RESEARCH

Glycemic Control and Hypoglycemia in Veterans Health Administration Patients Converted from Glyburide to Glipizide

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ABSTRACT

BACKGROUND: In 2009, the Veterans Health Administration (VHA) released a national bulletin regarding the risk of hypoglycemia associated with the use of glyburide in elderly patients with renal dysfunction. Providers were encouraged to avoid glyburide and use glipizide in patients with a calculated creatinine clearance (CrCl) of less than 50 mL per minute. Since this initiative, many veterans were converted by their providers from glyburide to glipizide regardless of renal impairment.

OBJECTIVES: To (a) identify whether hemoglobin A1c remained equivalent in patients converted from glyburide to glipizide, (b) evaluate the prevalence of hypoglycemia during treatment with glyburide or glipizide, (c) compare change in glycemic control for renally impaired versus nonimpaired patients, and (d) analyze dosage conversion ratios selected by providers and measures of patient follow-up after conversion including time until A1c measurement and number of glipizide dose titrations.

METHODS: This was a single-center, retrospective analysis of veterans converted from glyburide to glipizide from January 1, 2008, through May 31, 2010, who had documented A1c values concurrent with glyburide and glipizide use. A 2-sided equivalence analysis was used for the primary outcome. Equivalence was defined as a change in mean A1c of ±0.2. Hypoglycemia was defined as blood glucose of less than 70 mg per dL, symptoms of hypoglycemia, or hypoglycemia that led to a fall, loss of consciousness, emergency room visit, hospitalization, or death. The pre- to post-conversion change in rates of hypoglycemia was tested for significance using a McNemar's test.

RESULTS: In the 141 (99.3% male, 53.9% CrCl < 50 mL per minute, mean age = 74.0 years) patients meeting inclusion criteria between 2008-2010, the average change in A1c (+0.34) was nonequivalent after conversion from glyburide to glipizide (7.08% vs. 7.42%, respectively). Hypoglycemia occurred more frequently during treatment with glyburide than glipizide (31.2% vs. 12.8%, respectively, $P < 0.001$). Mean dose conversion ratios were consistent with VHA recommendations (1 mg per day glyburide = 1.26-1.55 mg per day glipizide).

CONCLUSIONS: Conversion from glyburide to glipizide was associated with an increase in A1c, but the incidence of hypoglycemia was reduced. Results of this study are consistent with the recommendation of the American Diabetes Association and European Association for the Study of Diabetes to use second-generation sulfonylureas other than glyburide. Patients converted to glipizide should be monitored closely to adjust therapy as appropriate to maintain glycemic control.

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What is already known about this subject

- Sulfonylureas effectively reduce hemoglobin A1c by an expected 1.0%-2.0%. Maintaining glycemic control has been shown to lower morbidity secondary to microvascular complications including retinopathy, neuropathy, and nephropathy.
- Glyburide is metabolized to active metabolites that may accumulate in patients with renal dysfunction and has been associated with a 2-fold incidence of hypoglycemia in elderly patients compared with glipizide.

What this study adds

- A pharmacy benefits management initiative to avoid use of glyburide in patients with creatinine clearance (CrCl) < 50 mL per minute implemented in a Veterans Affairs (VA) health care system of approximately 60,000 patients was associated with conversion from glyburide to glipizide in 298 patients regardless of renal impairment.
- Glycemic control was not equivalent following conversion from glyburide to glipizide, with a change in mean A1c of +0.34 (7.08% vs. 7.42%, respectively) at the doses used in this sample (11.4 mg vs. 14.0 mg per day, respectively).
- Conversion to glipizide was associated with significant reduction in hypoglycemic events in this sample ($P < 0.001$). Continued support of safety initiatives by the VA Pharmacy Service may lead to a reduction in adverse drug reactions in the veteran population.

