Secondary Failure of Metformin Monotherapy in Clinical Practice

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OBJECTIVE — We sought to document the secondary failure rate of metformin monotherapy in a clinical practice setting and to explore factors that predict therapeutic failure.

RESEARCH DESIGN AND METHODS — We studied 1,799 type 2 diabetic patients who, between 2004 and 2006, lowered their A1C to <7% after initiating metformin monotherapy as their first-ever anti-hyperglycemic drug. We examined all A1C values recorded through 31 December 2008 (2–5 years of follow-up), defining secondary failure as a subsequent A1C ≥7.5% or the addition or substitution of another anti-hyperglycemic agent. We used logistic regression to identify factors associated with the probability of secondary failure.

RESULTS — Of the 1,799 patients studied, 42% ($n = 748$) experienced secondary failure; the mean failure rate was 17% per year. However, patients who initiated metformin within 3 months of diabetes diagnosis failed at an age-and A1C-adjusted rate of 12.2% (10.5–14.4%) per year, and patients who initiated while A1C was <7% failed at an adjusted rate of 12.3% per year. An interaction term between duration of diagnosed diabetes and A1C was not significant. Age, duration, and A1C at initiation were the only factors that predicted secondary failure.

CONCLUSIONS — Although metformin failure may occur more rapidly in clinical practice than in clinical trails, initiating it soon after diabetes diagnosis and while A1C is low might preserve β-cell function, prolong the effectiveness of metformin, reduce lifetime glycemic burden, and prevent diabetes complications. Our findings support the current treatment algorithm for hyperglycemia management that recommends metformin initiation when diabetes is first diagnosed.

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The Diabetes Prevention Program and other primary prevention studies (1–3) have shown that metformin therapy can slow the deterioration of glycemic control in individuals with impaired glucose tolerance, thus delaying progression to diabetes. This suggests that initiation of metformin as soon as diabetes is diagnosed would also help to slow the trajectory of loss in insulin secretory capacity and glycemic control, delaying the need for subsequent therapy intensification and the substantial periods of chronic hyperglycemia that typically accompany anti-hyperglycemic failure. Therefore, the current American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines for the medical management of type 2 diabetes recommend the initiation of metformin concurrently with lifestyle intervention at diagnosis (4).

Observational studies indicate that initiation of metformin or sulfonylurea pharmacotherapy at lower levels of hyperglycemia appears to improve the effectiveness and durability of the therapy, but in these studies, duration of diabetes (delay in initiation of therapy) did not predict time to therapy failure (5,6). However, these studies were conducted when sulfonylureas were the first-line agent of choice, and they used an A1C cut point of 8% to define initial success and secondary treatment failure. To our knowledge, no studies have examined the potential benefits of immediate versus delayed metformin initiation used with a modern A1C treatment threshold of 7%. Furthermore, although metformin fails at a rate of ~4% per year in clinical trials (7), the failure rate in the real world of clinical practice has not been reported.

We therefore sought to estimate the rate of secondary metformin monotherapy experienced by unselected patients in a nonresearch setting who had a documented history of successfully lowering their A1C to <7% with metformin. We then sought to identify factors associated with slower loss of glycemic control. Our observational analyses were conducted within a managed care plan using electronic medical records with substantial information technology support, including built-in alerts for A1C testing.

RESEARCH DESIGN AND METHODS

Study site

Kaiser Permanente Northwest (KPNW) is a nonprofit group-model HMO that provides comprehensive prepaid coverage to ~470,000 members in Northwest Oregon and Southwest Washington. KPNW uses electronic health care utilization data to track and facilitate operations. An electronic medical record, in use since 1996, allows the attending clinician to record as many as 20 *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coded diagnoses at each ambulatory patient contact and up to nine discharge diagnoses for inpatient hospital admissions. An electronic problem list, also coded in ICD-9-CM, is available to the clinician at each contact. A single regional laboratory performs nearly all KPNW laboratory tests, and the results are stored in a searchable database. A pharmacy is located in each medical office, and most members have a pharmacy benefit, helping to ensure complete capture of pharmaceutical dispenses.

