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Initial Choice of Oral Glucose-Lowering Medication for Diabetes Mellitus

A Patient-Centered Comparative Effectiveness Study

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IMPORTANCE Although many classes of oral glucose-lowering medications have been approved for use, little comparative effectiveness evidence exists to guide initial selection of therapy for diabetes mellitus.

OBJECTIVE To determine the effect of initial oral glucose-lowering agent class on subsequent need for treatment intensification and 4 short-term adverse clinical events.

DESIGN, SETTING, AND PARTICIPANTS This study was a retrospective cohort study of patients who were fully insured members of Aetna (a large national health insurer) who had been prescribed an oral glucose-lowering medication from July 1, 2009, through June 30, 2013. Individuals newly prescribed an oral glucose-lowering agent who filled a second prescription for a medication in the same class and with a dosage at or above the World Health Organization's defined daily dose within 90 days of the end-of-day's supply of the first prescription were studied. Individuals with interim prescriptions for other oral glucose-lowering medications were excluded.

EXPOSURES Initiation of treatment with metformin, a sulfonylurea, a thiazolidinedione, or a dipeptidyl peptidase 4 inhibitor.

MAIN OUTCOMES AND MEASURES Time to addition of a second oral agent or insulin, each component separately, hypoglycemia, other diabetes-related emergency department visits, and cardiovascular events.

RESULTS A total of 15 516 patients met the inclusion criteria, of whom 8964 (57.8%) started therapy with metformin. In unadjusted analyses, use of medications other than metformin was significantly associated with an increased risk of adding a second oral agent only, insulin only, and a second agent or insulin ($P < .001$ for all). In propensity score and multivariable-adjusted Cox proportional hazards models, initiation of therapy with sulfonylureas (hazard ratio [HR], 1.68; 95% CI, 1.57-1.79), thiazolidinediones (HR, 1.61; 95% CI, 1.43-1.80), and dipeptidyl peptidase 4 inhibitors (HR, 1.62; 95% CI, 1.47-1.79) was associated with an increased hazard of intensification. Alternatives to metformin were not associated with a reduced risk of hypoglycemia, emergency department visits, or cardiovascular events.

CONCLUSIONS AND RELEVANCE Despite guidelines, only 57.8% of individuals began diabetes treatment with metformin. Beginning treatment with metformin was associated with reduced subsequent treatment intensification, without differences in rates of hypoglycemia or other adverse clinical events. These findings have significant implications for quality of life and medication costs.

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Invited Commentary

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With approximately 29 million Americans affected and annual costs upward of $176 billion, diabetes mellitus remains a national public health priority.[1] Organizations such as the American Diabetes Association[2] and the American College of Physicians,[3] as well as guidelines commissioned by the Agency for Healthcare Research and Quality,[4] advocate metformin as the initial pharmacologic agent for glucose-lowering therapy in type 2 diabetes. Despite this, gaps remain in the evidence base for this recommendation, particularly with regard to newer glucose-lowering medication.[5-8]

Long-term data on the use of metformin as a first-line agent to prevent diabetes complications comes largely from a single study.[5] Data used for drug approval and comparison of oral glucose-lowering medications consist primarily of analyses assessing the effect of the available medications on intermediate physiological outcomes, most notably hemoglobin A_{1c}.[9] Given the large number of agents that are now available and the increasing use of newer classes, such as dipeptidyl peptidase 4 (DPP-4) inhibitors,[10] there is an urgent need to clarify differences among the available therapies. Particularly relevant are patient-centric outcomes, such as the need to intensify treatment with a second oral agent or insulin to achieve a hemoglobin A_{1c} goal; this approach can reduce patient quality of life by the same amount as diabetes complications.[11,12] In addition, because the effect of medications in preventing diabetes complications may take years to become apparent, differences in short-term adverse events, such as hypoglycemia and emergency department visits, may be particularly relevant for patients initiating therapy and their physicians, although these differences have been insufficiently assessed. We sought to determine the effect of the initial oral glucose-lowering agent class on subsequent treatment intensification and 4 short-term adverse clinical events.

