

First 20 Months' Experience With Use of Metformin for Type 2 Diabetes in a Large Health Maintenance Organization

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OBJECTIVE — To assess adherence to prescribing guidelines, continuation rates, population effects on glycemic control, and occurrence of lactic acidosis during the first 20 months of the availability of metformin in a large health maintenance organization.

RESEARCH DESIGN AND METHODS — A retrospective cohort study was performed in the 90,000-member diabetes registry of Kaiser Permanente, northern California. Principal study measures were the proportions of patients started on metformin who met prescribing guidelines (previously on sulfonylureas, HbA_{1c}, obesity, creatinine), the change in HbA_{1c} at 6 months after starting metformin, and hospitalization rates for lactic acidosis.

RESULTS — A total of 9,875 patients received metformin during this interval. At least 74% were previously treated with sulfonylureas alone, 81% had baseline HbA_{1c} \geq 8.5%, 71% were obese, and 99% had a serum creatinine \leq 1.5 mg/dl. Among patients on sulfonylureas at baseline, those starting metformin had significantly lower HbA_{1c} levels 6 months later than those not started, after adjustment for age, sex, and the higher baseline levels in those started (adjusted difference: 0.5%, $P < 0.0001$). Patients starting metformin as initial monotherapy also improved significantly, but patients previously treated with insulin (with or without sulfonylureas) had slightly higher follow-up HbA_{1c} levels than similar patients not starting metformin. Continuation of metformin at 12 months was significantly higher for patients previously treated with sulfonylureas than other groups. One probable case of lactic acidosis was identified during 4,502 person-years on metformin.

CONCLUSIONS — Adherence to prescribing guidelines was relatively high during metformin's first 20 months of availability. Glycemic control improved substantially for patients previously treated with sulfonylureas. Lactic acidosis was rare.

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The approval of metformin for treating type 2 diabetes provides a new approach to management of a difficult-to-treat disorder (1–3). The drug features a novel and appealing mechanism of action, being the first to directly lower hepatic glucose production and peripheral insulin resistance, which are primary pathophysiological features of the disease (1).

However, metformin is relatively expensive in the U.S. (4), may rarely be associated with lactic acidosis (which can be fatal) (5), and is not thought to be effective when diabetes is primarily due to absolute insulinopenia (1). Improper dosing, either escalating the initial dosage too rapidly (leading to gastrointestinal side effects such as nausea and diarrhea) or fail-

ing to increase dosage sufficiently, would each be expected to lower metformin's effectiveness. For these reasons, guidelines for using metformin have identified appropriate target groups and have recommended a dosing schedule (2,6).

It is important to understand the clinical and economic impact of newly introduced technologies or medications. When guidelines are issued, it is important to measure the extent to which they are followed. This study describes patterns of use of metformin in diabetic patients in a large health maintenance organization (HMO) during the first 20 months after metformin's introduction onto the HMO's formulary. We assessed the extent of physician adherence to clinical guidelines for selection of patients and medication dosage, the continuation of metformin treatment once begun, the rate of hospital admission for lactic acidosis among metformin users, and the effectiveness of the drug for lowering HbA_{1c} levels.

RESEARCH DESIGN AND METHODS

Study population

This study used the diabetes registry of the Kaiser Permanente Medical Care Program of Northern California. Kaiser Permanente is a group model HMO serving ~2.7 million members. The registry (7) identifies diabetic patients from four automated clinical databases: inpatient and outpatient diagnostic files, pharmacy records of prescriptions for diabetic medications or supplies, and abnormal (\geq 6.7%) HbA_{1c} values. The registry contained ~90,000 members on 1 January 1996. At that point, the registry's sensitivity for diagnosed diabetes was estimated to be 96%. Approximately 2.5% of those in the registry appear not to have diabetes.