Diabetes mellitus is associated with significant morbidity and mortality and affects 25.8 million Americans, or 8.3% of the total U.S. population.[1] The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a stepped approach to treatment based on the most effective and cost-effective therapeutic strategy for achieving target glycemic goals.[2] Metformin is recommended as the initial pharmacological therapy for all patients with type 2 diabetes in the absence of specific contraindications, along with lifestyle interventions aimed to decrease weight and increase activity. If these interventions fail to achieve or sustain glycemic goals, additional therapy with sulfonylureas or insulin is recommended. Patients not at goal with a hemoglobin A1c less than 8.5% and a contraindication to metformin or who are unable or unwilling to use insulin may particularly benefit from the addition of a sulfonylurea.[2]

Sulfonylureas act primarily by stimulating pancreatic beta cells to secrete insulin; however, metabolism and elimination differ among members of the drug class. Glyburide and glipizide are second-generation sulfonylureas. The results of studies comparing efficacy and dose equivalences of glyburide and glipizide are conflicting. In a trial of 139 patients aged 65 years or older randomized to glyburide or glipizide, there was no significant between-group difference in fasting blood glucose or A1c.[3] Doses of the sulfonylureas were titrated over 4-8 weeks until patients entered a 4-month maintenance phase in which the mean dose of glipizide (15.4 milligrams [mg] per day) was approximately twice that of glyburide (8.5 mg per day).[3] Conversely, smaller randomized controlled trials have shown equipotency of the medications with similar fasting blood glucose and A1c levels at nearly equal daily doses (means of 14 mg vs. 15 mg and 10 mg vs. 11 mg per day for glyburide vs. glipizide, respectively).[4,5]

Glyburide is hepatically metabolized to active metabolites that are renally excreted. These metabolites may accumulate in patients with renal dysfunction, thereby increasing the risk of hypoglycemia, defined as blood glucose less than 70 mg per deciliter (dL).[2,6] In contrast, glipizide is metabolized to inactive metabolites and is not associated with an increased risk of hypoglycemia due to renal dysfunction (defined as glomerular filtration rate [GFR] less than 30 milliliters per minute [mL per min]).[7] The risk of serious hypoglycemia in the elderly (defined as hospitalization, emergency room [ER] admission, or death associated with blood glucose less than 50 mg per dL) was shown to be nearly 2-fold greater with glyburide than glipizide (median doses 5 mg vs. 10 mg per day, respectively) in a retrospective analysis involving 8,576 person-years of exposure to glyburide or glipzide in Medicaid enrollees aged 65 years or older.[8] The increased risk of hypoglycemia with glyburide was confirmed in a recent meta-analysis comparing glyburide with other sulfonylureas.[9] Consequently, the ADA and EASD recommend the use of second-generation sulfonylureas other than glyburide for the management of type 2 diabetes regardless of renal function.[2]

On July 29, 2009, the Veterans Health Administration (VHA) Pharmacy Benefits Management Service, Medical Advisory Panel, and Center for Medication Safety released a joint national bulletin regarding the risk of severe hypoglycemia with glyburide use in elderly patients (aged 65 years or older) with renal dysfunction.[10] Through the national bulletin, providers were advised to avoid glyburide in patients with a calculated creatinine clearance (CrCl) less than 50 mL per min. Glipizide was recommended as a possible alternative, with the suggested dosing conversion that a 5 mg dose of glipizide is approximately equivalent to 2.5-5 mg of glyburide. In addition to the national bulletin, providers at the Iowa City VA Health Care System (ICVAHCS) were alerted to the hypoglycemia risk through a monthly pharmacy newsletter distributed to all providers within the medical center.[11] In an August 2009 pharmacy benefits management initiative, clinical pharmacists at the ICVAHCS identified patients on glyburide with CrCl less than 50 mL per min and notified providers of the recommendation to switch patients to glipizide through notes in the electronic medical record (EMR). The decision to convert patients and the responsibility to monitor and adjust doses were deferred to the primary care provider.

Renal dysfunction is a common comorbidity in patients with type 2 diabetes, affecting 13% of those aged 40 years or older and 31.5% of those aged 65 years or older.[12,13] Because the proportion of the U.S. population aged 65 years or older is projected to increase dramatically in the coming decades and the prevalence of renal dysfunction increases with age, there is a growing concern regarding the continued use of glyburide in the aging population. Following the release of the pharmacy benefits management initiative, clinical pharmacists noted that several providers at the ICVAHCS were proactively converting patients from glyburide to glipizide regardless of renal function. To better understand the entire effect of the initiative, all patients converted from glyburide to glipizide regardless of renal function were included in the present study.