Methods

Setting and Data Source

The Brigham and Women's Hospital Institutional Review Board approved the study. Informed consent was not required for this secondary data analysis. We used a limited data set of medical and prescription claims data for commercial, fully insured members of Aetna, a large national health insurer, to create a cohort of patients who were prescribed an oral glucose-lowering medication from July 1, 2009, through June 30, 2013. These data contained complete paid claims for all procedures, physician encounters, hospitalizations, and filled prescriptions (including dose dispensed and amounts paid by the insurer and patient) and were linked to eligibility data that included patient age, sex, and zip code of residence. Aggregate data on socioeconomic status, race/ethnicity, and educational attainment were obtained by linking zip code of residence with data from the 2010 US Census, which specified the median household income and the distribution of race/ethnicity and educational attainment of the population for each zip code tabulation area.

Study Cohort

We created a cohort of individuals newly initiating use of an oral glucose-lowering agent during the study period by identifying patients who filled a prescription for metformin, a sulfonylurea, a thiazolidinedione, or a DPP-4 inhibitor who had not filled a prescription for any oral glucose-lowering medication in the previous 180 days. Because few patients initiated therapy with a meglitinide (n = 88) or an α-glucosidase inhibitor (n = 8), we excluded these patients from our sample. Because glucagon-like peptide 1 agonists, such as exenatide, were not approved as monotherapy at the beginning of the study period[13] and because they can be used off-label for weight loss, we excluded these agents as a category of initial treatment. A complete list of the agents included in each class is presented in eTable 1 in the Supplement. The date of the patient's first eligible prescription was defined as his or her index date. All patients were required to have maintained continuous insurance eligibility for at least 180 days before the index date.

To ensure that our cohort represented individuals who tolerated the therapy that they had started, analogous to the run-in period in a clinical trial, we restricted our analysis to patients who filled a second prescription for a medication in the same class within 90 days of the end-of-day's supply of the first and had no filled prescriptions for other oral glucose-lowering medications in the interim. As a result, we excluded patients who began taking 2 different medications simultaneously (including combination therapy) or who had a second medication added to their first shortly after treatment initiation. To ensure comparison of therapeutically effective and equivalent doses across medications and also to make options for dosage increase before adding another medication more similar, we required the dose of each patient's second filled prescription to be at or above the World Health Organization's defined daily dose[14] for the medication. If a patient had more than one eligible episode of treatment initiation during the study period, we considered only the first. We calculated that we had greater than 80% power to detect a 5% difference in intensification event-free survival.

Outcomes

Our primary outcome was time to treatment intensification, defined as the initiation of use of another class of oral glucose-lowering medication (including glucagon-like peptide 1 agonists, even though these are injectable) or insulin (eTable 1 in the Supplement). We also looked at time to intensification with either of these separately. Secondary outcomes included time to composite cardiovascular event (defined as a new diagnosis of coronary heart disease, congestive heart failure, unstable angina, ischemic stroke, acute myocardial infarction, or a revascularization procedure, based on *International Classification of Diseases, Ninth Revision [ICD-9]* and *Current Procedural Terminology* codes), congestive heart failure alone, an emergency department visit or hospital admission for hypoglycemia, and any other diabetes-related emergency department visit.[15] To avoid issues of immortal time bias, follow-up began when the second prescription of the index medication was filled.

Table 1. Characteristics of the Study Cohort[a]