Identification of metformin users and comparison group

Metformin became available on the Kaiser Permanente formulary in May 1995. Metformin users were identified from the HMO's pharmacy information management system for the period from 1 May

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Abbreviations: HMO, health maintenance organization; ICD-9, *International Classification of Diseases, Ninth Revision*

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

1995 through 31 December 1996. This database records complete prescribing information for all prescriptions filled at any of the HMO's 108 outpatient pharmacies. From this information, we could determine initial and subsequent daily dosages and number of days' supply for each prescription refill. Slightly more than 10% of Kaiser Permanente members did not have pharmacy benefits during this period. Some portion of these fill their prescriptions at outside pharmacies. Thus, use of Kaiser Permanente pharmacy data would be expected to slightly underestimate the total number of metformin users.

Continuous use of metformin was assumed as long as the interval between two prescription refills (or since the most recent prescription) was not >1 month longer than the number of days supply dispensed. Thus, if the last prescription provided a 3-month supply, we assumed that use continued for 4 months from the date of that prescription.

The pharmacy database was also used to characterize diabetes treatment during the 6 months immediately preceding each patient's first metformin prescription. Patients were characterized as users of sulfonylureas, insulin, both insulin and sulfonylureas, or no drug treatment. Among those who received prescriptions for "both" insulin and sulfonylureas, we could not accurately distinguish those who changed from one therapy to the other from patients using insulin and sulfonylureas concurrently. A small group was categorized as "unclear" if they joined the health plan <6 months before their first metformin prescription.

We assembled a comparison group of all registry members not started on metformin who remained in the health plan through December 1996 (so that we could be certain they were not started on metformin). Treatment for this group during the 6 months before metformin became available (i.e., before 1 May 1995) was categorized as for metformin users.

Identification of other patient characteristics

Automated laboratory databases provided information on HbA_{1c} and serum creatinine both before and after starting metformin. Because this is a clinical rather than a research database, tests were not uniformly performed on each patient. Nevertheless, results for each test were available for a majority of patients. Information on height and weight was obtained from a mailed

survey with telephone follow-up of nonresponders conducted during 1995–1996. The questionnaire requested current height and weight information. Overall response to the survey was 84%. Obesity was defined as a BMI >27.0 kg/m².

Identification of lactic acidosis

Cases of lactic acidosis requiring hospitalization were sought by linking the registry to the HMO's hospital discharge database, searching for principal or secondary discharge diagnoses of "acidosis" (*International Classification of Diseases, Ninth Revision* [ICD-9] code 276.2, which includes lactic acidosis as well as metabolic, respiratory and nonspecified acidosis) from 1 May 1995 through 31 December 1996. Medical charts of each potential case were reviewed by one of the investigators (B.E.). Cases of acidosis (pH <7.35) were classified as "probable" lactic acidosis if a lactic acid level >5 mmol/l was noted in the absence of serum ketones, as "possible" if a lactic acid level between 2 and 5 mmol/l was noted in the absence of serum ketones, as "indeterminate" if a lactic acid level was not obtained but serum ketones were either normal or missing, and as "not lactic acidosis" if a lactic acid was measured and was <2 mmol/l or if, in the absence of a lactic acid measurement, another cause for the acidosis was documented.

Description of the clinical guideline for use of metformin

The HMO chiefs of endocrinology, in consultation with the medical group's 45 practicing endocrinologists, developed and issued a guideline for use of metformin in May 1995. The guideline identified candidates for metformin as type 2 patients who were obese, were already using adequate doses of sulfonylureas, and had an HbA_{1c} ≥8.5%. Contraindications to use included a serum creatinine level >1.5 mg/dl, chronic liver disease, and congestive heart failure. Recommended starting doses were 500–1,000 mg daily with stepwise increases every 1–2 weeks to a maximum daily dose of 2,550 mg. The guideline did not recommend metformin for initial therapy because, in the view of the endocrinologists, an alternative (sulfonylureas) with a better-known safety profile was available.

The guideline was published in the *Pharmacy and Therapeutics Newsletter* which is mailed to all group physicians, and was also available to all physicians in an on-line reference database. The endocrinol-

ogists who developed the guideline work in the 32 facilities alongside primary care physicians and serve as opinion leaders.

