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Assessing use of patient-focused pharmacotherapy in glycemic management through the Diabetes Collaborative Registry (DCR)

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Abstract

Background: Although practice guidelines stress individualization of glucose management in patients with type 2 diabetes (T2D), the extent to which providers take patient factors into account when selecting medications is not well known. We used data from the Diabetes Collaborative Registry (DCR) to evaluate the current real-world use of glucose-lowering drugs in key subsets of patients with T2D.

Methods: DCR is the first large-scale US outpatient registry of patients with diabetes recruited from primary care, cardiology, and endocrinology practices and currently encompasses 374 practices and 5114 providers. T2D medications were grouped as those which may be suboptimal for key patient subgroups, including 1) obesity (i.e. propensity for weight gain): insulin, sulfonylurea, TZD; 2) elderly (i.e., high hypoglycemia risk): insulin, sulfonylurea; 3) advanced chronic kidney disease (CKD 4/5): metformin, sulfonylurea; and 4) coronary artery disease (i.e. potential safety issues): sulfonylurea. We examined patient factors associated with use of these groups of agents using 4 hierarchical (for both specialty and site) Poisson models, adjusting for HbA1c, number of T2D medications, and insurance status.

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Results: Overall, 157,551 patients with T2D were prescribed a glucose-lowering medication: metformin 75.1%, sulfonylurea 34.4%, insulin 27.7%, DPP-4i 18.3%, TZD 10.9%, GLP-1 RA 6.4%, SGLT2i 4.8%. After adjusting for patient factors, glycemic control, and insurance status, patients with morbid obesity were more likely treated with medications prone to cause weight gain (relative rate [RR] 1.09, 95% CI 1.07–1.11). Older patients were more likely to be treated with medications with increased risk of hypoglycemia (RR 1.04 per 5 years, 95% CI 1.04–1.05). Patients with CKD 4/5 were less likely to be treated with agents with known risk in patients with advanced CKD (RR 0.74, 95% CI 0.71–0.77). Patients with coronary artery disease were no more or less likely to be treated with medications with potential cardiovascular safety issues (RR 0.99, 95% CI 0.96–1.01).

Conclusions: In a large US-based registry of T2D patients, we observed some evidence for targeted use of glucose-lowering therapies in certain subgroups but also identified potential opportunities for better personalization of treatment. In an era of increasing number and complexity of medication choices with varying risks/benefits, data sources such as the DCR can highlight potential areas for improving targeted approaches to pharmacologic therapy in order to optimize selection of patients most likely to benefit (and least likely to be harmed) from treatments.

Keywords

diabetes mellitus; medications; registries; patient safety

The management of hyperglycemia in patients with type 2 diabetes mellitus (T2D) has become increasingly complex. While insulin, biguanides, and sulfonylureas were the only available pharmacologic treatment options in the US through the mid-1990s, a host of novel medications have been developed and introduced over the past two decades[1, 2]—innovation that does not appear to be slowing. The mechanisms of action of these drugs and their physiological effects vary substantially as do their side effect profiles, and, as a result, so do the optimal target patient populations for their respective use. For example, some medications are more likely to induce sustained weight loss and may be ideal for patients with obesity, while others cause weight gain. Some medications are more likely than others to cause hypoglycemia[3] and should be avoided, if possible, in elderly patients who are more likely to experience harms of abnormally low blood glucose.[1]

The personalization of glycemic management is critical for optimizing both the efficacy and safety of glucose-lowering medications and is recommended by practice guidelines.[4, 5] However, it is unknown to what degree these patient factors impact use of medications across subsets of patients. We used data from the Diabetes Collaborative Registry (DCR),[6] a large, real-world, quality improvement registry covering the spectrum from primary to specialty outpatient care of patients with diabetes in the US, to evaluate patterns of glycemic management in key subsets of patients with T2D. If we found suboptimal targeting of medications based on key patient factors, this would further highlight the need for decision-support tools in order to help clinicians optimize patient safety and outcomes.

METHODS

Patient Population.

