS

— The study subjects were members of a not-for-profit, group-model, health maintenance organization, Kaiser Permanente Northwest (KPNW), located in Oregon and southwestern Washington state. Demographically and economically, KPNW's 450,000 members resemble the area population (9): 47.0% male, 97.5% non-Hispanic, and 91.4% white. In 2002, 8.3% of the KPNW adult membership (>18 years of age) had diagnosed diabetes. For the time window used in this study, 1994–2002, HbA_{1c} averaged 7.6% across the entire KPNW registry. Nearly two-thirds (66.3%) of registrants had a mean HbA_{1c} of <8%, and 87.3% were <9% (10).

For this study, we selected all registrants who, between 1994 and 2002, initiated sulfonylurea monotherapy, metformin monotherapy, combination therapy, or were newly diagnosed and managed without drugs. To eliminate cases of primary (immediate) failure or intolerance, we excluded all registrants who did not maintain their new therapy for at least 12 months. Because we were studying only patients who experienced failure, we also eliminated all cases who did not ultimately change therapy during the study window. To demonstrate that a therapy had been newly begun, we required all subjects to have been a health plan mem-

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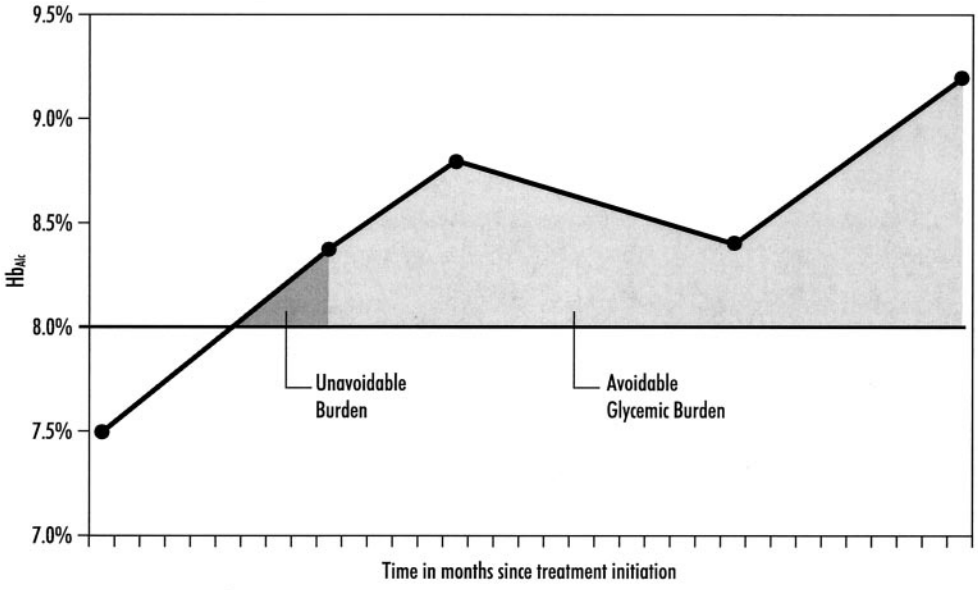
Abbreviations: ADA, American Diabetes Association; KPNW, Kaiser Permanente Northwest.

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



Total Burden $= \sum_{t=1}^{T}(G_t - K)$, where t indicates the number of months elapsed since diagnosis or treatment initiation; T is the number of months elapsed when a successor treatment in initiated; G_t is the actual or interpolated value of Hb_{A1c} in month t; and K is the base from which burden is calculated (in this example, $K = 8.0$).

Figure 1—*Hypothetical calculation of glycemic burden for an individual patient.*

ber for at least 12 months before their first purchase or diagnosis. (Most subjects had been members for many prior years.) Some patients had time to initiate two or even three qualifying therapies during the study window and therefore appear in more than one analysis.

Data sources and measures

We searched electronic pharmacy records back through 1987 to ascertain drug-use history. These records are very complete: 95% of KPNW members with diabetes report getting all or most of their medicines for diabetes from KPNW pharmacies (data not shown).