Characteristic	Metformin (n = 8964)	Sulfonylurea (n = 3570)	DPP-4 Inhibitor (n = 2034)	Thiazolidinedione (n = 948)	*P* Value[b]
Median follow-up, d	388	382	376	429	<.001
Amount patient spent on filling index prescription, mean (SD), $[c]	12.66 (14.83)	10.78 (8.33)	52.23 (55.42)	46.31 (57.37)	<.001
Female sex	4504 (50.3)	1510 (42.3)	950 (46.7)	321 (33.9)	<.001
Mean age, y	49.9	55.1	56.4	56.2	<.001
Age group, y					
18-54	5447 (60.8)	1603 (44.9)	810 (39.8)	384 (40.5)	<.001
55-64	2802 (31.3)	1372 (38.4)	895 (44.0)	407 (42.9)	
≥65	715 (8.0)	595 (16.7)	329 (16.2)	157 (16.6)	
Median household income by zip code, $					
<50 000	2609 (29.1)	1240 (34.7)	503 (24.7)	290 (30.6)	<.001
50 000-99 999	5658 (63.1)	2127 (59.6)	1344 (66.1)	599 (63.2)	
≥100 000	679 (7.6)	198 (5.6)	183 (9.0)	57 (6.0)	
Non-Hispanic black	18 (12.7)	21 (15.6)	18 (12.6)	19 (13.1)	<.001
High school education or more	10 (85.8)	10 (84.8)	9 (86.8)	1 (84.7)	<.001
Comorbidity					
Chronic kidney disease	145 (1.6)	230 (6.4)	104 (5.1)	50 (5.3)	<.001
Coronary artery disease	464 (5.2)	340 (9.5)	209 (10.3)	84 (8.9)	<.001
Ischemic stroke	102 (1.1)	62 (1.7)	36 (1.8)	17 (1.8)	.01
Congestive heart failure	104 (1.2)	112 (3.1)	52 (2.6)	14 (1.5)	<.001
Asthma or COPD	527 (5.9)	231 (6.5)	150 (7.4)	45 (4.8)	.02
Dementia	11 (0.1)	7 (0.2)	1 (0.1)	2 (0.2)	.46
Depression	441 (4.9)	129 (3.6)	94 (4.6)	47 (5.0)	.02
Hypertension	3699 (41.3)	1694 (47.5)	1156 (56.8)	478 (50.4)	<.001
Atrial fibrillation	104 (1.2)	74 (2.1)	51 (2.5)	10 (1.1)	<.001
Diabetes mellitus by *ICD-9* criteria before baseline	3827 (42.7)	1815 (50.8)	1263 (62.1)	518 (54.6)	<.001
Diabetes mellitus by *ICD-9* criteria after baseline[d]	1581 (17.6)	559 (15.7)	262 (12.9)	130 (13.7)	<.001
Combined comorbidity score, mean (SD)	0.00 (0.89)	0.23 (1.38)	0.11 (1.32)	0.05 (1.17)	<.001
Propensity score, mean (SD)	0.65 (0.15)	0.59 (0.15)	0.32 (0.23)	0.38 (0.23)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase 4; *ICD-9*, *International Classification of Diseases, Ninth Revision*.

[a] Data are presented as number (percentage) of patients at baseline unless otherwise indicated.

[b] χ^2 Test for binary variables, analysis of variance for continuous variables, and Kruskal-Wallis test for median days of follow-up.

[c] Sum of copayment, coinsurance, and deductible.

[d] After baseline refers to patients who had a diabetes diagnosis in the 180 days after the index date but not in the period before baseline.

Covariates

We considered several factors that occurred in the 180 days before each patient's index date that may have influenced the receipt of the index drug class or the study end points. These factors included age, sex, copayment amount for the index prescription, the presence of specific conditions assessed using *ICD-9* codes (chronic kidney disease, coronary heart disease, ischemic stroke, congestive heart failure, chronic obstructive pulmonary disease or asthma, depression, hypertension, and atrial fibrillation), the number of medications taken, the number of hospitalizations, and the number of physician visits. We also calculated a combined comorbidity score that combined conditions from the Charlson and Elixhauser measures.[16] Because individual-level race/ethnicity, educational attainment, and income data were not available, we used zip code–based indicators from the 2010 US Census to account for some of the compositional and contextual effects of these factors.

Statistical Analysis

We first performed descriptive statistical analysis and unadjusted comparisons using χ^2 tests for binary variables and analysis of variance for continuous variables. We created a multinomial propensity score using all of the covariates listed above to estimate the probability that a patient's initial medication was metformin, the index drug class with the largest share of new patients.[17]

To evaluate the association of the class of oral glucose-lowering agent on our study outcomes, we first plotted Kaplan-Meier curves and evaluated differences in survival with log-rank tests. We then constructed Cox proportional hazards models adjusting for all covariates, as well as the propensity score, and tested for violations of the proportional hazards assumption using Martingale residuals. Some crossing of hazards was observed in Kaplan-Meier plots among the nonmetformin drug classes. To address this, we repeated our analyses after adding a time-varying interaction for the index drug class, considering time dichotomized as 1 year or less vs more than 1 year from date of initiation.