Analysis plan

To assess compliance with the guideline, we compared prior therapy, most recent pre-prescription HbA_{1c} and serum creatinine levels, and obesity status for people starting metformin and those not starting metformin. Inappropriate metformin use in congestive heart failure or liver disease could not be readily estimated because automated databases did not identify such patients with sufficient accuracy. The χ^2 tests were used for comparisons of dichotomous and categorical variables, and *t* test statistics were used for continuous variables.

To study the population effectiveness of metformin, we modeled the change in HbA_{1c} (from baseline to follow-up) as a function of whether or not metformin was begun, using analysis of covariance. Change was calculated using each person's most recent HbA_{1c} value, provided it was drawn at least 2 months after metformin was initiated (or after 1 May 1995 for people who never started metformin). The average interval from baseline to the follow-up HbA_{1c} value used was 5.6 months. People with a baseline serum creatinine level >1.5 mg/dl were excluded from the analyses because they would have been considered ineligible for metformin (and should therefore not be included in the comparison group either). People with higher baseline HbA_{1c} values were more likely to be started on metformin. We would therefore expect that "regression to the mean" would lead to larger changes in people starting metformin even if it were not beneficial. To adjust for this effect, we included the baseline HbA_{1c}, along with patient age and sex, as covariates in the model. Analyses were conducted separately in strata based on prior treatment.

In a separate logistic regression analysis among metformin users, patients were categorized as "improved" if the follow-up level of HbA_{1c} was more than one half percentage point lower than baseline. Potential predictors of improvement included patient age, sex, baseline HbA_{1c}, prior treatment, starting dose of metformin, dose at 6 months, and obesity status.

Continuation of therapy was assessed using survival curves. Curves were constructed and compared for strata based on prior treatment and on response to treatment using the Lifetest procedure (SAS Institute, Cary, NC). Proportional hazards

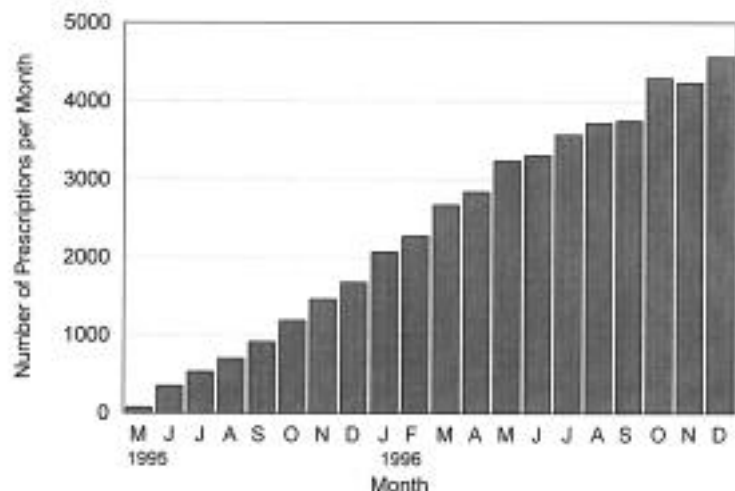


Figure 1—Number of metformin prescriptions per month (May 1995 to December 1996), Kaiser Permanente pharmacies, Northern California.

analysis was used to model time to stopping metformin as a function of prior therapy, the HbA_{1c} response, and other guideline parameters (obesity, serum creatinine, and starting dose) as well as age and sex.

RESULTS — The number of metformin prescriptions issued monthly rose steadily during the first 20 months of availability and had not plateaued by the end of 1996 (Fig. 1). At that point, 9,875 individuals had received one or more prescriptions.

Patient selection for metformin therapy

Patients started on metformin were overwhelmingly those previously treated with sulfonylureas (Table 1). Among this latter group, 23% of all diabetic members had begun metformin by the end of 1996. Additional sulfonylurea prescriptions were found during the first 4 months of metformin therapy for 68% of patients, suggesting that metformin was usually added to rather than substituted for the sulfonylurea. Fewer than 5% of patients starting metformin had no previous record of diabetes pharmacotherapy. For 84% of this small group, metformin appeared to be used as monotherapy. Among small numbers of patients previously treated with insulin, records of subsequent insulin prescriptions were found for 53%.