Sample selection

Using an observational cohort design, we identified all 3,388 type 2 diabetic

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patients (multiple ICD-9-CM diagnoses of 250.xx) who initiated metformin monotherapy as their first-ever anti-hyperglycemic drug between 1 January 2004 and 31 December 2006 and were KPNW members for at least 1 year before their first metformin dispense. We excluded 780 patients who experienced primary failure of metformin in the first 6 months of therapy, defined as *1*) receipt of only a single metformin dispense, *2*) receipt of less than a 90-day supply, or *3*) addition of a second anti-hyperglycemic agent. Because our focus was on secondary failure after initial success, we then excluded 709 patients who did not attain an A1C <7% despite ongoing therapy and 100 patients with missing A1C data for a final sample of 1,799.

Secondary failure

We defined secondary failure as *1*) the addition or substitution of a second anti-hyperglycemic agent or *2*) a subsequent A1C ≥7.5%, a level slightly above the action level of 7.0% currently recommended by the ADA and EASD (4). We used this higher threshold to provide certainty that A1C levels had risen durably above 7.0% and to account for recently published trials that report adverse effects or no beneficial effects of glycemic control below 7.0%. We tested the sensitivity of our results to A1C failure thresholds of 7.0 and 8.0% and also examined the two definitions of failure (A1C >7.5% or addition/substitution of a second drug) independently.

Analysis and covariates

We calculated age and duration of diabetes using the first metformin dispensing date as the index date. A1C before metformin was the last value recorded on or before the index date. Similarly, BMI, blood pressure, lipid levels, and estimated glomerular filtration rate were based on the last values recorded on or before the index date. Average daily dose of the initial metformin dispensed was calculated by summing the total number of milligrams dispensed and dividing by days of supply. The analysis period for estimating time to failure was from the date of the first A1C <7.0% until secondary failure or 31 December 2008, whichever occurred first. Patients who left the health plan were censored as of their termination date. To control for different patterns of medication-taking behavior among patients, we calculated a measure of adherence, the medication possession ratio, as a potential covariate. Because the duration of potential possession varied in our data depending on time to failure or censoring, we calculated the medication possession ratio using person-specific denominators. We estimated a logistic regression model to assess the independent contribution of demographic and patient characteristics, including medication possession ratio, to the probability of experiencing secondary failure. All candidate predictors were entered into the model simultaneously, and those that were statistically significant ($P < 0.05$) were retained in the final model. We used regression for incidence densities to estimate the secondary failure rate per 1,000 person-years but report the figures as percent per year to facilitate comparison to published data. When stratified by baseline A1C, the secondary failure rates were adjusted for age, sex, and duration of diabetes. When stratified by duration, the rates were adjusted for age, sex, and baseline A1C. All analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC).

Table 1—*Characteristics of patients who did and did not experience secondary failure of metformin monotherapy after achieving A1C <7%*

	Failed metformin	Did not fail metformin	*P*
n (%)	748 (41.6)	1,051 (58.4)	—
Age at initiation	57.7 ± 12.3	59.2 ± 11.3	0.008
Diabetes duration (months)	26.5 ± 29.6)	21.4 ± 28.0	<0.001
Last metformin dose	1,465 ± 564	1,342 ± 573	<0.001
A1C before metformin (%)	8.2 ± 1.8	7.9% ± 1.8	<0.001
% Male	50.0	47.3	0.257
% Non-white	10.0	10.2	0.904
Initial metformin dose (mg)	1,073 ± 502	1,076 ± 508	0.903
BMI (kg/m^2)	35.7 ± 7.7	35.6 ± 8.0	0.842
Systolic blood pressure (mmHg)	134 ± 13	135 ± 14	0.129
Diastolic blood pressure (mmHg)	79 ± 8	79 ± 9	0.823
LDL cholesterol (mg/dl)	111 ± 36	113 ± 34	0.319
HDL cholesterol (mg/dl)	42 ± 10	41 ± 11	0.443
Triglycerides (mg/dl)	256 ± 269	241 ± 244	0.255
Estimated glomerular filtration rate (ml/min)	93 ± 25	92 ± 26	0.262
% With cardiovascular disease	13.5	14.5	0.564
% With nephropathy	0.4	0.8	0.309
% With retinopathy	0.4	0.1	0.222
% with neuropathy	5.1	2.9	0.020
Medicine possession ratio ≥0.8	71.5	66.7	0.030
Months to failure or end	16.9 ± 12.2	27.6 ± 13.3	<0.001

Data are means ± SD or percent, unless otherwise indicated.