We conducted several additional sensitivity analyses to assess the robustness of our results. Because the standard *ICD-9* code–based diabetes definition (*ICD-9*: 250.x 2 outpatient or 1 inpatient diagnosis of diabetes) is relatively insensitive,[18,19] our

primary analysis included all patients who started taking an oral glucose-lowering agent. To check robustness, we fit models after restricting the cohort to patients with a recorded diabetes diagnosis in the 180 days before the index date. This approach also accounts for off-label, nondiabetes use of metformin, such as for prediabetes or weight loss.

Second, we studied the association of initial oral glucose-lowering drug class on cardiovascular outcomes among the subset of patients who had no history of cardiovascular disease before starting use of an oral glucose-lowering agent. We additionally redefined the cardiovascular outcome to exclude revascularization because this procedure is often discretionary. Third, to ensure we were evaluating patients who were adding medications, as opposed to merely switching therapies, we restricted our cohort to patients with the index medication on hand at the time of intensification, defined as patients with supply continuing past the date of intensification.

Fourth, to assess whether patients had the primary outcome of treatment intensification as a result of nonadherence to their index drug rather than the clinical necessity of better glycemic control, we examined 1-year adherence to the index drug among patients with 12 months or more of continuous eligibility after the index date, with adequate adherence defined as possession of medication for 80% of days or more.

Results

Overall, 15 516 patients met the inclusion criteria as new initiators of oral glucose-lowering medications (eFigure 1 in the Supplement). A total of 8964 patients (57.8%) initiated metformin therapy, with 3570 (23.0%) starting sulfonylurea therapy, 948 (6.1%) starting thiazolidinedione therapy, and 2034 (13.1%) starting therapy with DPP-4 inhibitors (**Table 1**). Across all medication categories, the mean age of patients was 52 years, and 7285 (47.0%) were women. Compared with users of other medication classes, those prescribed metformin were younger, more likely to be women, and less likely to have chronic kidney disease. The zip code–level indicators of educational attainment, income, and race/ethnicity were similar across medication classes. Out-of-pocket spending for the filling of the initial prescription was significantly higher for DPP-4 inhibitors and thiazolidinediones ($P < .001$). Median follow-up was similar for metformin (388 days), sulfonylureas (382 days), and DPP-4 inhibitors (376 days) but longer for thiazolidinedione initiators (429 days) ($P < .001$).

Treatment Intensification

Rates of treatment intensification by drug class were significantly different: 2198 patients (24.5%) prescribed metformin required a second oral agent, whereas 1323 of 3570 patients (37.1%) prescribed a sulfonylurea, 375 of 948 patients (39.6%) prescribed a thiazolidinedione, and 736 of 2034 patients (36.2%) prescribed a DPP-4 inhibitor did ($P < .001$) (**Table 2**). A total of 461 patients (5.1%) prescribed metformin later added insulin, whereas 326 patients (9.1%) prescribed a sulfonylurea, 113 patients (5.6%) prescribed DPP-4 inhibitors, and 59 patients (6.2%) prescribed thiazolidinediones did. Among metformin patients who added an oral agent, 1160 (52.8%) added a sulfonylurea. For all other medication classes, metformin was the most commonly prescribed oral agent for treatment intensification. Among patients who initiated therapy with a sulfonylurea and intensified to a second oral agent, 893 (67.5%) intensified to metformin. Similarly, 183 patients (48.8%) who started taking a thiazolidinedione and then added a second oral agent added metformin, as did 330 patients (44.8%) who started taking a DPP-4 inhibitor.

