

Patterns of Medication Initiation in Newly Diagnosed Diabetes Mellitus: Quality and Cost Implications

Nihar R. Desai, MD, MPH,^{a,b} William H. Shrank, MD, MSHS,^{a,c} Michael A. Fischer, MD, MS,^a Jerry Avorn, MD,^{a,c} Joshua N. Liberman, PhD,^d Sebastian Schneeweiss, MD, ScD,^a Juliana Pakes, MEd,^a Troyen A. Brennan, MD, JD, MPH,^d Niteesh K. Choudhry, MD, PhD^a

Divisions of ^aPharmacoepidemiology and Pharmacoeconomics and ^bCardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; ^cCenter for American Political Studies, Harvard University, Boston, Mass; and ^dCVS Caremark, Inc, Woonsocket, RI.

ABSTRACT

OBJECTIVE: Six oral medication classes have been approved by the Food and Drug Administration for the treatment of type 2 diabetes. Although all of these agents effectively lower blood glucose, the evidence supporting their impact on other clinical events is variable. There also are substantial cost differences between agents. We aimed to evaluate temporal trends in the use of specific drugs for the initial management of type 2 diabetes and to estimate the economic consequences of non-recommended care.

METHODS: We studied a cohort of 254,973 patients, aged 18 to 100 years, who were newly initiated on oral hypoglycemic monotherapy between January 1, 2006, and December 31, 2008, by using prescription claims data from a large pharmacy benefit manager. Linear regression models were used to assess whether medication initiation patterns changed over time. Multivariate logistic regression models were constructed to identify independent predictors of receiving initial therapy with metformin. We then measured the economic consequences of prescribing patterns by drug class for both patients and the insurer.

RESULTS: Over the course of the study period, the proportion of patients initially treated with metformin increased from 51% to 65%, whereas those receiving sulfonylureas decreased from 26% to 18% ($P < .001$ for both). There was a significant decline in the use of thiazolidinediones (20.1%-8.3%, $P < .001$) and an increase in prescriptions for dipeptidyl peptidase-4 inhibitors (0.4%-7.3%, $P < .001$). Younger patients, women, and patients receiving drug benefits through Medicare were least likely to initiate treatment with metformin. Combined patient and insurer spending for patients who were initiated on alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, or dipeptidyl peptidase-4 inhibitors was \$677 over a 6-month period compared with \$116 and \$118 for patients initiated on metformin or a sulfonylurea, respectively, a cost difference of approximately \$1120 annually per patient.

CONCLUSION: Approximately 35% of patients initiating an oral hypoglycemic drug did not receive recommended initial therapy with metformin. These practice patterns also have substantial implications for health care spending.

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Requests for reprints should be addressed to Niteesh K. Choudhry, MD, PhD, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120.

E-mail address: nchoudhry@partners.org

Diabetes mellitus has emerged as one of the most significant public health issues worldwide.¹ In the United States, more than 20 million individuals have diabetes, and an additional 6 million have undiagnosed disease.² The number of Americans with diabetes is projected to increase 165% by 2050.³ In the United States, this disease alone accounts for approximately \$200 billion in direct and indirect medical costs each year.⁴

Six different oral medication classes have been approved by the Food and Drug Administration for the treatment of type 2 diabetes. These include biguanides (eg, metformin),

sulfonylureas (eg, glipizide, glyburide), alpha-glucosidase inhibitors (eg, acarbose), thiazolidinediones (eg, rosiglitazone, pioglitazone), meglitinides (eg, repaglinide, nateglinide), and dipeptidyl peptidase-4 inhibitors (eg, sitagliptin, saxagliptin). Systematic reviews of controlled trials have found comparable efficacy for glucose lowering across different classes, notwithstanding significant differences in side effect profiles and tolerability.⁵ However, not all of these agents have demonstrated an ability to improve other diabetes-related outcomes. Only metformin has been shown to reduce all-cause mortality and diabetes-related death in patients with type 2 diabetes who are above ideal body weight.⁶ In contrast, rosiglitazone seems to be associated with an increased risk of myocardial infarction,⁷ and both available thiazolidinediones are associated with increased risk of congestive heart failure.⁸ The effects of other heavily marketed newer agents on major adverse cardiovascular events or mortality have not been adequately evaluated, although randomized trials are under way.^{9,10}