DCR is a prospective, outpatient, quality improvement registry of patients with diabetes and prediabetes, covering the spectrum from primary to specialty care in the US.[6] With administrative oversight by the American College of Cardiology National Cardiovascular Data Registries, DCR was launched in 2014 as a collaborative effort by several partner professional societies and includes primary care, endocrinology, and cardiology practices. Longitudinal patient data are collected at the point of care through an automated system integration solution that periodically extracts relevant data elements from electronic health records, including patient demographics, comorbidities, clinical factors, laboratory values, and medications. For patients with more than 1 clinic visit, the most recent visit was used for analysis. Because DCR participation requires no data collection beyond that of the routine clinical care, a waiver of written informed consent was granted by Chesapeake Research Review Incorporated.

Medication Grouping.

We identified 4 areas of interest for pharmacological personalization: obesity, older age, advanced chronic kidney disease (CKD), and coronary artery disease (CAD; defined as a chart diagnosis of CAD, prior myocardial infarction, coronary revascularization, or angina). For each of these areas, we identified the classes of medications that might be considered suboptimal (Supplemental Table 1). For patients with obesity, these included insulin, sulfonylureas, and thiazolidinediones (TZDs) due to increased risk of weight gain. For elderly patients, these included insulin and sulfonylureas due to increased risk of hypoglycemia. For patients with advanced CKD, metformin and sulfonylureas were considered suboptimal due to decreased clearance in the setting of declining renal function (metformin, certain sulfonylureas) or increased hypoglycemia risk (sulfonylureas). For patients with CAD, sulfonylureas were considered suboptimal due to potentially increased risk of ischemic events[7, 8] and angina.[9]

Statistical Analysis.

For these analyses, we restricted the cohort to patients ≥18 years of age with T2D who were on at least 1 glucose-lowering medication and who had an available HbA1c value. Amongst these patients, we constructed a series of 4 modified Poisson regression models, each one examining the association of the variable of interest with the likelihood of being prescribed a glucose-lowering medication that could potentially be suboptimal for patients with that particular characteristic. For example, we examined the association of age with the likelihood of being prescribed a medication more likely to cause hypoglycemia (insulin or sulfonylurea). Because use of the different classes of glucose-lowering medications was not rare, we estimated relative rates (RR) directly using Poisson regression.[10, 11] All models included the 4 variables of interest (age, body mass index [BMI] by categories: <30 kg/m^2, 30 to <40 kg/m^2, ≥40 kg/m^2], advanced CKD [estimated glomerular filtration rate <30 mL/min/1.73m^2; if glomerular filtration rate missing, a chart diagnosis of CKD was used], CAD) as well as HbA1c level, number of glucose-lowering medications, and medical insurance. For patients missing insurance status, this was imputed as Medicare if age ≥65

years and private insurance if age <65 years. For the age, CKD, and CAD models, missing BMI values were imputed as the median level; no imputation was done for the BMI model, as this was the key variable of interest. There were no missing data for the remaining variables. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Analytic Population.

Among 228,663 adult patients in DCR from 374 US sites with HbA1c data available, 157,551 (68.9%) were taking at least 1 glucose-lowering medication and were included in the analytic cohort. Mean age was 68.1 years, 57.2% were men, and 84.6% were White (Table 1). Cardiac comorbidities and cardiac risk factors were common, with 87.4% of patients having hypertension, 87.6% having dyslipidemia, 56.2% having CAD, and 24.5% having heart failure. Mean HbA1c was 7.7% ± 2.0%, and patients were on an average of 1.9 ± 1.2 glucose-lowering medications. Metformin use was most commonly used in 75.1%, followed by sulfonylurea in 34.4%, insulin in 27.7%, dipeptidyl peptidase-4 inhibitor (DPP-4i) in 18.3%, TZD in 10.9%, glucagon-like peptide 1 receptor agonist (GLP-1 RA) in 6.4%, and sodium-glucose cotransporter-2 inhibitor (SGLT2i) in 4.8%..

Age.

There were 35.3% of patients who were <65 years of age, 34.3% who were 65 to <75 years of age, and the remaining 30.4% who were 75 years of age and older. The oldest patients were more likely than younger patients to be prescribed sulfonylureas and TZDs and less likely to be prescribed insulin, metformin, GLP-1 RAs, or SGLT2is (Table 2). In the multivariable model that accounted for glycemic control and other clinical factors, older age was associated with a higher rate of prescription of a glucose-lowering medication with a higher risk of hypoglycemia (RR per 5 years: 1.04, 95% CI 1.04–1.05, p<0.001).

BMI.