All HbA_{1c} tests were performed by a single in-house laboratory using the Diamat assay, the standard method used in the Diabetes Control and Complications Trial (1). The normal range for this assay is 5.05 ± 0.5%. During the study window, the laboratory performed more than three ambulatory HbA_{1c} tests per average registrant per year, not counting test results obtained during hospital stays, during emergency room visits, or from portable glucometers.

To ensure complete histories of antihyperglycemic treatment, we included only individuals who had had their diabetes diagnosed while they were members of KPNW (80% of registrants). We assumed a member was diagnosed by KPNW if he or she had at least 1 full year of membership before diagnosis, without any of the following indications of diabetes: antihyperglycemic drug use, purchase of supplies for blood glucose testing, outpatient diagnostic notations of diabetes, inpatient discharge diagnoses of diabetes, participation in diabetes education, or a diagnostically elevated glucose or glycated hemoglobin level (using current ADA criteria [11]).

Analytic methods

Glycemic burden. We defined total glycemic burden as the cumulative amount by which HbA_{1c} has exceeded a specified treatment goal or threshold, the area above a line. In this report, we calculated total glycemic burden as the sum of the differences between the patient's actual or interpolated HbA_{1c} and 8.0% (or, alternatively, 7.0%), during each month that a patient was using a therapy under study and had an HbA_{1c} >8.0 or >7.0%. Figure 1 illustrates burden graphically for a hypothetical individual subject, using a treatment threshold of 8.0%, and shows the formula. To interpolate HbA_{1c} during months when no measurement was taken, we calculated the slope of the straight line connecting the two nearest measurements. We defined a second measure, avoidable glycemic burden, as the portion of total glycemic burden that occurs after the first HbA_{1c} test that revealed that a patient had exceeded goal or threshold (see Fig. 1).

Likelihood of further deterioration. A key uncertainty for physicians treating type 2 diabetes is whether future HbA_{1c} values will continue to deteriorate after a patient has crossed a threshold. To calculate the likelihood of further deterioration, we estimated the proportion of cases in which HbA_{1c} increased after each of 10 HbA_{1c} thresholds was first exceeded. In these analyses, we limited the study samples to subjects *1*) who had at least one additional HbA_{1c} measurement between 2 and 12 months after crossing the threshold (and before initiating a successor therapy) and *2*) who had at least one HbA_{1c} measurement after initiating the therapy but before crossing the threshold. These criteria exclude cases of primary failure as well as individuals who switched out of therapy before a follow-up measurement was taken.

Additionally, to define rules to assist clinicians in predicting when HbA_{1c} will continue to deteriorate, we estimated multivariate logistic regression models that predicted further deterioration. The dependent variable in these models was the log odds that HbA_{1c} would increase by >0.10 percentage points. Predictor variables were centered at their means and always included the immediately pre-

Table 1—*Patient characteristics, clinical behavior, and glycemic burden by treatment*