Accordingly, the 2006 consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommended only metformin as the evidence-based initial agent for patients with type 2 diabetes, whereas the 2009 updated statement endorses metformin or sulfonylurea as first-line therapy.¹¹

Despite the widespread dissemination of the ADA and other professional society recommendations, little is known about current clinical practice patterns for patients who initiate an oral hypoglycemic agent. We therefore explored patterns of use and temporal trends in the use of different drugs in the initial management of type 2 diabetes. Because there are substantial price differences between agents, we also estimated the financial implications of current practice patterns and the potential savings derivable through ADA/EASD consensus recommendation concordant care for type 2 diabetes.

MATERIALS AND METHODS

Study Cohort

We used prescription claims data from CVS Caremark, a pharmacy benefit manager with more than 50 million beneficiaries across the United States to create a cohort of patients, aged 18 to 100 years, who were newly initiated on oral hypoglycemic monotherapy between January 1, 2006, and December 31, 2008.

Patients were included in the cohort if they filled a new prescription for an oral hypoglycemic agent (ie, biguanides, sulfonylureas, alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, and dipeptidyl peptidase-4 inhibitors) during the study period. The date of each patient's first eligible prescription was defined as the index date. All patients were required to have maintained continuous insurance eligibility for 6 months before their index date; we excluded patients who had filled a prescription for any diabetes agent (including insulin) in the 6 months before their index date or who filled prescriptions for 2 or more antidiabetic agents on their index date.

Data Sources

Our prescription drug data sources contained information on drug name, dosage, date dispensed, the amount paid by the insurance company to the pharmacy, and the patient's copayment. These data were linked to eligibility data indicating patient age, gender, and

ZIP code of residence. Data on socioeconomic status were obtained by linking ZIP code of residence with data from the US Census, which specified the median income of the geographic population associated with each ZIP code. ZIP-code specific income was categorized into quintiles.

We determined each patient's drug coverage plan using enrollment files and categorized patients into the following groups: employer sponsored, health insurer carve-out (ie, beneficiaries fully insured through a commercial health insurer but whose prescription drug coverage was provided separately by a pharmacy benefit manager), Medicare, or other (Medicaid beneficiaries, cash card holders, and off-shore customers). All traceable person-specific identifying factors were transformed into anonymous, coded study numbers to protect subjects' privacy. The institutional review board of Harvard University approved the study.

Patterns and Predictors of Medication Initiation

We categorized patients on the basis of the class of medication on which they were initiated and then plotted trends in medication initiation over time. We assessed the use of each class over time using bivariate linear regression models. The models provide an estimate (with 95% confidence intervals) of the rate of change in the proportion of prescriptions accounted for by each therapeutic class on a monthly basis over the study period. We assumed that errors were normally distributed. We repeated these analyses within the

CLINICAL SIGNIFICANCE

- Approximately 35% of patients newly initiated on oral hypoglycemic therapy were not started on metformin as the American Diabetes Association recommends.
- There was a steady decline in the use of sulfonylureas and thiazolidinediones accompanied by a marked increase in the use of dipeptidyl peptidase IV inhibitors.
- Increased use of metformin holds the potential to realize significant savings for patients, payors, and the entire health care system.

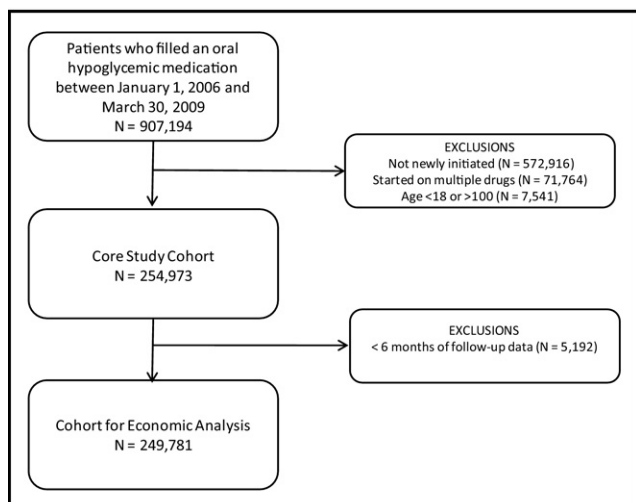


Figure 1 Study cohort.

thiazolidinedione class to specifically evaluate trends in rosiglitazone and pioglitazone prescribing.