There were 40.1% of patients who had a BMI <30 kg/m^2, 46.1% of patients with BMI 30 to <40 kg/m^2, and 13.8% of patients with BMI ≥40 kg/m^2. Patients with higher BMIs were more likely to be on insulin, TZDs, GLP-1 RAs, and SGLT2is and less likely to be on sulfonylureas or DPP-4is (Table 2). After accounting for glycemic control and other clinical factors, higher BMIs were associated with a higher rate of prescription of a glucose-lowering medication known to be associated with a higher risk of weight gain (obesity I/II: RR 1.02, 95% CI 1.00–1.03; obesity III: RR 1.09, 95% CI 1.07–1.11, p<0.001).

CKD.

There were 35.0% of patients with stage 3 CKD and 4.5% with stage 4/5 CKD. Insulin, sulfonylureas, TZDs, and DPP-4is were more likely to be used in patients with advanced CKD while metformin, GLP-1 RAs, and SGLT2is were less commonly used (Table 2). After adjusting for glycemic control and other clinical factors, CKD 4/5 was associated with a lower rate of prescription of a T2D medication with a higher risk of potential adverse effects in these patients (RR 0.74, 95% CI 0.71–0.77, p<0.001).

CAD.

There were 56.2% of patients who had an established diagnosis of CAD, which was a history of myocardial infarction in 13.8%. Patients with CAD were more likely prescribed insulin, metformin, TZDs, DPP-4is and were less likely prescribed sulfonylureas, GLP-1 RAs, and SGLT2is. In the multivariable model, CAD was not associated with prescription of a sulfonylurea (RR 0.99, 95% CI 0.96–1.01, p=0.349).

DISCUSSION

In a large cohort of US patients with T2D, we found that providers may be considering some of the patient factors we analyzed in their decisions when choosing glucose-lowering medications—mainly in their consideration of advanced kidney disease. However, other factors that might influence treatment decisions—age, obesity, and CAD—did not appear to substantially affect choices of medications. In fact, older patients and those with obesity were more likely to be prescribed medications that could be potentially suboptimal given their greater risk of hypoglycemia or weight gain, respectively. While the variables included in the models are only some of the factors that influence the complex treatment decisions in patients with T2D, they suggest that some patient characteristics do not strongly influence choices of glucose-lowering medications. In an era of increasing number and complexity of glucose-lowering medication choices with varying risks/benefits, these decisions are clearly complicated, and decision-support tools may be useful in facilitating better personalization of pharmacologic therapy in order to optimize patient outcomes.

It is interesting to note the strong association of kidney dysfunction with lower prescription of medications that could be potentially harmful to these patients. The reason for this may lie in concern for the impact that kidney dysfunction could have (i.e., the severity of the interaction) or in more awareness of kidney dysfunction in the selection of all medications (not just those for glucose-lowering). For example, in electronic and print resources that aid in drug dosing, renal dosing of medications is prominently displayed. In contrast, patient factors where the disadvantages of certain medications may not be as readily available to providers do not seem to be influencing these treatment decisions as much. For example, the potential risk of sulfonylureas in patients at advanced age may not be well known to healthcare providers and is not addressed in medication prescribing resources. Alternatively, the potential risks of these medications in vulnerable patient groups may be perceived to be of lower clinical importance (e.g., the impact of further weight gain in obese patients may not be considered a high priority as compared to the frightening risk of diabetes and CKD). The more frequent use of newer medications in some subsets of patients (e.g., younger patients with few comorbidities) argues against a simple lack of knowledge or familiarity with these medications. Perhaps providers are more hesitant to use newer medications in complex patients where they have less personal experience and greater safety concerns, notably in stark contrast with the evolving evidence suggesting these are the patients most likely to benefit.[12]

Clinical Implications.