RESULTS — Of the 1,799 patients who achieved A1C <7% with the initiation of metformin monotherapy as their first-ever anti-hyperglycemic, 42% (*n* = 748) experienced secondary failure (Table 1) within the 2-to 5-year follow-up period, a rate of 17.0% (15.8–18.2%) per year. Younger age (57.7 vs. 59.2 years, $P = 0.008$), longer duration of diabetes before therapy (26.5 vs. 21.4 months, $P < 0.001$), and higher A1C at metformin initiation (8.2 vs. 7.9%, $P < 0.001$) were associated with failure. Individuals who failed did so within a mean of 16.9 months. Individuals who did not fail were followed for a mean of 27.6 months ($P < 0.001$). Of the 748 patients who experienced secondary failure, 70% reached an A1C >7.5, and 30% added a second drug, most of whom did so while continuing metformin (data not shown).

As displayed in Table 2, we observed considerable variation in the time between diabetes diagnosis and the start of metformin: 40% of patients who initiated metformin did so within 3 months of diagnosis, but 25% waited 36 or months or longer. Failure was less likely among individuals who started metformin sooner (*P* value for χ^2 of distribution <0.001). A1C at metformin initiation also varied, with 27% initiating while A1C was <7 and 23% initiating while A1C was ≥9.0%. Failure was slower among individuals who started metformin when A1C

Table 2—*Distribution of diabetes duration and A1C at metformin initiation and parsimonious logistic regression of the probability of secondary failure of metformin*

	Failed metformin (n = 748)	Did not fail metformin (n = 1,051)	Odds ratio	95% CI	P
Mean age*	57.7 (12.3)	59.2 (11.3)	0.98	0.97–0.99	<0.001
Duration of diabetes (months)†					
0–3	34.2%	44.4%	1.00	—	—
4–11	11.0%	11.0%	1.56	1.12–2.18	0.008
12–23	14.8%	11.6%	2.09	1.53–2.87	<0.001
24–35	10.7%	10.7%	1.59	1.13–2.24	0.007
>36	29.3%	22.3%	2.2	1.68–2.87	<0.001
A1C (%)†					
<7.0	20.5%	30.9%	1.00	—	—
7.0–7.9	35.8%	33.3%	1.53	1.19–1.98	0.001
8.0–8.9	17.9%	14.9%	1.73	1.27–2.35	<0.001
>9.0	25.8%	20.8%	2.04	1.54–2.72	<0.001
Hosmer-Lemeshow χ^2			8.3		0.405
c Statistic			0.613		

*P = 0.008. †χ^2 for distribution P < 0.001.

was lower (P value for χ^2 of distribution <0.001).

In the multivariable analysis, only three of the 20 patient characteristics described in Table 1 were independent predictors of the odds of secondary failure of metformin monotherapy: younger age, time between diagnosis and therapy, and A1C before therapy initiation. Compared with patients who initiated metformin within 3 months of diabetes diagnosis, those who initiated in 4–11 months were 56% more likely to experience secondary failure (odds ratio 1.56, 95% CI 1.12–2.18), and patients who initiated 36 or more months after diagnosis were more than twice as likely to fail (2.20, 1.68–2.87). Similarly, patients with A1C at metformin initiation of 7–7.9, 8–8.9, and ≥9.0% were 53% (1.53, 1.19–1.98), 73% (1.73, 1.27–2.35), and 104% (2.04, 1.54–2.72) more likely to experience secondary failure, respectively, relative to those with A1C <7.0%. However, these effects were independent: an interaction term linking duration of diabetes to A1C was not significant. The multivariable statistical model had modest discrimination (c statistic = 0.613) and adequate fit (Hosmer-Lemeshow χ^2 = 8.3, P = 0.405).

Expressed as a rate, after adjustment for age and A1C before therapy, metformin failed in 12.2% (10.5–14.4%) of patients who initiated metformin within 3 months of diabetes diagnosis each year, compared with 17.8–21.9% of other patients (Fig. 1). Patients who started metformin while A1C was <7% failed at an age-and duration-adjusted rate of 12.3% per year, compared with 17.8–19.4% in other A1C categories (Fig. 2).