	Diet and exercise	Sulfonylurea monotherapy	Metformin monotherapy	Sulfonylurea and metformin combination therapy
n	2,319	3,394	513	982
Age (years)	57.7 ± 12.2	55.7 ± 11.8	55.5 ± 11.6	57.8 ± 11.4
Men (%)	52.6	52.5	48.5	52.6
Duration of diabetes (years)	0.0	0.6 ± 1.3	2.0 ± 2.3	4.3 ± 2.3
BMI (k/m^2)	34.1 ± 7.2	34.4 ± 7.4	34.9 ± 7.7	34.6 ± 7.8
Last HbA_{1c} before treatment (%)	—	9.6 ± 2.1	8.8 ± 1.8	9.2 ± 1.7
First HbA_{1c} on treatment (%)	7.4 ± 1.5	7.6 ± 1.5	8.2 ± 1.8	8.4 ± 1.5
Best HbA_{1c} on treatment (%)	7.2 ± 1.4	7.1 ± 1.4	7.7 ± 1.6	7.7 ± 1.3
Mean HbA_{1c} on treatment (%)	7.9 ± 1.3	8.2 ± 1.3	8.4 ± 1.5	8.8 ± 1.2
Last HbA_{1c} on treatment (%)	8.6 ± 1.6	9.1 ± 1.7	8.8 ± 1.7	9.6 ± 1.7
Months on treatment	29.8 ± 14.7	35.1 ± 17.8	26.5 ± 13.5	33.9 ± 16.9
No. of HbA_{1c} tests	4.0 ± 2.8	5.8 ± 4.0	4.3 ± 3.2	6.6 ± 4.5
HbA_{1c} tests >8.0% (%)	35.5	48.7	49.6	66.6
Months HbA_{1c} >8.0%	8.7 ± 12.5	20.5 ± 18.0	14.5 ± 13.7	25.6 ± 17.2
Total glycemic burden (months)				
Base HbA_{1c} 8.0%	8.6 ± 22.4	19.4 ± 31.8	17.0 ± 25.8	29.9 ± 35.6
Base HbA_{1c} 7.0%	22.5 ± 32.0	41.5 ± 43.4	33.5 ± 34.7	58.3 ± 46.2
Avoidable burden (months)				
Base HbA_{1c} 8.0%	4.4 ± 14.8	16.5 ± 28.3	12.3 ± 21.3	26.0 ± 30.6
Base HbA_{1c} 7.0%	15.8 ± 24.6	36.6 ± 39.6	25.9 ± 30.1	51.1 ± 41.6
Subsequent therapy (proportions)				
Sulfonylurea	0.736	—	0.916	—
Metformin	0.226	0.913	—	—
Other oral agent	0.003	0.015	0.021	0.123
Insulin	0.036	0.071	0.062	0.877
Total	1.000	1.000	1.000	1.000
Switched after HbA_{1c} first exceeded 8.0% or before (% subjects)	66.6	35.3	44.6	18.6

Data are means ± SD, unless noted otherwise.

ceding HbA_{1c} value, age, sex, number of months on the therapy of interest, and, except in the case of nonpharmacologic therapy, an index of medication adherence. The adherence index was the ratio of the "days-supply" recorded for the prescription divided by mean observed days between medication refills.

To ascertain whether primary care physicians differed in their propensity to change therapy early in the secondary treatment failure process, we calculated, for each treatment category and for each KPNW primary care clinician who had at least five patients who failed therapy in the category, the proportion of their patients who were switched to a new or additional therapy before specified HbA_{1c} levels were reached. For each treatment category and HbA_{1c} threshold, we then performed statistical tests for homogeneity to test whether the observed pattern of physician behavior could have occurred by chance. Further analyses were planned if these tests disconfirmed the hypothesis that switching thresholds were random.

RESULTS — A total of 7,208 episodes of treatment initiation and eventual secondary failure qualified for inclusion in the study. Most of the episodes were in the diet-and-exercise (n = 2,319) and sulfonylurea monotherapy (n = 3,394) categories. Table 1 describes these episodes and the glycemic burden they imposed. The last HbA_{1c} value before starting therapy ranged from a high of 9.6% before sulfonylurea monotherapy (at the end of nonpharmacologic therapy) to 8.8% before metformin monotherapy (always, in these data, after a course of sulfonylurea monotherapy). The mean first HbA_{1c} value after treatment (or after diagnosis, in the case of nondrug therapy) was lowest for nonpharmacologic therapy (7.4%), followed by sulfonylurea monotherapy (7.6%), metformin monotherapy (8.2%), and, finally, sulfonylurea/metformin combination therapy (8.4%). Glucose control usually improved further with time, dropping ultimately to between 7.1% (sulfonylurea monotherapy) and 7.7% (metformin monotherapy and combination therapy). The last HbA_{1c} value before treatment abandonment or supplementation ranged from 8.6% in the nonpharmacologically treated group to 9.6% for combination therapy. The mean number of months that elapsed until a new or additional treatment was started ranged from 26.5 months (metformin monotherapy) to 35.1 months (sulfonylurea monotherapy).