Personalizing the use of glucose-lowering medications is complex and becoming increasingly challenging given the growing number of medication classes and individual agents available, all with different mechanisms of action and potential off-target effects. Our findings highlight several examples of what may represent suboptimal personalization of care—including greater use of medications the cause hypoglycemia in the elderly and greater use of medications that cause weight gain in the obese. Importantly, our analyses only considered potential harms and did not focus on potential benefits that certain medications could provide for particular patient subgroups. For example, for patients with obesity, we only examined the prescription of medications that cause weight gain, whereas some medication classes (i.e., SGLT2i, GLP-1 RA, metformin) actually promote weight loss and may be preferred for these patients. In addition, there are other factors that could be considered when attempting to optimize patient outcomes in T2D (e.g., pioglitazone for patients with recent stroke,[13] empagliflozin or canagliflozin [and possibly dapagliflozin[14]] for patients at risk for heart failure[15, 16]) that we did not examine. In fact, in unadjusted analyses, patients with established CAD were less likely to be treated with SGLT-2i and GLP1-RAs—both of which have been shown to reduce cardiovascular risk in these patients—suggesting a possible risk-treatment paradox. Examining use of these particular medications over time will be important as the potential benefits of these medications are now better disseminated throughout the clinical community.

There appears to be a strong rationale and clinical need for both provider education as well as decision-support tools that can integrate relevant patient factors and potential risks and benefits of various therapies and, therefore, assist in a shared-decision making process at the point of care. Prior work in decision support for medication choices in patients with T2D has focused on tools for patients—helping them weigh adverse effects, administration, self-monitoring demands, and impact on glucose levels with the goal of improving adherence and glycemic control.[17–19] For example, the Mayo Clinic has freely available decision aid cards to help patients choose glucose-lowering medications based on 7 issues that they have identified as potentially of interest to the patient (HbA1c reduction, daily routine, low blood sugar, cost, daily sugar test, weight, and side effects).[20] However, as these decisions become even more complicated—incorporating the risks of future cardiovascular events, renal complications, etc.—decision support is going to need to move more upstream, in order to allow healthcare providers to integrate multiple clinical factors and help them provide treatment recommendations that optimize patient outcomes.

Limitations.

These observations should be interpreted in the context of the following potential limitations. First, there are some patient factors that may have impacted choice of medications that were not captured (e.g., inadequate response to earlier therapies [of particular importance with insulin, which is most often used when others have failed], inability or refusal to use injectables, insurance/formulary coverage for specific medications, other side effects), biasing the results to underestimate the degree of personalization. Also, certain characteristics may lead clinicians to favor certain therapies despite their potential risk. One example would be the use of insulin sensitizing TZDs in obesity, which is a marker

of insulin resistance. We acknowledge that these treatment decisions are complicated and the data supporting avoidance of certain classes of medications in some patient groups are often not definitive or strong. For example, the recent TOSCA.IT trial of pioglitazone versus sulfonylureas (in addition to metformin), although an underpowered study, showed no difference in cardiovascular mortality and only moderate weight gain (~2 kg over 5 years) in both groups.[21] The risk of sulfonylureas in patients with CAD is more complicated, and data have been somewhat conflicting[7–9, 22, 23] with potential differences among individual medications (e.g., less concern regarding cardiovascular risk with glimepiride,[24, 25] which comprised ~40% of sulfonylurea use in our cohort). While we believe the data are sufficient to consider avoiding sulfonylureas in patients with established cardiovascular disease, we acknowledge this relationship remains an area of controversy. Despite these limitations, we have identified some factors that appear to be influencing drug choice (e.g., kidney disease) more than others (e.g., obesity) and have highlighted the need for greater attention to patient factors when selecting glucose-lowering medications.

Second, our analytic population has a high burden of cardiovascular disease and risk factors, as many practices currently providing data to DCR are cardiology practices (due to an established mapping infrastructure developed for PINNACLE, another American College of Cardiology National Cardiovascular Data Registry). While this allowed us an opportunity to examine the associations between patient factors and selection of glucose-lowering medications in complicated patients, personalization may be more common in patients with a lower burden of relevant comorbidity (e.g., isolated obesity). Furthermore, due to the high proportion of subspecialty sites and the fact that included sites had electronic health records, our cohort had under-representation of patients who were younger (with no comorbidities), non-White race, and lower socioeconomic class. As such, it is unclear if these results are generalizable to patients groups with different demographics. Third, at least for the issue of obesity, there is the possibility of reverse causality, where the medication choice resulted in obesity rather than obesity influencing the choice of medication. Unfortunately, serial weight measurements and response to treatment, which would also be informative when selecting (or stopping) medications, were unavailable in DCR. Finally, DCR is a US-based registry, and thus it is unknown whether personalization occurs more or less commonly in other regions of the world. This may be relevant in countries with nationalized health care services and greater patient access to newer medications.