We then used multivariable logistic models to identify predictors of patients being initiated on metformin, as recommended by the 2006 ADA consensus statement that was in effect during the study period. Potential predictors in these models included age, gender, insurance type, income, comorbidity, and calendar time. We defined comorbidity as the number of unique medications filled by each patient in the 6 months before their index date. Statistical significance was based on an alpha level of 0.05.

Economic Analysis

To evaluate the economic impact of initiating therapy with a given drug class, we restricted our cohort to those individuals with a minimum of 180 days of continuous eligibility after their index date. The cohort was divided into 3 groups on the basis of the class of their index medication: metformin, sulfonylurea, or other. For each patient, we calculated total patient out-of-pocket (ie, copayments) and insurer (ie, allowed amount) spending for all diabetes medications (including insulin) during the 180 days after treatment initiation. We then subdivided these estimates into copayments and allowed amounts for drugs in the index class itself and for other diabetes medication classes.

We estimated the cost implications of initiating therapy with a drug other than metformin or sulfonylurea by determining the difference in total expenditures (copay and allowed amount) over 6 months for patients initially treated with metformin or sulfonylurea compared with subjects receiving other therapy.

RESULTS

The cohort consisted of 254,973 patients newly initiated on oral hypoglycemic monotherapy (**Figure 1**). Baseline characteristics for study subjects are presented in **Table 1**. Pa-

tients had a mean age of 58 years and were evenly distributed between genders. They had a median income of \$50,000, and 72.0% received pharmacy coverage through employer-sponsored insurance or a health plan with an additional 17.4% and 1.7% covered by Medicare or Medicaid, respectively.

Average patient out-of-pocket costs for initial oral diabetes medication varied widely by therapeutic class (**Table 1**). Patient copayments for metformin and sulfonylurea were \$8.90 and \$8.00 monthly, respectively. Those for other therapeutic classes were substantially higher, for example, \$39.60 for thiazolidinediones such as rosiglitazone (Avandia; GlaxoSmithKline, London, UK) and pioglitazone (Actos; Takeda Pharmaceutical Co Limited, Osaka, Japan) and \$44.00 for dipeptidyl peptidase-4 inhibitors such as sitagliptin (Januvia, Merck & Co, Inc, Whitehouse Station, NJ) and saxagliptin (Onglyza, Bristol-Meyers Squibb, New York, NY). The insurer's share of medication cost ranged from \$7.60 per month for sulfonylureas to \$185.00 for dipeptidyl peptidase-4 inhibitors.

Patterns of Medication Initiation Over Time

Figure 2 displays the proportion of newly initiated medications accounted for by each pharmacologic class over the study period. In July 2006, 51.0% of patients were started on metformin, 26.2% were started on a sulfonylurea, 20.1% were started on a thiazolidinedione, and a small proportion of patients were started on a meglitinide, alpha-glucosidase inhibitor, or dipeptidyl peptidase-4 inhibitor.