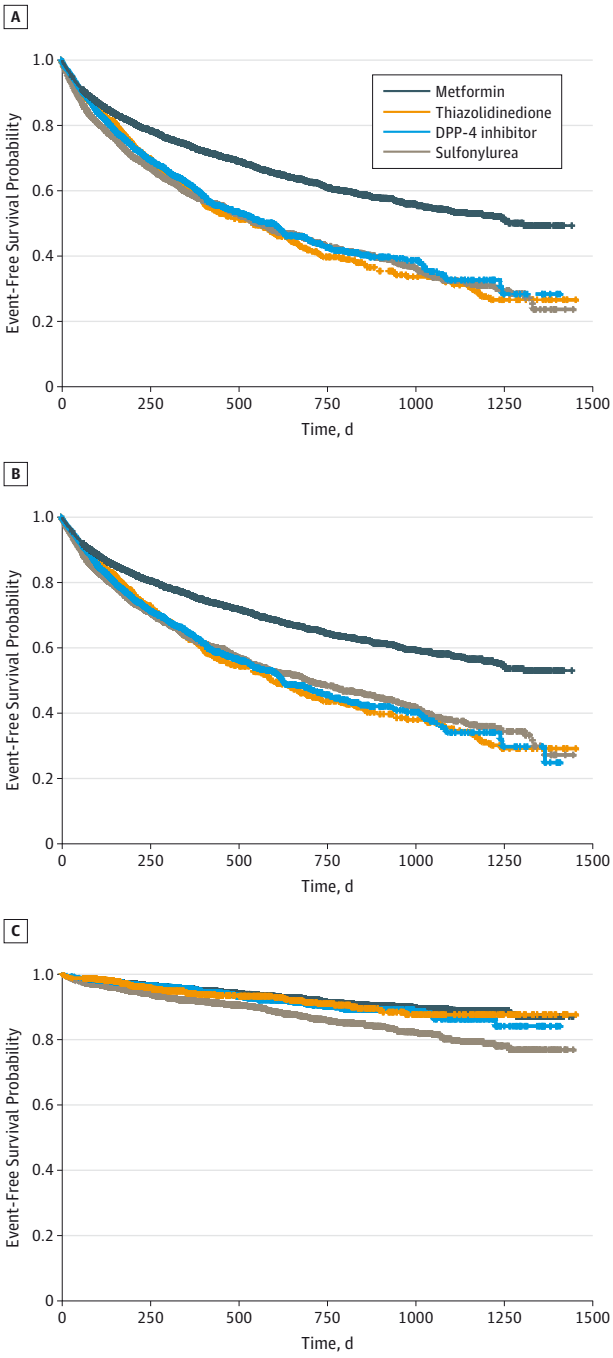
In unadjusted analyses, patients who started taking sulfonylureas, DPP-4 inhibitors, and thiazolidinediones were more

Table 2. Intensification to Additional Oral Glucose-Lowering Agent

Agent Added by Index Class	No. (%) of Patients Who Added an Oral Agent
Metformin	
Sulfonylurea	1160 (52.8)
DPP-4 inhibitor	405 (18.4)
Combination	246 (11.2)
GLP-1 receptor agonist	190 (8.6)
Thiazolidinedione	170 (7.7)
Meglitinide	17 (0.8)
α-Glucosidase inhibitor	9 (0.4)
Pramlintide	1 (0)
Total	2198/8964 (24.5)
DPP-4 inhibitor	
Metformin	330 (44.8)
Sulfonylurea	173 (23.5)
Combination	133 (18.1)
Thiazolidinedione	42 (5.7)
GLP-1 receptor agonist	41 (5.6)
Meglitinide	14 (1.9)
α-Glucosidase inhibitor	3 (0.4)
Total	736/2034 (36.2)
Sulfonylurea	
Metformin	893 (67.5)
DPP-4 inhibitor	181 (13.7)
Combination	122 (9.2)
Thiazolidinedione	79 (6.0)
GLP-1 receptor agonist	36 (2.7)
Meglitinide	9 (0.7)
α-Glucosidase inhibitor	3 (0)
Total	1323/3570 (37.1)
Thiazolidinedione	
Metformin	183 (48.8)
Sulfonylurea	79 (21.1)
Combination	50 (13.3)
DPP-4 inhibitor	43 (11.5)
GLP-1 receptor agonist	15 (4.0)
Meglitinide	4 (1.1)
α-Glucosidase inhibitor	1 (0)
Total	375/948 (39.6)

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1.