At baseline, poor glycemic control was more frequent among patients started on metformin; mean baseline HbA_{1c} level was 1.5 percentage points higher than for those not started. The most recent prior HbA_{1c} was ≥8.5% for 81% of those starting met-

formin. Control was substantially and statistically significantly worse for patients starting metformin in each prior treatment category (data not shown). This difference was greatest for patients previously on oral hypoglycemics (mean baseline HbA_{1c}: 10.2

vs. 8.5%, $P < 0.0001$) and least for those previously on insulin only (mean baseline HbA_{1c}: 9.6 vs. 9.0%, $P < 0.01$), suggesting that among insulin-using patients, physicians started metformin in those with less severe glycemic control problems.

Patients started on metformin were somewhat more likely to have reported being obese when surveyed in 1995. Nevertheless, 29% had not reported obesity. Baseline serum creatinine levels were identified in the laboratory database for 73% of patients starting metformin; only 90 (1.3%) had creatinine levels >1.5 mg/dl before beginning treatment. Subsequent creatinine values were available for 74 of these patients; 34 of these were ≤1.5 mg/dl. Thus, at most, 0.6% of the patients receiving metformin had persistent serum creatinine levels above the guideline recommendation.

Starting dosages of metformin were ≤1,000 mg per day for 92% of patients (Fig. 2). By 6 months of therapy, the median dose was still 1,000 mg, but >20% of patients were prescribed daily doses of ≥1,500 mg. Of 4,364 patients whose 6-month dose was less than maximal (2,550 mg daily), the most

Table 1—Characteristics of diabetic patients starting and not starting metformin between May 1995 and December 1996

	Started metformin	Did not start metformin*
<i>n</i>	9,875	54,382
Age (years)		
0–18	11 (0.1)	796 (1.5)
19–29	115 (1.2)	949 (1.8)
30–49	2,524 (25.6)	11,438 (21.0)
50–69	5,652 (57.2)	27,410 (50.4)
≥70	1,573 (15.9)	13,789 (25.4)
Sex (% female)	52.5	46.4
Prior therapy		
Oral hypoglycemics	7,339 (74.3)	22,329 (41.0)
Insulin only	766 (7.8)	14,227 (26.2)
Both insulin and oral hypoglycemics	741 (7.5)	4,207 (7.8)
Neither	311 (3.1)	13,619 (25.0)
Unclear	718 (7.3)	—
Most recent HbA _{1c} † (%)		
<8.0	12.2	41.7
8.0–8.4	7.1	10.7
8.5–9.4	17.7	18.3
≥9.5	63.0	29.3
Percent obese‡	71.0	60.7
Percent with serum creatinine >1.5 mg/dl§	1.3	9.6

Data are *n* (%) or %. *Restricted to members who were in the health plan before May 1995 and remained members through December 1996. †Baseline HbA_{1c} levels were available for 85.2% of patients starting metformin and for 57% of those not starting. ‡Obesity status available for respondents to the registry survey: 69% of those starting metformin; 70% of those not starting. §Serum creatinine available for 73% of patients starting metformin; 46% of those not starting.

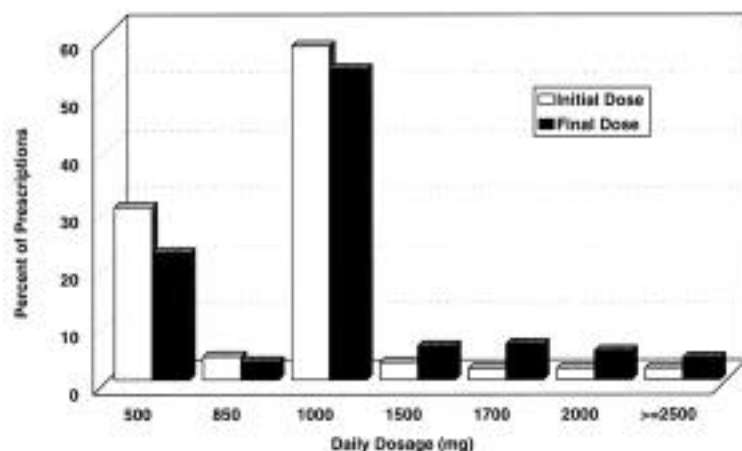


Figure 2—Percent distribution of daily metformin doses, for starting (□) and for final dose (■) in people using metformin for at least 6 months.