Between July 2006 and December 2008, the proportional share of new prescriptions accounted for by metformin increased from 51% to 65%, or 0.56% per month ($P < .001$). Over the same time period, the proportion of new prescriptions accounted for by sulfonylureas significantly decreased by 0.22% per month ($P < .001$), from 26.2% in July 2006 to

Table 1 Baseline Characteristics, Copayment, and Amount Paid Across Therapeutic Class

| | |
|--|-----------------|
| Age, mean years (SD) | 58.2 (14.5) |
| Male gender, % | 52.7 |
| Income, mean (standard) | 51,774 (17,644) |
| Drug insurance coverage, % | |
| Employer-sponsored | 56.2 |
| Health plan | 15.8 |
| Medicare | 17.4 |
| Medicaid | 1.7 |
| Other | 8.9 |
| Average monthly copayment for index medication, \$ | |
| Alpha-glucosidase inhibitor | 25.20 |
| DPP-4 inhibitor | 44.00 |
| Metformin | 8.90 |
| Meglitinide | 38.80 |
| Sulfonylurea | 8.00 |
| Thiazolidinedione | 39.60 |

SD = standard deviation; DPP-4 = dipeptidyl peptidase-4.

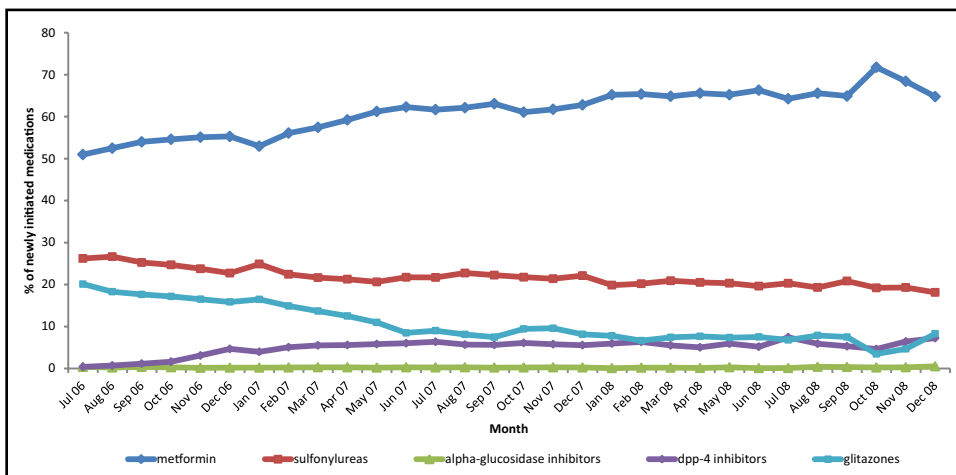


Figure 2 Temporal trends in medication initiation by therapeutic class, July 2006 to December 2008.

18.1% in December 2008. There also was a substantial reduction in the number of prescriptions for thiazolidinediones from 20.1% to 8.3%, or 0.46% per month ($P < .001$). The greatest relative change in initial oral antidiabetic medication class for the study period was observed for the dipeptidyl peptidase-4 inhibitors, increasing from 0.4% to 7.3%, or 0.15% per month ($P < .001$).

Trends in thiazolidinedione initiation stratified by individual medication are shown in **Figure 3**. In July 2006, rosiglitazone and pioglitazone accounted for 7.9% and 12.2%, respectively, of newly initiated oral hypoglycemics. Subsequently, there was a steady decline in the use of both ($P < .001$ for both), with a more rapid decrease for rosiglitazone after publication of the meta-analysis, suggesting possible adverse cardiovascular effects in May 2007.⁷

Predictors of Initiating Treatment with an American Diabetes Association-Recommended Medication

Table 2 shows the results of a multivariate logistic regression model for predicting initial therapy with metformin. Compared with subjects aged 70 years or more, younger subjects (aged 18-39, 40-54, or 55-69 years) were 33% to 73% less likely to receive recommended care ($P < .001$ for all). Women were 31% less likely to be initially treated with metformin than men. Patients living in ZIP codes with lower median income levels were less likely to receive ADA-recommended therapy ($P < .001$), as were patients with higher levels of comorbidity ($P < .001$). Patients who had Medicare prescription drug coverage were significantly less likely to receive ADA consensus recommendation concordant care compared with patients with employer-sponsored plans ($P < .001$).