Glycemic burden varied widely across treatments and reached high levels. When a threshold of HbA_{1c} 8.0% was used, total glycemic burden ranged from 8.6 HbA_{1c}-months for individuals on diet and exercise to 29.9 HbA_{1c}-months for

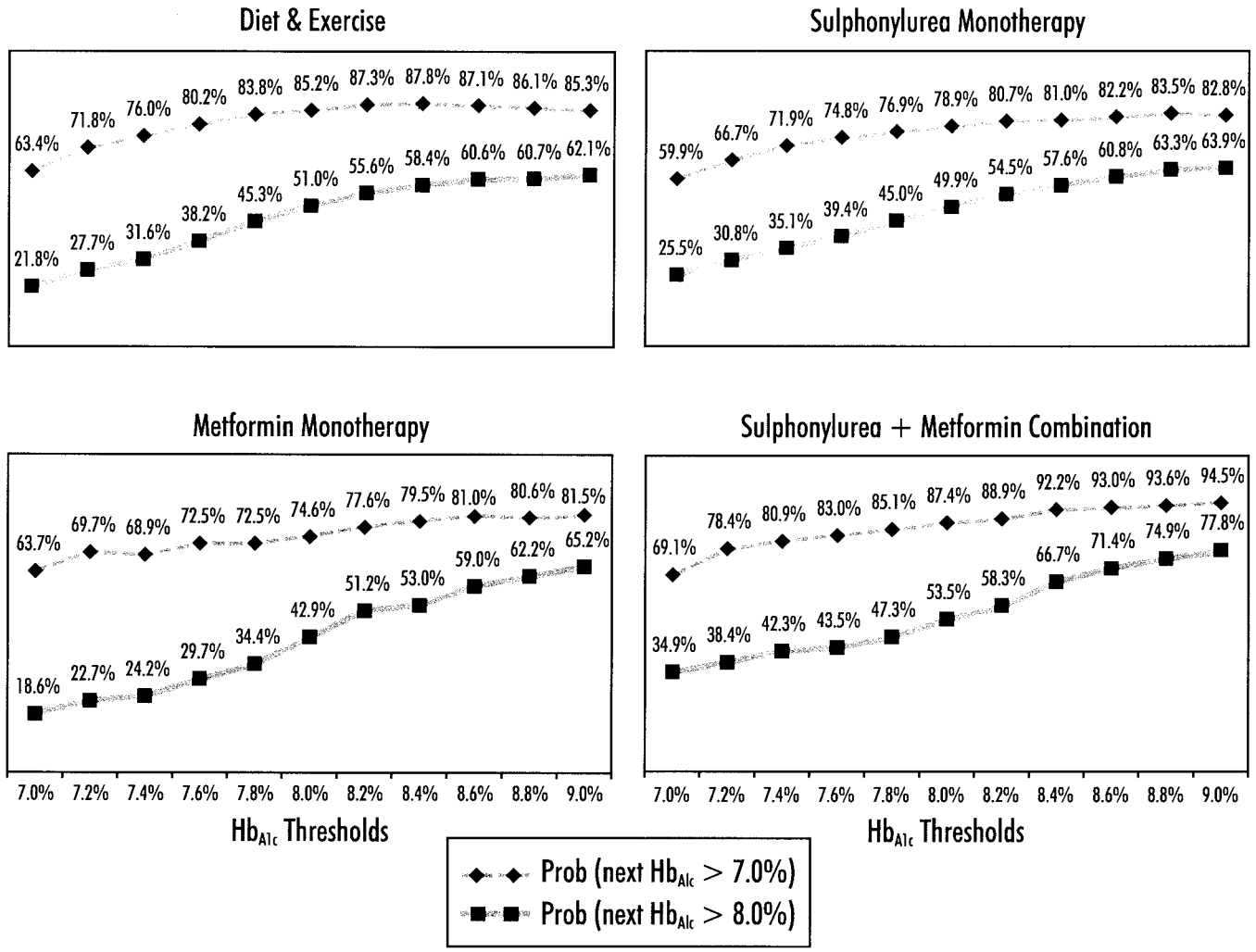


Figure 2—*Probability that the next HbA_{1c} measurement will exceed 7 or 8% after HbA_{1c} crosses each of 10 hypothetical treatment thresholds between 7.0 and 9.0%.*

individuals on combination therapy. Total burden for sulfonylurea and metformin monotherapy averaged 19.4 and 17.0 HbA_{1c}-months, respectively. Avoidable burden (at the 8.0% threshold) averaged 3.5 months less than total burden, a reduction that varied little across treatment groups.

Glycemic burdens were much greater when calculated from a base of 7.0%. Using this base, total glycemic burden (HbA_{1c}-months) averaged 22.5 for nonpharmacologic therapy, 41.5 for sulfonylurea monotherapy, 33.5 for metformin monotherapy, and 58.3 for combination therapy.

Most nonpharmacologically treated subjects (73.6%) switched to sulfonylurea therapy. (Although, in later years, metformin monotherapy became a common initial pharmacotherapy, few such patients had experienced treatment failure by the end of 2002.) Most sulfonylurea monotherapy episodes (91.3%) progressed to the substitution or, more typically, to the addition of metformin. Conversely, most metformin monotherapy episodes (91.6%) terminated with the addition of a sulfonylurea. Most combination therapy episodes ended with the initiation of insulin (87.7%).

Two-thirds (66.6%) of nonpharmacologically treated patients switched to an oral agent as soon as, or before, their HbA_{1c} first exceeded 8.0%. The corresponding proportions for sulfonylurea and metformin monotherapy were 35.3 and 44.6%. Only 18.6% of combination therapy subjects switched before exceeding this threshold.

Likelihood of worsening glycemic control