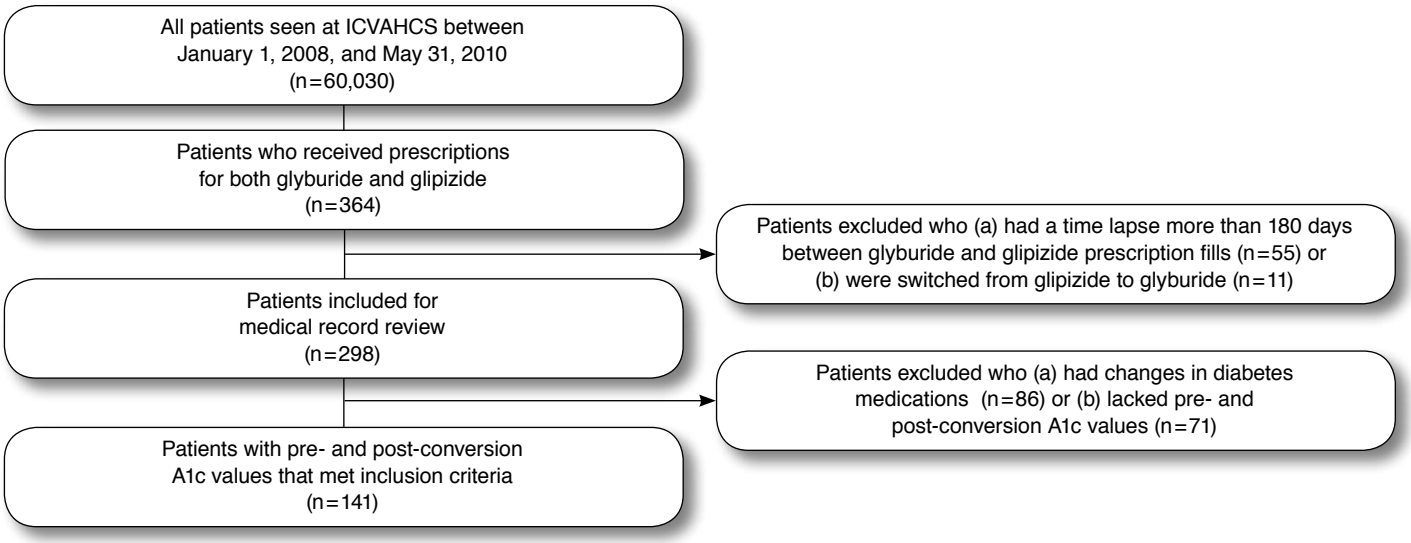
Because the recommendation to switch was predicated on reduction of hypoglycemia, not on improved glycemic control, the effect of the switch from glyburide to glipizide on A1c was not initially considered. The present study was conducted to analyze the effect of conversion from glyburide to glipizide on glycemic control (A1c) and the incidence of hypoglycemic events in patients at the ICVAHCS. The primary objective assessed whether A1c was equivalent in veterans converted from glyburide to glipizide. Secondary objectives (a) evaluated whether episodes of hypoglycemia were more prevalent during treatment with glyburide or glipizide; (b) compared glycemic control in patients with normal renal function (CrCl at least 50 mL per min) and renal insufficiency (CrCl less than 50 mL per min); and (c) analyzed dosage conversion ratios and the number of glipizide dose titrations. Regarding secondary objective (b), we hypothesized that patients with renal dysfunction would have a greater increase in A1c due to accumulation of active glyburide metabolites compared with patients with normal renal function. For secondary objective (c), we compared patients who had an A1c that met the definition of equivalence with those who did not in an attempt to find predictors for equivalence.