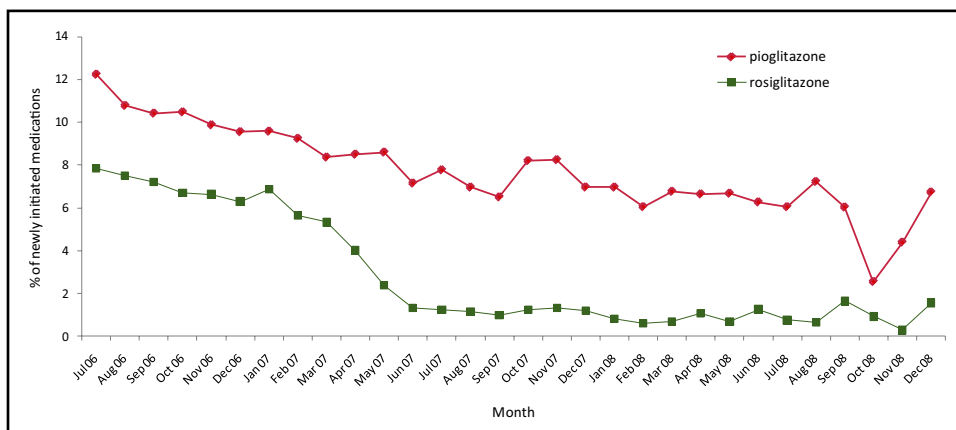


Figure 3 Temporal trends in rosiglitazone and pioglitazone July 2006 to December 2008.

Table 2 Predictors of Receiving Metformin as Initial Oral Hypoglycemic Therapy

| Characteristic | Odds Ratio (95% CI) | P Value |
|--|---------------------|----------|
| Age | | |
| 18-39 y | 0.67 (0.65-0.69) | <.001 |
| 40-54 y | 0.50 (0.49-0.52) | <.001 |
| 55-69 y | 0.27 (0.26-0.27) | <.001 |
| >70 y | 1.00 | Referent |
| Female gender | 0.69 (0.68-0.70) | <.001 |
| Income (per additional \$10,000 annual income) | 1.05 (1.04-1.05) | <.001 |
| Drug insurance coverage | — | — |
| Employer | 1.04 (1.02-1.07) | <.001 |
| Health plan | 1.36 (1.32-1.49) | <.001 |
| Other | 0.74 (0.72-0.77) | <.001 |
| Medicare | 1.00 | Referent |
| Comorbidity (per additional prescription) | 0.97 (0.97-0.97) | <.001 |
| Calendar time (mo) | 1.03 (1.03-1.03) | <.001 |

CI = confidence interval.

Economic Impact of Initial Medication Choice

The average costs incurred by patients and insurers for diabetes medications after they started an oral hypoglycemic are shown in **Figure 4**. Out-of-pocket and insurer costs for patients started on metformin or a sulfonylurea were substantially lower than those for patients started on other medications. During the 6 months after treatment initiation, cumulative copayments for patients starting on metformin were \$38.70 (\$32.40 for metformin and \$6.30 for other diabetes medications, including insulin). Corresponding copayments for patients initiated on sulfonylurea were \$40.80 (\$30.60 for sulfonylureas and \$10.20 for other diabetes medications). In contrast, patients who initially received oral antidiabetic therapy with an alpha-glucosidase inhib-

itor, a thiazolidinedione, a meglitinide, or a dipeptidyl peptidase-4 inhibitor had average cumulative copayments of \$132.80 during this period (\$127.90 for the class on which they were initiated and \$4.90 for other diabetes medications).

The share of prescription costs paid by insurers for patients initiated on sulfonylurea or metformin over the following 6 months was \$77.00 (**Figure 4**). In contrast, insurer costs for patients starting on alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, or dipeptidyl peptidase-4 inhibitors averaged \$544.40, of which the majority (\$535.10, 98.3%) was for medications in the class on which patients were first initiated.

Combined patient and insurer spending for patients who were initiated on alpha-glucosidase inhibitors, thiazolidinediones, meglitinides, or dipeptidyl peptidase-4 inhibitors was \$677.20 over a 6-month period compared with \$116.10 for patients initiated on metformin. This represents a potential cost difference of approximately \$560 per patient and aggregate potential savings of \$26.8 million over 6 months or \$53.6 million annually.