recent HbA_{1c} was >8.5% in 44.2%, suggesting that subsequent doses may have been increased further.

Glycemic response to metformin

Follow-up HbA_{1c} values were available for 6,259 patients starting metformin (80% of those with a baseline value) and for 22,078 of those not starting (41% of those with a baseline value). Overall, the average decrease in HbA_{1c} for those starting metformin was 1.4% (Table 2), with 76% of all patients showing improvement (defined as a decrease in HbA_{1c} of at least 0.5% from baseline). Compared with people not starting metformin, decreases were substantially greater for metformin users among those previously treated with sulfonylureas and those previously on no diabetes drugs.

Not surprisingly, the strongest predictor of the change in HbA_{1c} was the baseline level. People with higher baseline levels in

each treatment group had greater declines. However, after adjustment for baseline HbA_{1c} as well as age and sex, a sizeable benefit of metformin persisted for patients previously treated with sulfonylureas and for those with no previous pharmacotherapy. Patients previously treated with insulin, with or without sulfonylureas, appeared to do slightly worse after addition of metformin.

In a multivariate logistic regression model among 2,257 metformin users who continued the drug for at least 6 months (and had available values for all key variables), we examined predictors of improvement in HbA_{1c} (a decrease of $\geq 0.5\%$ at follow-up). Compared with those aged <50 years, older persons were more likely to achieve a significant reduction (odds ratios: 1.92 [95% CI 1.49–2.46] and 3.08 [95% CI 2.13–4.43] for patients 50–69 years and ≥ 70 years, respectively). Women were more likely than men to improve

(odds ratio: 1.36 [95% CI 1.10–1.95]). Patients previously treated with insulin only were much less likely to experience improvement than those previously on sulfonylureas only (odds ratio: 0.42 [95% CI 0.29–0.61]). Prior treatment with both insulin and sulfonylureas or with no pharmacotherapy was also associated with lower likelihood of improvement (odds ratios: 0.84 and 0.66, respectively), but these differences did not reach statistical significance because of the low numbers of such patients included in the models. There was a trend toward greater probability of improvement when a larger starting dose was used. Compared with people started at 1,000 mg per day, those on smaller starting doses were 24% less likely (95% CI 0.0–42.0%) and those with higher doses were 56% more likely (95% CI –14.0 to 178.0%) to improve. The 6-month metformin doses were unrelated to follow-up level of HbA_{1c}. Patients who reported not being obese were 36% more likely to have improvement in HbA_{1c} than obese patients.

Predictors of continuing treatment

For all metformin starters, probability of continuing it for at least 1 year was 0.57. Those previously treated only with sulfonylureas were more likely to remain on metformin than other groups (Fig. 3A). Patients whose HbA_{1c} levels improved were more likely to continue treatment (Fig. 3B). A proportional hazards model confirmed that patients previously treated with insulin only (hazard ratio: 1.41 [95% CI 1.23–1.63]), with both insulin and sulfonylureas (hazard ratio: 1.19, [95% CI 1.02–1.37]), or with no previous therapy (hazard ratio: 1.82 [95% CI 1.50–2.20]) were each more likely to stop metformin than patients previously on sulfonylureas.