Methods

Patients and Study Methods

This was a single-center, retrospective study of patients who were converted from glyburide to glipizide. Patients at the ICVAHCS with a prescription for both glyburide and glipizide

FIGURE 1 Selection of Patients Switched from Glyburide to Glipizide



A1c = hemoglobin A1c; ICVAHCS = Iowa City Veterans Affairs Health Care System.

from January 1, 2008, through May 31, 2010, indicating a conversion between the agents, were identified using Fileman, an electronic database management program used to access and retrieve VA data. Those with documented A1c measurements concurrent with glyburide and glipizide use during the data collection period (January 1, 2007, through August 27, 2010) were included in the primary analysis. The expanded duration of the data collection period allowed for collection of A1c values up to 1 year prior and at least 75 days following conversion to glipizide. Subjects were excluded if (a) there were changes in the diabetes regimen other than glyburide or glipizide, (b) greater than 180 days lapsed between the last glyburide and the first glipizide prescription fill dates, or (c) patients were converted from glipizide to glyburide. For each study subject, individual A1c values were included if there were no dose changes for glyburide and glipizide within 75 days prior to the A1c measurement; otherwise, the A1c value was not considered stable because it could reflect a carryover effect from the previous dose. The A1c collected during glyburide treatment (pre-conversion) was the most recent measurement within 365 days prior to conversion. The A1c collected during glipizide treatment (post-conversion) was the measurement closest to 90 days post-conversion (within 75-365 days).

Hypoglycemic events were collected through an EMR review of progress notes and laboratory values within 365 days before and after the conversion. Hypoglycemia was defined as blood glucose less than 70 mg per dL identified in the ICVAHCS electronic laboratory records, home glucometer results documented in progress notes, or patient-reported symptoms of hypoglycemia documented in progress notes (e.g., tremor, fatigue, blurred vision attributed to low blood glucose). Hypoglycemia was considered severe if it resulted in a fall, loss of consciousness, ER visit, hospitalization, or death. A secondary analysis comparing patients with calculated CrCl at least 50 mL per min with those with CrCl less than 50 mL per min was planned. Additionally, all A1c measurements during the 75-365 days following conversion (barring any concurrent diabetes regimen changes) were analyzed to identify characteristics of patients whose A1c met the pre-determined definition for equivalence at any time during follow-up, comparing the most recent measurement in the 365-day period pre-conversion with any measurement during the 75- to 365-day post-conversion period. This study was approved by the University of Iowa Institutional Review Board and the Iowa City VA Research and Development Committee in September 2010.

Statistical Analysis

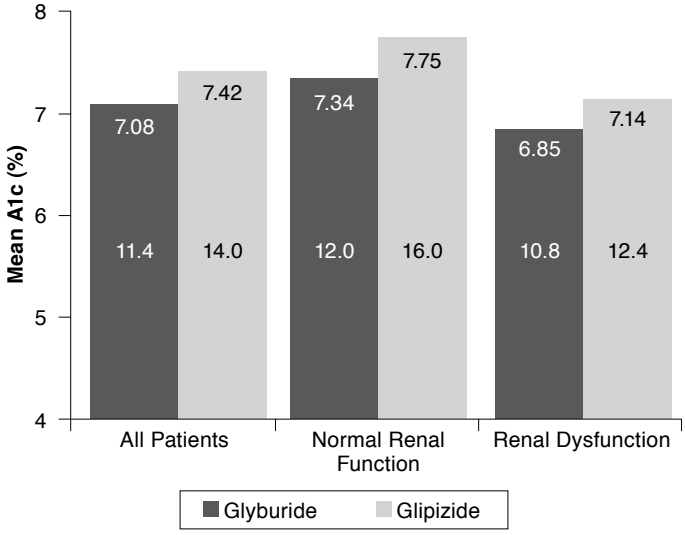
Our primary analysis was an equivalence comparison of A1c utilizing a pre/post design without a comparison group. An equivalence margin of A1c of 0.2 or less was chosen for the absolute difference post-conversion. This boundary was chosen because a change in A1c of at least 0.5 is commonly used in superiority trials to define a clinically significant difference. Setting the 2-sided equivalence bounds at 0.2 (absolute range 0.4) provides more narrow boundaries for equivalence than those used to define superiority. Based on published pharmacokinetic data of glyburide and glipizide, we estimated that 100 paired samples would be required to show equivalence

TABLE 1 Baseline Characteristics of Patients with Diabetes Prior to Switching from Glyburide to Glipizide (n=141)

Male gender – % (n)	99.3	(140)
Mean [SD] age, years	74.0	[8.8]
Mean [SD] estimated CrCl, mL per min	52.1	[17.2]
Mean [SD] weight, kg	100.9	[20.6]
Concomitant diabetes medications	%	(n)
Metformin	48.2	(68)
Thiazolidinediones	9.2	(13)
Insulin	7.1	(10)
Glucosidase inhibitors	0.7	(1)
No concomitant diabetes medications	42.6	(60)

CrCl = creatinine clearance, calculated via the Cockcroft-Gault equation; kg = kilograms; mL per min = milliliters per minute; SD = standard deviation.