DISCUSSION

This study of a large cohort of patients starting oral hypoglycemic monotherapy demonstrates substantial variability in treatment choices. By the beginning of 2009, 65% of patients were initiated on ADA-recommended care with metformin, representing a modest increment over the prior 3-year period. However, 35% of patients begun on treatment for diabetes did not receive the recommended first-line drug. Further, the medication costs for this subgroup of patients comprised 66.3% of the total expenditures for hypoglycemic drugs in the entire cohort. Even according to the ADA/EASD recommendations that were released after our study period in 2009,¹² and that recommended metformin or sulfonylurea as initial therapy, approximately 20% of pa-

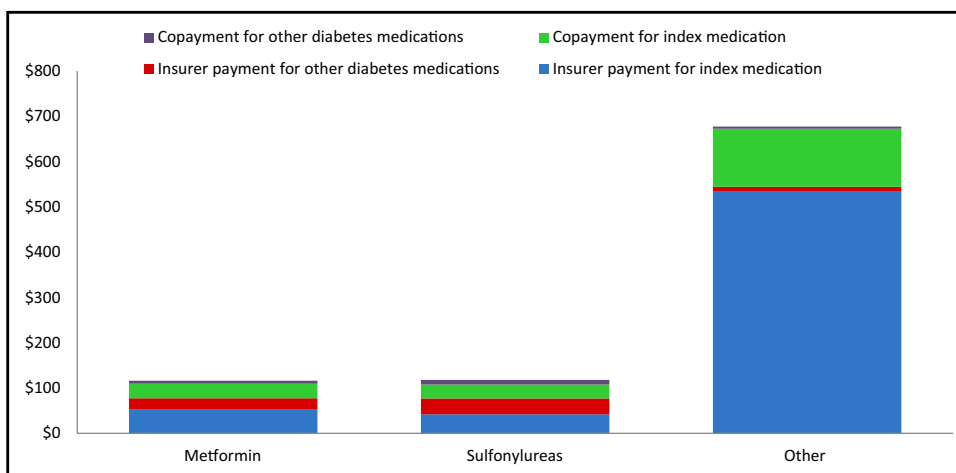


Figure 4 Total patient and insurer spending during 6 months after initiation stratified by class of medication on which patients were started.

tients did not receive pharmacotherapy concordant with consensus recommendations.

Over this time, we observed a steady decline in the use of thiazolidinediones accompanied by a marked increase in the use of the heavily marketed dipeptidyl peptidase-4 inhibitors. The evidence supporting the use of dipeptidyl peptidase-4 inhibitors and other newer agents is limited with respect to clinically important outcomes. Thus, although 65% of patients we studied received care consistent with ADA consensus statements, our results highlight remaining gaps between practice recommendations and contemporary pharmacotherapy for diabetes mellitus. Younger patients, those with lower incomes, women, and those receiving prescription drug coverage through their employer were least likely to receive ADA/EASD-recommended care. Income- and educational-based disparities in the quality of care have been well documented, and there are many possible reasons for the observed association, such as the ability of better-educated patients to seek out more cost-effective care¹³ and their more accurate perceptions about drug effects, among others.

Our study results also demonstrate the reductions in thiazolidinedione use that has accompanied the recognition of the cardiovascular risks associated with this class of medications. Moreover, although the proportion of individuals initiating treatment with rosiglitazone or pioglitazone decreased significantly over the study period, rosiglitazone use essentially disappeared by the end of the study period. The residual use of rosiglitazone would be expected to continue to wane given continued controversy regarding its marketing and approval, as well as recent Food and Drug Administration decisions to substantially restrict its use.¹⁴

There are, of course, circumstances under which metformin may not be appropriate initial therapy for patients with diabetes, and practice guidelines integrate the best available evidence at the time of writing and may not reflect scientific discoveries or pharmacotherapeutic developments that occur after the guideline process has begun. For example, metformin is contraindicated in patients with significant renal dysfunction and should be used cautiously in patients with advanced heart failure. Avoiding metformin in patients with milder forms of these conditions also may be appropriate. As such, it is certainly possible that some proportion of patients whose initial therapy was metformin had an absolute or relative contraindication to this drug. That said, even the most recent version of the ADA/EASD consensus recommendations¹² do not advocate initiating therapy with a dipeptidyl peptidase-4 inhibitor or one of the other newer classes of oral hypoglycemic agents.