Figure 2 displays, for 10 potential treatment-switching thresholds from HbA_{1c} 7.0 to 9.0%, the percentage of cases in which the next postthreshold HbA_{1c} result exceeded 8.0 and 7.0%. Out of necessity, these analyses include only patients who remained on their therapy after crossing a threshold. (These are the only patients whose follow-up test results could be observed.) Fig. 2 shows the likelihood that this failure to switch was potentially a poor decision because it was followed by further deterioration of HbA_{1c}. In general, as the switching threshold was increased, the likelihood that the next HbA_{1c} measurement would exceed 8.0% also increased. In all groups except the one for metformin mono-

Table 2—*Probability that the next HbA_{1c} changes by >0.10 percentage points: multivariate logistic regression models*

	Parameter estimate	SE	Wald χ^2	*P*	Odds ratio	95% CI
Diet and exercise (n = 6,561; entropy = 6.7%)						
Prior HbA_{1c}	−0.563	0.029	385.5	0.0001	0.569	0.538–0.602
Age	−0.014	0.002	38.3	0.0001	0.986	0.982–0.991
Male sex	0.206	0.053	15.3	0.0001	1.228	1.108–1.362
Months on therapy	0.024	0.002	164.9	0.0001	1.024	1.020–1.028
Sulfonylurea monotherapy (n = 14,904; entropy = 7.6%)						
Prior HbA_{1c}	−0.476	0.014	1,134.0	0.0001	0.621	0.604–0.639
Age	−0.011	0.002	51.2	0.0001	0.989	0.986–0.992
Male sex	0.054	0.035	2.4	0.125	1.055	0.985–1.130
Months on therapy	0.018	0.001	292.2	0.0001	1.018	1.016–1.020
Medication adherence	−0.372	0.078	22.7	0.0001	0.689	0.592–0.803
Metformin monotherapy (n = 1,642; entropy = 9.2%)						
Prior HbA_{1c}	−0.458	0.042	117.5	0.0001	0.632	0.582–0.687
Age	−0.026	0.005	30.5	0.0001	0.974	0.965–0.983
Male sex	0.019	0.106	0.03	0.860	1.019	0.827–1.255
Months on therapy	0.027	0.004	44.0	0.0001	1.027	1.019–1.035
Medication adherence	−0.808	0.208	15.0	0.0001	0.446	0.296–0.671
Sulfonylurea/metformin combination (n = 5,871; entropy = 7.1%)						
Prior HbA_{1c}	−0.497	0.024	446.1	0.0001	0.609	0.581–0.637
Age	−0.021	0.003	65.0	0.0001	0.980	0.975–0.984
Male sex	0.023	0.055	0.17	0.684	0.978	0.877–1.090
Months on therapy	0.013	0.002	48.5	0.0001	1.013	1.009–1.017
Medication adherence	−0.657	0.137	22.9	0.0001	0.518	0.396–0.679