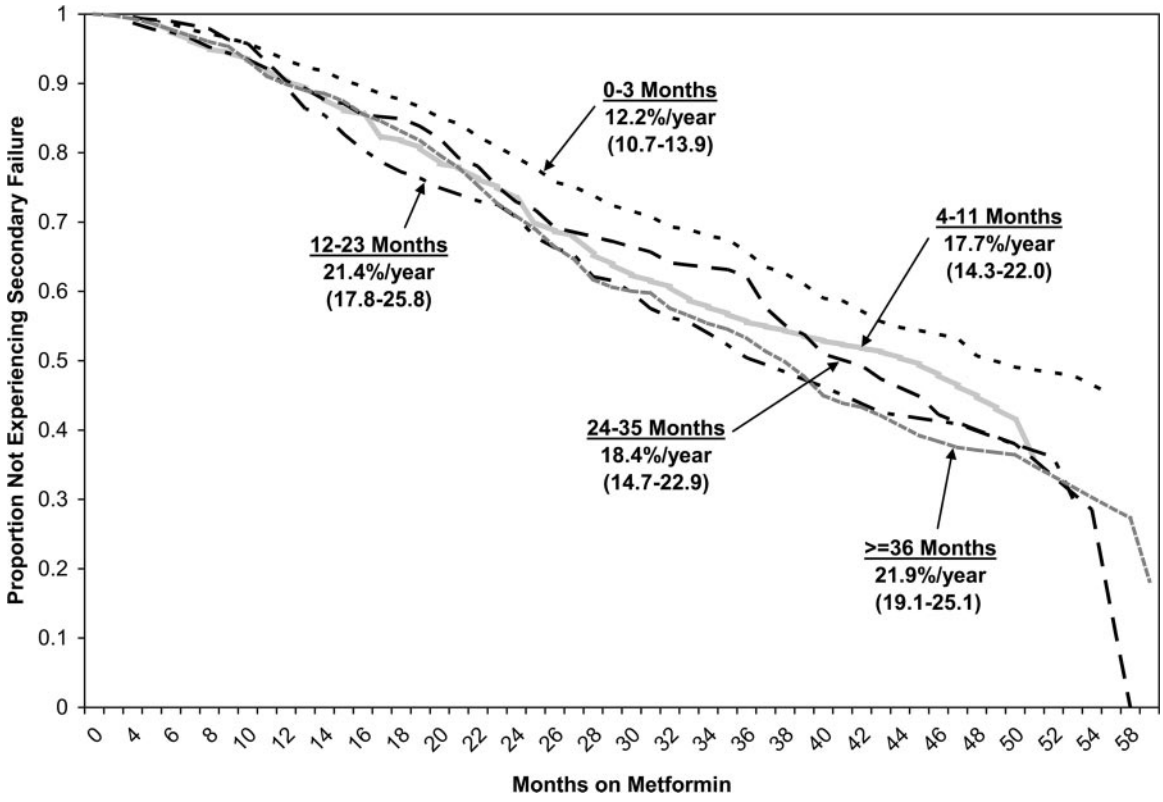

Figure 1—*Kaplan-Meier plot of secondary failure of metformin monotherapy by categories of duration of diabetes at metformin initiation adjusted for age and A1C at initiation and the percent per year (95% CIs) experiencing secondary failure.*