Our analysis also demonstrates that variations in adherence to clinical practice recommendations have important financial consequences for patients, payors, and the health care system. Metformin and sulfonylureas, the oldest and best studied agents, were the least expensive for patients and payors alike. It is not surprising that the newest, least well studied, and most heavily marketed agents, including the

thiazolidinediones and dipeptidyl peptidase-4 inhibitors, were the most expensive in terms of copayments and insurer contributions to drug costs. Over the 6-month period after treatment initiation, this amounted to approximately \$560 per patient, or \$1120 annually. These differences were largely attributable to marked differences in the cost of the medication classes initially prescribed, rather than adjunctive therapeutic classes started later. Thus, influencing initial medication choices represents an opportunity for payors and policy makers to help mitigate the costs of prescription drug costs for diabetic patients while also improving the quality of care they receive. Further, our findings of persistent use of non-recommended medications despite relatively large differences in copayment amounts between these drugs and metformin imply that the differences in the copayments are insufficient to pose an adequate barrier to the use of alternative, more expensive classes of drugs that offer no clear therapeutic benefits.¹⁵

Our study is the first, to our knowledge, to define the fiscal implications of therapeutic choices in a large population of patients with diabetes mellitus. Nationally, with approximately 2 million new cases of diabetes each year, if the medication patterns and insurance coverage for our cohort are representative of the US population, an excess expenditure of \$1120 per patient per year would translate to more than \$420 million in additional direct medication costs for diabetes therapy outside established ADA/EASD consensus recommendations. Because the prevalence of diabetes is increasing dramatically, the potential savings from improved adherence to these recommendations could far exceed these estimates.

Study Limitations

There are several limitations to our analysis. We studied a large cohort of patients receiving prescription drug benefits through a national pharmacy benefit manager. Although patients in our cohort represented a broad range of demographic characteristics, including Medicare beneficiaries, the results may not be generalizable to other groups, such as the uninsured. We relied on pharmacy claims data to perform our analyses, and thus we did not have access to detailed clinical or behavioral information about patients in our cohort or the physicians who made the prescribing decisions. As such, we are unable to identify the specific reasons why providers selected particular pharmacologic agents for individual patients. For example, some believe that sulfonylureas are associated with an increased risk of adverse cardiovascular events¹⁶ despite the absence of such signals from randomized controlled trials, which may influence their therapeutic choices. Likewise, we are unable to account for differences in plan design, such as the use of disease-management programs, which may have influenced patients' medication-taking behavior. Further, our analysis is unable to capture prescriptions filled without insurance coverage, for example, through low-cost generic drug programs, including those at discount retailers or mail order services, which have become increasingly accessible to pa-

tients.¹⁷ In addition to the well-established ADA consensus recommendations on the management of diabetes, which we used for our analysis, there are others from the American Association of Clinical Endocrinologists and the American College of Endocrinology that offer slightly different recommendations. Finally, we restricted our analysis to patients who had not filled a prescription for an oral antidiabetic agent within the preceding 6 months. This approach would have misclassified patients who were started on metformin and then only many months later restarted on an alternative agent.

CONCLUSIONS

Our results demonstrate the variability in contemporary clinical practice for patients initiating oral hypoglycemic monotherapy. Approximately 35% of patients in this study cohort did not receive metformin as the initial oral antidiabetic agent as recommended by the ADA/EASD consensus statement. Further, 1 in 5 patients in this large population of typical patients with diabetes did not receive initial therapy with metformin or sulfonylurea, leading to considerable excess cost. These findings highlight a situation in which consensus statement–recommended care, clinical efficacy, and cost-conscious prescribing are all aligned. Pharmacotherapy for diabetes presents a significant opportunity for quality- and performance-improvement initiatives and holds the potential to realize significant savings for patients, payors, and the entire health care system.

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