FIGURE 2 A1c with Associated Mean Dosage for All Patients and Categorized by Renal Function Pre- and Post-Conversion from Glyburide to Glipizide[a]



[a]Renal dysfunction was defined as CrCl less than 50 mL per minute (n=76); normal renal function was defined as CrCl of 50 mL per minute or more (n=65). Dosages shown in the center of the bar are expressed as milligrams per day and were calculated by averaging subjects' daily doses at the time of the A1c measures collected for the primary study outcome.
A1c = hemoglobin A1c; CrCl = creatinine clearance, calculated via the Cockcroft-Gault equation; mL = milliliters.

with 95% power.[14] Equivalence was tested using Schuirmann 1-sided test/two 1-sided test (OST/TOST).[15] Change in prevalence of hypoglycemia from pre- to post-conversion was analyzed with McNemar's test. A Student's t-test compared change in A1c for renally impaired with nonimpaired patients. Baseline characteristics of the sample are presented as means (SD) or frequencies, as appropriate. All tests were 2-tailed, and type 1 error for significance was set at 0.05. Equivalence was tested utilizing EquivTest v2 (Statistical Solutions, Cork, Ireland). All other analyses were performed with SPSS, v19 (SPSS Inc., Chicago, IL).

Results

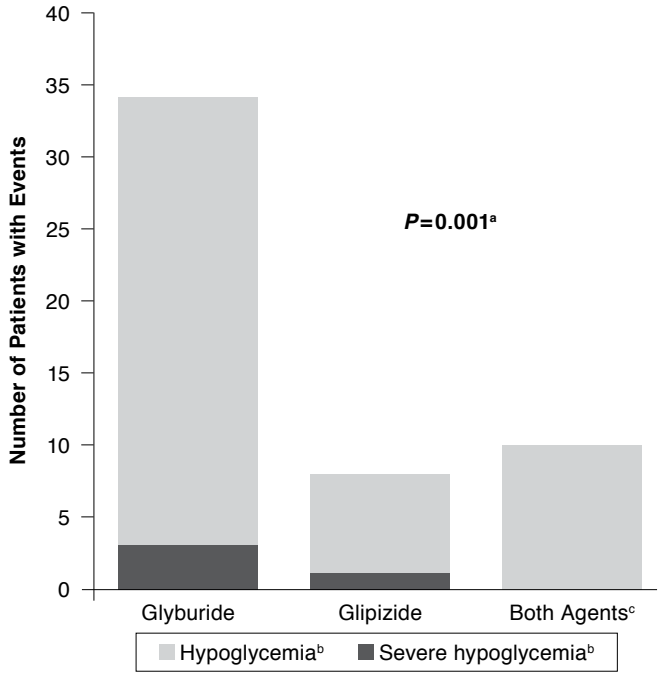
Of the 60,030 unique patients in the health care system, 364 (0.6%) received prescriptions for both glyburide and glipizide from January 1, 2008, through May 31, 2010 (Figure 1). Of these, 141 patients (38.7%) were switched from glyburide to glipizide with no more than a 180-day gap between the 2 drugs, had A1c measurements that met the inclusion criteria, and had no other changes in diabetes medications. The majority of patients were elderly males (99.3% male, mean age 74.0 years, range 55-89 years; Table 1). Concurrent diabetes medications included metformin (48.2%), thiazolidinediones (9.2%), insulin (7.1%), and glucosidase inhibitors (0.7%).