Figure. Product-Limit Survival Estimates



A, Unadjusted time to intensification to second oral agent or insulin ($P < .001$). B, Intensification to second oral agent only. C, Intensification to insulin only. Log-rank test $P < .001$. DPP-4 indicates dipeptidyl peptidase 4.

likely than those who started taking metformin to add an oral agent or insulin, a second oral agent only, or insulin only ($P < .001$ for all 3 comparisons) (**Figure**). These results remained significant in multivariable Cox proportional hazards models, with sulfonylurea (hazard ratio [HR], 1.68; 95% CI, 1.57-1.79), thiazolidinedione (HR, 1.61; 95% CI, 1.43-1.80), and DPP-4 inhibitor (HR, 1.62; 95% CI, 1.47-1.79) all associated with an increased hazard of addition of an oral agent or insulin compared with metformin (**Table 3**). The results were similar when considering only the addition of a second oral drug class or only the addition of insulin. When considering that the HR may vary by period, results revealed an even larger hazard of intensification compared with metformin after the first year (sulfonylurea: HR, 1.76; 95% CI, 1.51-2.06; thiazolidinedione: HR, 2.08; 95% CI, 1.66-2.60; DPP-4 inhibitor: HR, 2.06; 95% CI, 1.69-2.51), whereas the hazard of intensification in the first vs later years was similar to the non-time-varying results (sulfonylurea: HR, 1.66; 95% CI, 1.54-1.78; thiazolidinedione: HR, 1.50; 95% CI, 1.31-1.71; DPP-4 inhibitor: HR, 1.54; 95% CI, 1.39-1.72) (eTable 2 in the Supplement).

Secondary Outcomes

Sulfonylurea use was associated with an increased hazard of composite cardiovascular events (HR, 1.16; 95% CI, 1.04-1.29) and congestive heart failure (HR, 1.19; 95% CI, 1.10-1.28) (Table 3). There was no evidence of differential hazards for composite cardiovascular event with thiazolidinedione. Although the HR for congestive heart failure with thiazolidinediones was 1.08, this increase was not statistically significant (95% CI, 0.93-1.26).

Only 72 patients had a diagnosis of hypoglycemia recorded during follow-up. After adjustment for propensity score alone, sulfonylurea was associated with increased risk of hypoglycemia (HR, 2.71; 95% CI, 1.58-4.66), whereas thiazolidinediones (HR, 0.36; 95% CI, 0.08-1.64) and DPP-4 inhibitors (HR, 0.37; 95% CI, 0.11-1.17) were not. No statistically significant difference was found among drug classes with regard to nonhypoglycemia diabetes-associated emergency department visits (Table 3).

All results were robust to the sensitivity analyses (eTable 3 in the Supplement). Overall, patients with a diabetes diagnosis recorded before the index date had a greater risk of intensification compared with metformin than the full cohort. Patients with no history of cardiovascular disease and treated initially with DPP-4 inhibitors or sulfonylureas had a risk of cardiovascular events similar to the full cohort, whereas the risk for those taking thiazolidinediones was attenuated. Among patients with index medication on hand at the time of addition of a second oral agent, the hazard of intensification was essentially unchanged compared with the full cohort.

Finally, in a subset of patients with at least 12 months of follow-up, 4776 patients (28.2%) prescribed metformin had adequate adherence compared with 1880 patients (28.9%) taking sulfonylurea ($P = .45$), 532 patients (32.5%) taking thiazolidinedione ($P = .02$), and 1063 patients (41.6%) taking DPP-4 inhibitors ($P < .001$).