Conclusion.

In a large US cohort of patients with T2D, we observed some targeted use of glucose-lowering therapy across several common patient factors—in particular, patients with advanced CKD were less commonly given medications with greater potential risks in this subgroup. However, potential risks of hypoglycemia, weight gain, and complications of CAD did not appear to factor substantially into decision making. As the management of T2D is becoming increasingly complicated, with a growing number medication classes and individual agents available, all with different mechanisms of action, potential off-target effects and impact on cardiovascular events, decision-support tools may be useful to improve pharmacologic personalization and, as a result, optimize patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of Patient Cohort (n=157,551)

Age (years)	68.1±11.7
Male sex	57.2%
White race	84.6%
Insurance status	
Private	84.4%
Public	15.0%
None	0.3%
Other	0.3%
Body mass index	
<30 kg/m^2	40.1%
30 to <40 kg/m^2	46.1%
≥40 kg/m^2	13.8%
Hypertension	87.4%
Systolic blood pressure (mmHg)	129.8±17.3
Diastolic blood pressure (mmHg)	73.5±10.6
Dyslipidemia	87.6%
Tobacco use	
Never	50.2%
Current	14.5%
Former	35.3%
Coronary artery disease	56.2%
Prior myocardial infarction	13.8%
Prior coronary artery bypass graft surgery	13.4%
Prior stroke	12.1%
Peripheral artery disease	18.7%
Heart failure	24.5%
Atrial fibrillation	22.0%
Chronic kidney disease	11.8%
Estimated glomerular filtration rate	
<30 mL/min per 1.73 m^2	4.5%
30 to <60 mL/min per 1.73 m^2	35.0%
≥60 mL/min per 1.73 m^2	60.5%
HbA1c (%)	7.7±2.0
Number of glucose-lowering medications	1.9±1.2
Use of individual glucose-lowering medications	
Metformin	75.1%
Sulfonylurea	34.4%
Insulin	27.7%
Dipeptidyl Peptidase-4 Inhibitor	18.3%
Thiazolidinedione	10.9%

Glucagon-Like Peptide-1 Receptor Agonist	6.4%
Sodium-glucose Cotransporter-2 Inhibitor	4.8%

Table 2.

Use of classes of glucose lowering medications by patient characteristics

	n	Metformin	SU	Insulin	DPP-4i	TZD	GLP-1 RA	SGLT2i
Age								
<65 years	55,618	81.0%	27.9%	28.8%	18.2%	9.2%	9.4%	8.3%
65 to <75 years	54,092	77.1%	34.7%	28.2%	18.4%	11.6%	6.7%	4.0%
≥75 years	47,841	66.1%	41.6%	25.8%	18.2%	12.0%	2.7%	1.6%
p-value		<0.001	<0.001	<0.001	0.924	<0.001	<0.001	<0.001
Body mass index								
<30 kg/m2	43,738	73.6%	34.9%	23.7%	19.4%	9.4%	3.5%	3.8%
30 to <40 kg/m2	50,182	75.4%	34.5%	30.1%	19.2%	10.6%	7.8%	5.4%
≥40 kg/m2	15,040	73.2%	32.3%	37.3%	17.0%	11.6%	11.2%	5.6%
p-value		0.095	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Estimated GFR								
<30 mL/min per 1.73 m^2	3,585	26.8%	43.4%	62.5%	20.0%	12.5%	5.2%	0.7%
30 to <60 mL/min per 1.73 m^2	27,779	61.8%	42.8%	36.5%	21.8%	13.1%	6.6%	3.2%
≥60 mL/min per 1.73 m^2	48,000	82.3%	31.1%	24.5%	18.3%	10.3%	6.8%	5.7%
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	0.008	<0.001
Coronary artery disease								
Yes	88,475	37.7%	71.6%	32.2%	18.6%	11.4%	5.9%	4.0%
No	69,076	30.1%	79.6%	21.9%	17.9%	10.3%	7.2%	5.8%
p-value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

SU, sulfonylurea; TZD, Thiazolidinedione; DPP-4i, Dipeptidyl Peptidase-4 inhibitors; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonists; SGLT2i, Sodium-glucose co-transporter 2 inhibitors; GFR, glomerular filtration rate

p-values correspond to the unadjusted comparisons across groups using chi-square tests