Mean (SD) A1c during glyburide treatment was 7.08% (1.08%) measured 54.1 (70.3) days prior to conversion; mean (SD) dose was 11.4 (7.2) mg per day (Figure 2). Mean (SD) A1c during glipizide treatment increased to 7.42% (1.37%) measured 156.0 (61.2) days following conversion; mean (SD) dose was 14.0 (10.1) mg per day. The increase in A1c of 0.34 did not demonstrate equivalence (equivalence boundaries ±0.2, $P = 0.962$) and indicated a decline in glycemic control following conversion.

Hypoglycemia was confirmed in 44 (31.2%) patients during glyburide treatment and in 18 (12.8%) patients during treatment with glipizide (Figure 3). Of these, 10 patients experienced hypoglycemia on glyburide that continued despite being switched to glipizide. The increased prevalence of hypoglycemia with glyburide was statistically significant ($P < 0.001$). Hypoglycemic events were derived primarily by documentation in progress notes of patient reported symptoms (53.2%) and home glucometer results (40.3%) and less commonly from ICVAHCS laboratory results (6.5%). Severe hypoglycemia occurred infrequently; 2 patients presented to the ER, and an additional patient was hospitalized during treatment with glyburide, compared with 1 patient experiencing loss of consciousness during treatment with glipizide ($P = 0.625$).

Upon grouping the sample by renal function, 76 patients had CrCl less than 50 mL per min, and 65 patients had CrCl of at least 50 mL per min (Table 2). Patients with renal dysfunction tended to be older and weigh less. Metformin was prescribed less frequently in patients with renal dysfunction. Change in A1c was not significantly different among patients with normal renal function versus those with renal dysfunction (means of +0.4 vs. +0.3, respectively, $P = 0.457$; Figure 2). There were 54 patients whose A1c on glipizide 75-365 days after conversion was ±0.2 compared with their A1c on

FIGURE 3 Prevalence of Hypoglycemic Events in Patients with Diabetes During Glyburide or Glipizide Treatment



[a]P value calculated using McNemar's test.
[b]Hypoglycemia = blood glucose less than 70 mg per dL, patient reported symptoms of hypoglycemia; severe hypoglycemia = hypoglycemia causing fall, loss of consciousness, emergency room visit, hospitalization, or death.
[c]Both Agents = patients who experienced hypoglycemia during glyburide treatment that continued after conversion to glipizide.
mg per dL = milligrams per deciliter.

TABLE 2 Patient Characteristics Categorized by Renal Function[a]

	Normal n = 65	Renal Dysfunction n = 76	*P* Value[b]
Male gender % (n)	100.0 (65)	98.7 (75)	1.00
Mean [SD] age, years	70.1 [8.3]	77.3 [7.9]	<0.001
Mean [SD] estimated CrCl, mL per min	67.0 [14.9]	39.0 [7.8]	<0.001
Mean [SD] weight, kg	104.8 [20.3]	97.5 [20.3]	0.043
Concomitant diabetes medications	% (n)	% (n)	
Metformin	69.2 (45)	30.3 (23)	<0.001
Thiazolidinediones	9.2 (6)	9.2 (7)	0.997
Insulin	6.2 (4)	7.9 (6)	0.688
Glucosidase inhibitors	0.0 (0)	1.3 (1)	0.353
No concomitant diabetes medications	26.2 (17)	56.6 (43)	<0.001

[a]Renal dysfunction was defined as CrCl less than 50 mL per minute; normal renal function was defined as CrCl of 50 mL per minute or more.
[b]P value calculated with Student's t-test (age, CrCl, weight), Pearson chi-square test (diabetes medications), or Fisher's exact test (gender) comparing normal renal function group with renal dysfunction group.
CrCl = creatinine clearance, calculated via the Cockcroft-Gault equation; kg = kilograms; mL per min = milliliters per minute; SD = standard deviation.

glyburide, meeting our definition of equivalence. Conversely, 87 patients' A1c changes never met equivalence (n = 56 with A1c increase of more than 0.2, n = 31 with A1c decrease of more than 0.2). Dosing conversion ratios, time until A1c measurement, and number of glipizide dose titrations were similar for the equivalent and nonequivalent groups (Table 3). Mean dosing conversion ratios for glyburide versus glipizide were 1:1.26 mg per day in the equivalent group, 1:1.53 mg per day in patients with change in A1c exceeding 0.2, and 1:1.55 mg per day in patients with decrease in A1c more than 0.2. Weight remained consistent throughout as the mean (SD) changes in weight following conversion were –1.7 (4.0) kilograms (kg) in the equivalent group and –0.7 (4.0) kg in the nonequivalent group (data not shown).