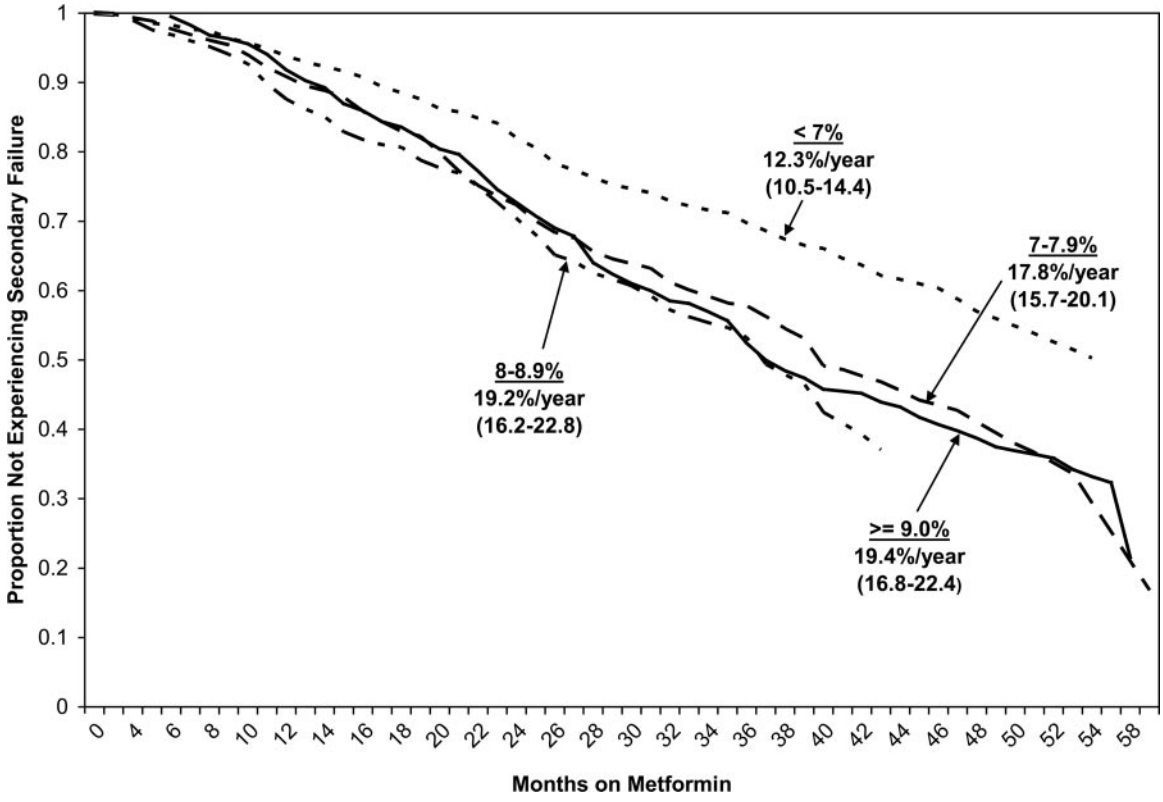

Figure 2—*Kaplan-Meier plot of secondary failure of metformin monotherapy by categories of A1C at metformin initiation adjusted for age and diabetes duration at initiation and the percent per year (95% CIs) experiencing secondary failure.*

CONCLUSIONS — In this observational cohort study of 1,799 patients who lowered their A1C to below 7% using metformin monotherapy as their first-ever anti-hyperglycemic agent, we found that initiating metformin within 3 months of diabetes diagnosis was associated with a substantial reduction in the odds of secondary loss of glycemic control. This result is consistent with the hypothesis that early initiation of metformin preserves β-cell function and supports the current ADA/EASD hyperglycemia treatment algorithm (4), which recommends metformin therapy as soon as type 2 diabetes is diagnosed. We also found that lower A1C at treatment initiation was independently associated with a reduced risk of secondary failure. Importantly, only subjects with the shortest diabetes duration (0–3 months) and the lowest baseline A1C (<7%) benefited; overlapping confidence intervals among the other categories of duration and A1C suggested no difference in the probability of failure.

Of metformin initiators, 42% experienced secondary failure within a mean follow-up period of 27.6 months (2 years and 2 months). This equates to an annual failure rate of 17%, substantially greater than the 4% per year reported in ADOPT (A Diabetes Outcome Progression Trial) (7). ADOPT defined failure as fasting plasma glucose >180 mg/dl, a level that correlates to an A1C of ~8% (8), whereas we used an A1C cut point of 7.5%. We also included the addition or substitution of other anti-hyperglycemic agents within our definition of failure. Metformin monotherapy might therefore be less durable than the experience of highly screened volunteers treated by research physicians would suggest. Discrepancies between real-world "effectiveness" studies and trials of clinical efficacy are not uncommon (9). In addition, our results are consistent with one prior observational study of untreated patients with A1C <7.0% that similarly found that lower baseline A1C and younger age were the major independent predictors of progression (A1C ≥7% or initiation of therapy) (10). We also note that sensitivity analyses examining the two definitions of failure independently, and alternative A1C thresholds of 7 and 8%, did not change our results.

Long-term observational follow-up of the UK Prospective Diabetes Study cohort showed that intensively treated patients maintained lower risks for any diabetes-related end point, microvascular disease, myocardial infarction, and all-cause mortality well after between-group differences in glycemic control disappeared (11). The UK Prospective Diabetes Study observations support the hypothesis that early control of hyperglycemia creates a beneficial "legacy effect" in cardiovascular disease prevention. A recent joint statement of trialists and scientific associations further supports this point of view (12). The association between immediate metformin initiation and preservation of glycemic control that we now report might therefore have significant health and economic benefits.