Discussion

We evaluated whether class of oral glucose-lowering agent first prescribed to a patient with diabetes influenced patients' likelihood of treatment intensification and short-term harms, such as cardiovascular events, emergency department visits, and hypoglycemia. We found that patients initially prescribed met-

Table 3. Hazard Ratios (95% CIs) for Primary Therapy Intensification and Secondary Clinical Outcomes[a]

Index Drug Class	Metformin	DPP-4 Inhibitor	Sulfonylurea	Thiazolidinedione
Primary outcome				
Therapy intensification: second oral agent or insulin	1.0 [Reference]	1.62 (1.47-1.79)[b]	1.68 (1.57-1.79)[b]	1.61 (1.43-1.80)[b]
Therapy intensification: second oral agent only	1.0 [Reference]	1.68 (1.52-1.87)[b]	1.65 (1.54-1.77)[b]	1.62 (1.44-1.83)[b]
Therapy intensification: insulin only	1.0 [Reference]	1.35 (1.06-1.74)	1.73 (1.49-2.00)[b]	1.24 (0.93-1.67)
Secondary outcome				
Diabetes-related ED visit	1.0 [Reference]	1.04 (0.79-1.36)	1.23 (1.04-1.46)	1.24 (0.91-1.70)
Composite cardiovascular outcome[c]	1.0 [Reference]	0.99 (0.85-1.16)	1.16 (1.04-1.29)	1.05 (0.87-1.27)
Congestive heart failure	1.0 [Reference]	1.13 (1.00-1.28)	1.19 (1.10-1.28)[b]	1.08 (0.93-1.26)

Abbreviations: DPP-4, dipeptidyl peptidase 4; ED, emergency department.

[a] Values adjusted for age, sex, index copayment, race, income, educational attainment, number of medications, number of physician visits, number of hospitalizations, specific conditions, combined comorbidity score, and propensity score.

[b] Significant at $P < .001$.

[c] New diagnosis of coronary heart disease, congestive heart failure, unstable angina, ischemic stroke, acute myocardial infarction, or a revascularization procedure.

formin were significantly less likely to require treatment intensification than those who started taking sulfonylureas, thiazolidinediones, or DPP-4 inhibitors. Furthermore, we found no compensatory advantages for other agents with regard to other short-term clinical outcomes. In fact, we found that sulfonylureas, the second most commonly prescribed initial class, were associated with increased risk of cardiovascular events and hypoglycemia.

Previous comparative effectiveness studies[3,4,9] in diabetes have largely focused on intermediate clinical end points, such as reducing hemoglobin A_{1c}, and found little difference between medication classes with respect to this outcome. In its most recent comparative effectiveness report, the Agency for Healthcare Research and Quality[4] did not consider issues of durability of glycemic response and regimen intensity, which it said "may best be addressed using long-term well-designed observational studies." In the A Diabetes Outcomes Progression Trial (ADOPT) study,[20] rosiglitazone, a thiazolidinedione no longer in widespread use in the United States[21] and not marketed in Europe,[22] was superior to metformin and glyburide with regard to time until fasting plasma glucose level exceeded 180 mg/dL (to convert to millimoles per liter, multiply by 0.0555), which could translate into reduced need for additional glucose-lowering agents. In contrast, we found that initial therapy with thiazolidinediones, largely pioglitazone, was associated with an increased hazard of adding additional therapeutic agents. Our results likely differ from those of ADOPT because, as opposed to considering only glucose level, in real-world practice, treatment intensification decisions may involve multiple considerations, including cost, safety, tolerability, patient preference, and effectiveness. Thus, although some have suggested that a treatment strategy that includes thiazolidinediones as insulin-sensitizing agents could delay the need for treatment intensification,[23] we found no evidence of this when compared with metformin. In contrast, our data support previously raised concerns[23] that DPP-4 inhibitors, despite their increasing popularity, may not be potent enough to delay treatment intensification significantly. These findings may be particularly relevant because the greater adherence to DPP-4 inhibitor and thiazolidinedione medication use that we observed should, if anything, have reduced treatment intensification.