therapy, at the ADA's then-recommended treatment threshold of 8.0%, patients were as likely to experience an HbA_{1c} <8.0% at their next assay as they were to experience a >8.0% result. (For metformin monotherapy, the threshold of maximum possible uncertainty was slightly higher, 8.2%.) For patients on diet and exercise, sulfonylurea monotherapy, or metformin therapy, the probability that a patient's next HbA_{1c} measurement would be <8.0% exceeded one-third, even when the switching threshold was set as high as 9.0%.

When we calculated whether the next HbA_{1c} would exceed 7.0% (the higher curves in Fig. 2), the likelihood of an elevated result tended to flatten out at higher switching thresholds, especially for nondrug therapy and sulfonylurea monotherapy. Even at the lowest switching threshold (7.0%), subsequent HbA_{1c} values stayed above 7.0% for a large majority of patients (59.9–69.1%). Consequently, we observed no 50/50 "threshold of maximum uncertainty" for any treatment or threshold level when a target value of 7.0% was specified. In addition, the probability that patients would return to an HbA_{1c} <7.0% once they experienced an HbA_{1c} ≥8.0% was small (0.126–0.254).

Table 2 shows the results of multivariate modeling of the log odds that the next HbA_{1c} measurement will increase by 0.10 percentage points for each treatment group. With the exception of male sex in the pharmacologically treated groups, all of the predictor coefficients were highly statistically significantly different from zero. In all models, a higher prior level of HbA_{1c} decreased the likelihood of a clinically significant increase in HbA_{1c}, after controlling for age, sex, months on therapy, and medication adherence. Older age decreased the odds of further deterioration of HbA_{1c}, as did evidence of better medication adherence. A longer duration in a therapy predicted higher odds of deterioration.

Despite these consistent, statistically significant results, the entropy statistics for these models are relatively low (6.7–9.2%), indicating that they predict only a small proportion of the total observed variation in change in HbA_{1c}. In homogeneity tests, we were unable to reject the null hypothesis that differences in clinicians' propensity to initiate new treatment at various thresholds of HbA_{1c} were due to chance.

CONCLUSIONS — In type 2 diabetes, the successive failure of nonpharmacologic therapy and oral antihyperglycemic agents eventually burdens patients with a heavy history of uncontrolled hyperglycemia. When this glycemic burden is defined as HbA_{1c}-years >8.0%, the total burden ranges from three-fourths of an HbA_{1c}-year (8.6 HbA_{1c}-months) in individuals failing diet and exercise to ~2.5 HbA_{1c}-years (29.9 HbA_{1c}-months) for individuals failing combination therapy. When it is defined as HbA_{1c}-years >7.0%, the total burden is much higher, from 1.9 to 5.9 HbA_{1c}-years (22.5–58.3 HbA_{1c}-months). If, before starting insulin, a hypothetical patient were to progress from nonpharmacologic treatment through sulfonylurea or metformin monotherapy to combination oral agent therapy, as patients typically do in our study setting, he or she would accumulate nearly 5 HbA_{1c}-years of total burden >8.0% and about 10 HbA_{1c}-years of total burden >7.0%. The latter figure exceeds the mean reduction in glycemic burden (9.0 HbA_{1c}-years) achieved over 10 years by the U.K. Prospective Diabetes Study (3).