Table 2—Change in HbA_{1c} values after initiation of metformin treatment, by previous treatment, and compared with patients not starting metformin

Previous treatment	Started metformin*	Did not start metformin*	Adjusted difference (metformin versus control)†	P value†
Sulfonylureas only	–1.58	–0.27	–0.51	<0.0001
Insulin only	–0.56	–0.47	0.12	0.04
Insulin and sulfonylureas	–0.81	–0.89	0.06	0.42
No medical therapy	–1.06	–0.13	–0.33	<0.001
Unclear	–1.52	—	—	—
Total	–1.41	–0.38	—	—

*Follow-up HbA_{1c} values (most recent HbA_{1c} obtained at least 2 months after initiation of metformin therapy) were available for 80% of metformin users with baseline values and for 41% of those not starting metformin. †From an analysis of covariance model that excludes patients with baseline serum creatinine levels >1.5 mg/dl and adjusts change in HbA_{1c} for age, sex, and baseline HbA_{1c} level.

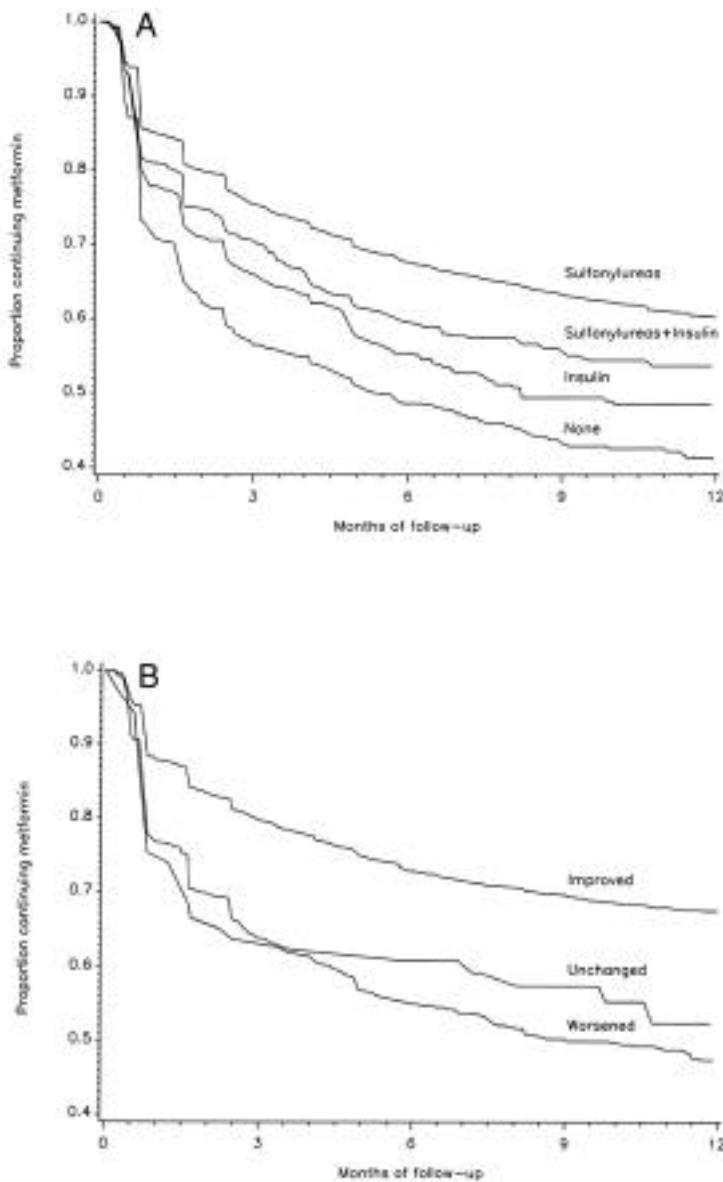


Figure 3—Survival curves for proportion of people remaining on metformin to 12 months, stratified by prior diabetes therapy (A) and by HbA_{1c} response to metformin (B).

Patients with a baseline creatinine >1.5 mg/dl were much more likely to have the medication stopped (hazard ratio: 2.45 [95% CI 1.79–3.35]). Starting dose of metformin was negatively related to staying on treatment. Compared with those starting at 1,000 mg daily, those starting on lower doses were 24% less likely ($P < 0.0001$) and those starting at higher dosages were 21% more likely ($P = 0.02$) to stop the

drug. Older age was related to greater likelihood of remaining on the medication. Compared with those <50 years old, patients 50–69 years were 26% less likely and those ≥ 70 years were 20% less likely to stop treatment ($P < 0.01$ for each).