Our study focused on treatment intensification, which can be aversive to patients[11,12,24] and inherently associated with increased adverse effects and costs. Although we agree that patient education is important, particularly with the message that treatment intensification is part of the normal progression of diabetes, and does not represent a personal failure, our study provides useful information to physicians to guide selection of initial oral glucose-lowering agent because delaying treatment intensification when safe to do so offers benefits to patients and the health care system. This finding is particularly relevant because patients and physicians have little information at their disposal when deciding about initial diabetes therapy, especially for many of the newer agents. Metformin has been well documented to reduce end-organ damage in patients with diabetes,[5,25] as opposed to most of the newer oral agents, which generally lack evidence of their capacity to protect patients from macrovascular or microvascular complications of diabetes.[4] Thus, our data support guideline recommendations that metformin be used as the first-line therapy for patients with diabetes.[2]

Our study adds to an increasing body of evidence that suggests that sulfonylureas may be associated with increased risk of cardiovascular disease. In particular, this study adds data on women, compared with a prior study[26] based in the Veterans Affairs system that found an adjusted increase of 2.2 cardiovascular disease events per 1000 users of sulfonylureas compared with metformin. In contrast to an earlier study,[27] we found no evidence that thiazolidinediones increased the rate of a new diagnosis of congestive heart failure. This lack of evidence may be partly due to a small sample size of initiators of thiazolidinedione therapy in our analysis because we observed an elevated HR of clinically meaningful magnitude but not of statistical significance. In addition, in the face of widespread warnings about this adverse event with thiazolidinedione use, physicians may now guide high-risk patients away from this medication class.[28] The lack of other differences in outcomes among medication classes is to be expected given the relatively short follow-up timeframe of this study.

Our study has several notable strengths. We evaluated a large, nationally representative data set of insured patients, which provides evidence regarding real-world clinical practice but also restricts some demographic heterogeneity to

help provide a more equal comparison. We had access to accurate records regarding all filled prescriptions, not just prescribing records. We used the defined daily dose to ensure comparison of therapeutically equivalent medication doses. Finally, although changes in oral medication could conceivably be related to formulary issues, treatment with insulin unequivocally represents intensification, especially given widespread patient and physician resistance to beginning insulin therapy.[24]

Our results should be interpreted in the context of several methodologic limitations. We did not have access to the reason for initial medication selection in this data set, which raises the possibility of confounding by indication. Although the propensity score method we used accounts for the measured differences among the groups that we present, unmeasured confounding may remain. Such confounding could include controversy over diabetes treatments, different prescribing patterns and demographic differences among physicians, history of gastrointestinal disorders, patient weight, and gastrointestinal adverse events. The main contraindication for metformin is reduced renal function, and it is reassuring that less than 10% of patients who used medication classes other than metformin met criteria for chronic kidney disease and that the hazard of treatment intensification persisted even after adjustment for this diagnosis. In addition, patients who intensified to a second oral agent usually intensified to metformin, suggesting that there was no contraindication. Because we required all patients in the cohort to have filled 2 prescriptions for their index medication at therapeutically equivalent doses, intolerance of metformin was unlikely to have driven medication selection. Because we did not have laboratory data, we do not know the level of hyperglycemia at baseline or when intensification occurred. Differences in these attributes across classes, although unlikely by the nature of our study design, could have influenced our results. For this study, we required each patient to fill a second prescription at a therapeutically effective dose to allow for a fair comparison of different agents. Although this approach enhances internal validity, it may also produce selection bias. However, because the question of which initial agent to select to delay future treatment intensification is most relevant for those patients who can tolerate effective doses of their initial agent, the sample we analyzed is likely similar to those patients for whom the results are most applicable in general practice. For the hypoglycemia outcome, we were unable to evaluate episodes of hypoglycemia that did not result in emergency department visits; thus, we only have data on the most severe cases of hypoglycemia. A final limitation of our analysis is that we lacked access to information regarding glycemic control among prescriber patient populations. Different prescribing patterns among prescribers may have influenced the decision to intensify treatment.

Conclusions

These findings indicate that the initial use of metformin was significantly associated with a lower risk of subsequent treatment intensification compared with other oral agents. These other agents offered no compensatory benefits over metformin with regard to the adverse events we evaluated. In fact, we found that sulfonylurea was associated with increased harms. Because underuse of metformin may lead to important harms and costs in the treatment of patients with diabetes, multilevel interventions to increase prescribing quality may be needed.

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