In our data, the importance of early initiation of metformin applied to the full range of patients with recently diagnosed type 2 diabetes. Presence of microvascular and macrovascular comorbidities did not affect this finding, nor did other predictors including A1C at initiation, BMI, blood pressure, lipids, adherence, or estimated glomerular filtration rate. However, it is important to note that our results are limited to the subset of metformin initiators who succeeded in lowering their A1C to <7%. We were sur-

prised to find that this subset included only 53% of the 3,388 patients who initiated metformin monotherapy as their first-ever anti-hyperglycemic drug. Although metformin is reported to be well tolerated and effective (13,14), in our sample, 780 (23%) patients either did not refill their initial dispense, refilled sporadically, or added or switched to a second agent within 6 months of metformin initiation. Another 709 patients were unable to reduce their A1C to below 7%. Clinicians wishing to optimize their patients' glycemic control should recognize that metformin may be less tolerable, less effective, and less durable than is commonly believed and be prepared to respond to failure quickly.

Our results show an association between earlier use of metformin and lengthened effectiveness of the drug, possibly resulting from more effective preservation of β-cell function. Therapeutic effectiveness requires therapeutic adherence, but adherence was not an independent predictor of success in our data, probably because it was relatively high among all patients. This is likely due to the study design, which limited the study sample to patients who had initially succeeded with metformin therapy. In fact, in univariate analysis, adherence (medication possession ratio ≥80%) was somewhat greater among patients who subsequently failed metformin. This is consistent with a previous study in which patients with the highest adherence had greater odds of therapy intensification after an elevated A1C (15).

Our findings must be interpreted with caution for two reasons. First, patients who initiated metformin while A1C was lower likely achieved the lowest A1C levels. If so, it would be expected that they would be able to remain below 7.5% for longer periods. However, all patients achieved an A1C below 7%. Second, patients with longer duration of diabetes before metformin initiation may have been in good control for much of that untreated period, in which case their total time in control before metformin failure could have actually been greater than patients who initiated metformin immediately. Our objective was to assess the success of metformin therapy in drug-naïve patients and to identify predictors of metformin durability. Thus, we chose to evaluate only treated time in our analyses.

As an observational analysis, our study has some inherent limitations. Our results could be affected by measurement of A1C levels at irregular intervals and frequencies. We could not observe whether patients who added another agent before an elevated A1C did so because of metformin's known gastrointestinal side effects or whether their doctors were more aggressive proponents of tight glycemic control. Furthermore, the organizational structure of KPNW and the existence of an electronic medical record with substantial information technology support, including built-in alerts for A1C testing, may limit the generalizability of our study to other real-world settings.

Diabetes is a progressive disease that typically requires ongoing therapeutic adjustments to maintain glycemic control (16). As therapies lose their effectiveness, long delays frequently result in substantial glycemic burden that accumulates over time (17). Our study suggests that initiating metformin soon after diabetes diagnosis and while A1C is low may improve the durability of metformin, thereby delaying the need for therapeutic adjustments and reducing the glycemic burden associated with its failure. Further research should focus on whether earlier metformin monotherapy reduces the risk of microvascular and macrovascular complications.

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References

1. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
2. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
3. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V, Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289–297
4. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B, American Diabetes Association, European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
5. 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
6. 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
7. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G, ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
8. American Diabetes Association. Standards of medical care in diabetes–2009. Diabetes Care 2009;32 (Suppl. 1):S13–S61
9. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA 2007;298:1209–1212
10. Pani LN, Nathan DM, Grant RW. Clinical predictors of disease progression and medication initiation in untreated patients with type 2 diabetes and A1C less than 7%. Diabetes Care 2008;31:386–390
11. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
12. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P, Sherwin RS, American Diabetes Association, American College of Cardiology Foundation, American Heart Association. Inten-

sive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009;32:187–192
13. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1995;333:541–549
14. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996;334:574–579
15. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, Meigs JB, Ross-Degnan D. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care 2007;30:807–812
16. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA 1999;281:2005–2012
17. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care 2004;27:1535–1540