Discussion

Results of this study did not demonstrate equivalent glycemic control with glyburide compared with glipizide at the doses reported. The increase in A1c of 0.34 with glipizide may be less clinically significant than once thought based on the results of recent randomized controlled trials. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) studies did not show a significant difference in macrovascular outcomes between the intensive (mean A1c in ADVANCE and VADT 6.5% and 6.9%, respectively) or standard glucose control groups (mean A1c 7.3% and 8.4%, respectively).[16,17] Furthermore, the ADVANCE investigators found that severe hypoglycemia was significantly more common in the intensive glucose control group (2.7% vs. 1.5% in standard control group, hazard ratio = 1.86, $P < 0.001$). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial involving 10,251 patients with type 2 diabetes and an increased risk of cardiovascular disease found an increase in mortality with intensive therapy (targeted to A1c <6%) compared with standard therapy (targeted to A1c from 7.0%-7.9%) after a mean follow-up of 3.5 years.[18]

These studies have important implications for target A1c recommendations. While a target hemoglobin A1c of less than 7% is generally accepted for most healthy older adults, some organizations allow for less stringent targets for individual patients with a limited life expectancy based on their expected risks and benefits of intensive glucose control. The American Geriatrics Society considers a less stringent target, such as less than 8%, appropriate for frail older adults, persons with a life expectancy of less than 5 years, and others in whom the risks of intensive glycemic control appear to outweigh the benefit.[19]

TABLE 3 Patient Follow-Up After Conversion to Glipizide

	Equivalent[a] A1c n = 54		Nonequivalent A1c n = 87	
Mean [SD] days until A1c measurement following glipizide initiation	157	[63]	155	[60]
Number of dose titrations	%	(n)	%	(n)
0	85.2	(46)	72.4	(63)
1	9.3	(5)	20.7	(18)
2 or more	5.6	(3)	6.9	(6)

[a]Change in A1c met definition of ± 0.2 within 365 days of switch.
A1c = hemoglobin A1c; SD = standard deviation.

The VA and Department of Defense guidelines recommend setting target A1c ranges based on individual patients' microvascular complications, comorbid conditions, and life expectancy, with a recommended target range of 8%-9% in those with advanced microvascular complications or life expectancy of less than 5 years.[20] The ADA states that "less stringent A1c goals may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain" but does not specify the target.[21] Based on the trials described above and these guidelines, patients with an A1c near those of the intensive-control study groups or with significant comorbidities may be well suited for conversion from glyburide to glipizide, in addition to those patients with renal dysfunction.

Risks and benefits of any treatment method must be assessed for each patient individually. In the present study, converting patients from glyburide to glipizide was associated with a decline in glycemic control but decreased risk of hypoglycemia. The reduction in hypoglycemia with glyburide is noteworthy for this sample of older adults (mean age 74 years). Advanced age is a well-known risk factor for severe hypoglycemia. In a study of diabetic patients taking sulfonylureas, those aged 65 years or older had an annual risk of hypoglycemia of 2.0% compared with a 1.4% annual risk for people younger than 65 years (relative risk = 1.36, 95% confidence interval [CI] = 1.25-1.63).[22] Greco et al. (2010) analyzed episodes of hypoglycemia requiring hospital admission in patients aged 80 years or older with type 2 diabetes and found that of 591 admissions in an 8-year period, 16.8% (99 cases) were due to severe hypoglycemia. Patients presented with coma (19.2%); somnolence (51.5%); and disorientation, cerebral seizures, or psychiatric disturbances (29.3%).[23] Of the sample patients, 61.6% experienced protracted hypoglycemia lasting 12-72 hours which contributed to the median (SD) duration of hospitalization of 5.5 (2.4) days. Causes of increased hypoglycemia risk in the elderly include frequent comorbid conditions, polypharmacy, age-associated decline in hepatic and renal function, and blunting of symptom recognition and counterregulatory responses to hypoglycemia with advanced age.[23] These findings suggest that avoidance of hypoglycemia and potentially serious and costly complications may outweigh the risk of worsened glycemic control in the present study sample of older adults.