Occurrence of lactic acidosis

A total of 25 hospital discharge diagnoses of “acidosis” (ICD-9-CM code 276.2) were

identified through December 1996. At chart review, only one proved to be a probable case of metformin-related lactic acidosis. A 39-year-old African-American man, whose diabetes was very well controlled on metformin (500 mg b.i.d.), was admitted for an exacerbation of chronic asthma. A PO_2 level on 2 l/min O_2 was normal; however, hypoxia before admission was possible. Other medications included prednisone (40 mg q.d.), Theo-Dur (300 mg b.i.d.), albuterol inhaler, and L-thyroxine (0.125 mg q.d.). On admission, pH was 7.23, and lactic acid level was 13.2 mmol/l. Serum ketones were negative, serum creatinine was 1.0 mg/dl. After treatment with bicarbonate and discontinuation of metformin, recovery was uneventful. A second case was classified as indeterminate. An 82-year-old Caucasian woman had been switched from tolinaise to metformin (500 mg q.d.) 1 week before admission. She took no other medications. Her renal function 6 months before admission was normal (serum creatinine 0.8). On the day of admission, she developed weakness, abdominal pain, and obtundation. Admission laboratory tests showed serum glucose 850 mg/dl, creatinine 2.7 mg/dl, and arterial pH 6.97. Ketonemia was not present, and a lactate level was not measured. She was treated with fluids and intravenous insulin and made an uneventful recovery. On discharge, her creatinine level was 0.9 mg/dl. This one (or possibly two) case in 9,875 metformin users with 4,502 person-years of use yields an incidence of 2.2 (or possibly 4.4) cases per 10,000 person-years of use.

CONCLUSIONS — Metformin use increased rapidly after its appearance on the formulary of this large HMO. For the most part, physicians appeared to follow medical group guidelines in prescribing metformin. These guidelines identified obese patients with normal renal function who were poorly controlled on sulfonylureas as the ideal candidates for metformin. During the next 20 months, the majority of patients begun on metformin met these criteria. Approximately 1% of subjects beginning metformin had serum creatinine levels >1.5 mg/dl. However, a third of these had lower levels (≤ 1.5 mg/dl) upon repeat testing. Patients with increased baseline creatinine levels were also more likely to stop metformin promptly.

A significant fraction (29%) of the metformin recipients did not report being obese when surveyed in 1995. Interestingly, this subgroup had a somewhat better

glycemic response to metformin than the majority. Although treatment guidelines recommend metformin only in obese type 2 patients, two previous randomized trials have also found that the glycemic response to metformin is at least as great for nonobese type 2 patients (8,9).

Patients who were previously treated with sulfonylureas were much more likely than those who previously used insulin, with or without sulfonylureas, to show improvement in HbA_{1c} and were also more likely to continue on metformin at 12 months. Patients starting metformin as initial therapy experienced improvement in HbA_{1c} level, but were the least likely to still be taking the drug at 12 months. Higher starting doses of metformin were associated with greater likelihood of improvement in HbA_{1c}, but also with somewhat lower continuation at 1 year, suggesting the importance of adequate dosages but also the possibility that side effects may have been dose-dependent, particularly early in the course of treatment.

Our findings confirm, at the population level, those of smaller clinical studies in volunteer samples showing an important antihyperglycemic effect for metformin in patients failing sulfonylurea treatment (2,3). The adjusted decrease in HbA_{1c} of 0.51% for people previously treated with sulfonylureas is a conservative estimate of metformin's benefit. First, rather than comparing metformin with a placebo, our estimate is based on comparing metformin's effect with that of any other maneuvers physicians may have tried for patients with similar HbA_{1c} values. Follow-up pharmacy data indicated that 16% of patients not starting metformin were begun on insulin, 10% had their sulfonylurea dosage increased, and 22% were switched to a different sulfonylurea drug. Second, the effect estimate considers all metformin recipients, whether or not they were still taking metformin when HbA_{1c} was remeasured. Thus, this is an "intention-to-treat" analysis and the effect was seen despite the inclusion of noncompliant patients and those who discontinued the drug.