Our earlier retrospective study of KPNW members who switched to or added metformin after sulfonylurea therapy suggested that HbA_{1c} levels rise inexorably to levels well above 9.0% before clinicians respond (8). The present study confirms that HbA_{1c} levels reach at least 9.6% on average before combination therapy is attempted, but it also reveals a very "noisy" or jagged process of HbA_{1c} deterioration before these levels are reached. Perversely, the noise in this process is greatest at the very level (8.0%) at

which (until 2004) clinicians have been asked to make new therapy decisions. In fact, when HbA_{1c} first crosses the formerly ADA-recommended treatment threshold of 8.0%, patients who are not immediately switched to new treatment are about as likely to experience a following result of <8.0% as they are to continue to deteriorate. This short-term unpredictability must make it almost impossible for clinicians to predict HbA_{1c} from test to test, when HbA_{1c} is allowed to approach 8.0%.

The present study has several important limitations. First, because a long time window is needed to observe the course of treatment failure, our results generally describe older treatment patterns, before thiazolidinediones, for example, were available for use and before metformin was used (in our setting) as a first-line agent. Also, patients were available for follow-up for various durations of time, depending on whether they initiated treatment earlier or later in the study window. Consequently, an average of 60% of subjects had not switched treatment by the end of the study window and were not, therefore, included in glycemic burden calculations. Our results therefore oversample patients who switched sooner rather than later and may therefore underestimate the total glycemic burden caused by failure. This is confirmed by the fact that the last HbA_{1c} value before the abandonment of nondrug therapy in episodes that ended during our study window averaged 9.6%, whereas the last HbA_{1c} value in episodes that both began and ended during our study window averaged 8.6%, a much lower number.

Another limitation is our inability to observe dosage increases as responses to loss of glycemic control. This may have contributed to our finding that, at higher thresholds of HbA_{1c}, subsequent HbA_{1c} tests were as or more likely to decrease as they were to increase. However, the impact of unobserved uptitration will have been limited by the fact that for the oral agents we studied, glyburide and metformin, uptitration yields only minimal additional glycemic control once recommended initial dosages are reached. Intensification of diet-and-exercise therapy could have had more significant effects, both during nonpharmacologic treatment and alongside oral agents. This, however, would not have alleviated much predictive uncertainty for clinicians because adherence to behavioral recommendations is itself hard to predict.

We found that terminal levels of HbA_{1c} increased substantially as patients progressed from nondrug therapy through combination therapy. The reasons for this cannot be identified in our data, but may include deterioration of β-cell function, probably exacerbated by lapses of metabolic control during treatment failure; increased insulin resistance, due to aging; increasingly sedentary lifestyle and weight-gain; psychological resistance to the use of insulin; loss of therapeutic motivation by patients or clinicians; and characteristics of the therapies themselves.

Our attempts to develop multivariate equations to aid clinicians in the prediction of future glycemic test results failed to explain most of the prospective variance in HbA_{1c}. A more practical aid would be the following simple rule: do not allow HbA_{1c} to get near 8.0% in the first place. An action threshold of 7.0% yields better predictive characteristics than a threshold of 8.0%. Between 60 and 70% of patients are likely to experience a continuing increase in HbA_{1c} after their results on this assay rise above 7.0%. If the target for glucose control is an HbA_{1c} <7.0%, our results strongly suggest that the recommended threshold for action should be 7.0% or lower. An even stronger signal would be provided by a treatment threshold of 6.0%, which has proved widely achievable in the test phase of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (12).

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