Multiple factors may have contributed to the increase in A1c that was associated with the conversion to glipizide in the study sample. First, the prevalence of hypoglycemia was significantly reduced during treatment with glipizide; hence, patients experienced blood glucose levels less than 70 mg per dL less often. Since A1c is a reflection of a patient's average blood glucose, this change would be expected to increase A1c. Conversely, an increase in A1c would not necessarily result in less frequent hypoglycemia if the patient has significant fluctuations in blood glucose levels. Second, the ADA recommends performing A1c tests every 3 months in patients whose therapy has changed;[21] however, the majority of the study sample patients had their first A1c measurements on a stable dose of glipizide approximately 5 months after conversion (mean [SD] 156.0 [61.2] days). The cause for the delay in follow-up A1c measurements is unknown, but it may be a reflection of scheduling delays due to high workload, missed appointments, or unfamiliarity with the guidelines. Third, approximately 80% of patients never had their initial dose of glipizide titrated within 1 year following conversion. We propose that if A1c was monitored as recommended by the ADA with subsequent dosing titrations of glipizide as appropriate, mean A1c during treatment with glipizide may have been sustained or returned to pre-conversion levels. This plan would be expected to initially increase therapeutic workload and associated costs, but we believe it would not preclude conversion from glyburide to glipizide in most patients. Body weight was considered a proxy for lifestyle modification, and the absence of change in average body weight in the post-conversion sample suggests that body weight was not a factor in glycemic control in the present study.

The VA initiative was directed towards patients with renal dysfunction; therefore, we compared the changes in A1c for those who were described by the national bulletin with those who had normal renal function. We hypothesized that patients with renal dysfunction would have a greater increase in A1c due to accumulation of active glyburide metabolites compared with patients with normal renal function. However, we found no significant difference in change in A1c between the 2 groups. Of note, patients with renal dysfunction were prescribed metformin less often, which is consistent with the contraindication based on the increased risk of lactic acidosis in patients with renal impairment.[2]

We compared patients with an A1c that met the definition of equivalence with those who did not in an attempt to find predictors for equivalence. However, we were unable to derive any meaningful differences between the management of patients, including dose conversion ratios, days until follow-up, or dose titrations.

Limitations

First, because the study utilized a pre/post design without a comparison group, causality cannot be inferred from the results. In addition, this design is vulnerable to regression toward the mean. Second, it was not possible to fully determine patient compliance to either glyburide or glipizide or to determine when patients began taking glipizide following its initial fill. This limitation was somewhat minimized by collecting A1c measurements at least 75 days from the initial glipizide fill to avoid a carry-over effect from glyburide, although compliance may still have played a role in our study's findings. For example, it is possible that patients with hypoglycemic events were less compliant as a result of their negative experiences, which may have impacted the primary results. Third, the study relied on provider documentation of non-VA laboratory records, which may have been incomplete, and patient-reported symptoms of hypoglycemia and home blood glucose results, which may be less reliable than laboratory results. Fourth, diabetes is a progressive disease, and the increase in A1c may reflect disease progression rather than the change from glyburide to glipizide. Fifth, there may have been changes in medications that affect blood glucose (e.g., corticosteroids), which were not accounted for. Sixth, some important patient factors, specifically duration of diabetes and duration of glyburide therapy prior to the medication conversion, were not available for analysis. Seventh, factors affecting the accuracy of A1c, such as changes in erythrocyte lifespan, were not collected. Eighth, A1c was used as a biomarker for glycemic control and as a surrogate may not fully be specific to the vascular risk associated with diabetes. Finally, the generalizability of the present study is limited by the gender, race, and geographic characteristics of the sample but likely accurately represents the veteran population taking these medications.

Conclusions

The results of this study are consistent with the ADA and EASD recommendation to use second-generation sulfonylureas, such as glipizide, instead of glyburide due to the increased risk of hypoglycemia. In order to reduce the effect of the conversion from glyburide to glipizide on A1c, we suggest timely monitoring and adjustment of glipizide to help maintain glycemic control.

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DISCLOSURES

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