These same factors may help to explain our inability to detect a population benefit of metformin for patients previously treated with insulin. In addition, we could not document continued insulin treatment from our automated data sources for 47% of patients starting metformin. This may indicate that some physicians were attempting to either substitute metformin for insulin or at least decrease insulin dosages as metformin was

begun. Three prior randomized trials (10–12) found substantial improvements in glycemic control when metformin is added to insulin in poorly controlled type 2 patients, but in these studies, insulin dosages were not lowered as metformin was begun.

Reasons for the discontinuation rate of 43% at 12 months undoubtedly include both treatment failure and adverse effects, among others. Continuation was lowest for persons starting metformin as initial therapy (and therefore, perhaps, with more treatment alternatives) and for those whose HbA_{1c} worsened during treatment. These continuation rates are comparable to those seen for other chronically used medications. Jones et al. (13) found that 40 to 50% of new users of each of four classes of antihypertensive medications discontinue use by 6 months. Psaty et al. (14) observed similar rates of changing or quitting of hypertension medications in elderly people during a 1-year period. Avorn et al. (15) reported that only 50% of patients starting lipid-lowering medications were still taking any lipid-lowering medication 5 years later.

One, or possibly two, episodes of lactic acidosis were identified in this cohort during 4,500 person-years of metformin use. No lactic acidosis-related deaths occurred. This event rate is about 10-fold higher than previous estimates (1,5). However, one of these cases was not confirmed as lactic acidosis and the second occurred in a patient with hypoxia that might possibly have contributed to the development of lactic acidosis. Moreover, with only one to two cases, confidence intervals about our estimate are quite wide. Our observed rates may also be somewhat higher because the majority of observation time in this study was during the first 6 months of therapy.

This report is by far the largest assessment of the effectiveness of metformin published since its introduction to the U.S. market. Nevertheless, limitations of our approach should be recognized. First, this observational database is not equivalent to a randomized trial of metformin versus usual care. Patients who started metformin differed in many ways from those who did not. We were, however, able to include a comparison group, to adjust for age, sex, and baseline differences in glycemic control between users and nonusers, and to exclude patients who would have been ineligible for metformin because of an elevated serum creatinine level. The observational nature of these data also renders them unhelpful for estimating associations

of dosage with glycemic response, as poor responsiveness undoubtedly led to higher dosage in at least some instances.

The registry is also not comparable to an epidemiological cohort in which laboratory tests are obtained at fixed intervals on all members. Values are available only if the clinician orders the test. Values for key variables (HbA_{1c}, serum creatinine) in these analyses were available for three-quarters or more of subjects. Values for people with missing data may differ from those of patients having the test. However, when comparing metformin users and nonusers, these missing data should not lead to bias unless the reasons for not having the test differed for the two groups, which seems unlikely. Unfortunately, the paucity of follow-up data on lipids during this relatively brief interval made it impossible to examine effects of metformin on population lipid values. We are also unable to describe possible effects of metformin on weight because weight is not routinely captured in our databases.

Finally, in addition to missing a small proportion of metformin users in our automated data, we cannot accurately measure compliance or identify the small number of patients who may have been instructed by their physician to stop the drug shortly after filling a prescription. Such misclassification should lead to modest underestimation of the effects of the drug (both beneficial and harmful). This lack of clinical detail also prevents us from describing reasons for stopping metformin.

In conclusion, metformin improved glycemic control for patients with diabetes in this HMO. Metformin was most effective, in terms of lowering HbA_{1c} levels, and had the highest continuation rates in patients previously treated with sulfonylureas, with over 60% of patients in this subgroup continuing use at 1 year. Lactic acidosis was rare.

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