

Adding Glucose-Lowering Agents Delays Insulin Initiation and Prolongs Hyperglycemia

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According to the CDC, more than 29 million Americans are currently diagnosed with diabetes, with the projected lifetime risk of developing the disease near 40%.¹ The prevalence of diabetes in the veteran population is estimated at 25% for a variety of reasons, including older average age and previous exposure to Agent Orange during the Vietnam era.² More than 85% of Americans with diabetes are prescribed a glucose-lowering agent (GLA), with the majority using noninsulin therapy.¹

Medical costs associated with diabetes are staggering and create a financial burden on the healthcare system.³ In 2012, the estimated total cost of diabetes in the United States was \$245 billion, with direct medical expenses responsible for more than 70% of the total. In the United States, more than 60% of the cost for diabetes care is provided by the government (including Medicare, Medicaid, and the military), with the majority of costs secondary to hospitalizations from diabetes-related complications. Given the increased prevalence and progressive nature of diabetes, this cost burden will likely continue to rise.³

The progressive nature of type 2 diabetes (T2D) requires prescribers to modify, and often intensify, diabetes regimens over time.⁴ Metformin is recommended as the initial GLA for most patients with T2D, but evidence to guide treatment after metformin monotherapy is limited.⁴ There are currently 9 different classes of GLAs that healthcare providers can prescribe prior to starting insulin (Table 1). The Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guidelines for Management of Diabetes (last published in 2010) and the American Diabetes Association (ADA) Standards of Medical Care in Diabetes contain algorithms to guide providers in making treatment decisions.^{4,5} In the VA/DoD guidelines, metformin with a sulfonylurea is the preferred oral combination when monotherapy no longer provides adequate glycemic control.⁵ Alternative agents can be considered for patients unable to use metformin or a sul-

ABSTRACT

Objectives: Nine classes of glucose-lowering agents (GLAs) are available for patients with type 2 diabetes prior to starting insulin. This study's aim was to determine if the number of GLAs is associated with a difference in glycated hemoglobin (A1C) at insulin initiation in the US Department of Veterans Affairs Health Care System (VAHCS).

Study Design: Retrospective cohort study.

Methods: A retrospective cohort with national Veterans Health Administration data was created. Veterans with type 2 diabetes and first insulin prescription filled in the VAHCS between January 1, 2009, and August 28, 2013, were identified. Included veterans refilled insulin within the first year, had an A1C >7% (53 mmol/mol) at least 60 days prior to insulin initiation, and received a GLA within 6 months prior to insulin. Veterans were grouped into 4 cohorts according to the number of GLAs used.

Results: A total of 90,497 veterans with type 2 diabetes met inclusion criteria. Insulin was initiated at a mean A1C of 9.9% (85 mmol/mol). The mean A1Cs prior to insulin for 1, 2, 3, or >3 GLAs were 10.3% (89 mmol/mol), 9.9% (85 mmol/mol), 9.6% (81 mmol/mol), and 9.6% (81 mmol/mol), respectively. Months to insulin increased with the number of GLA trials and prolonged the time veterans were exposed to A1C >8% (64 mmol/mol).

Conclusions: Multiple glucose-lowering drug classes are associated with a numerical, but not a clinical, difference in A1C at insulin initiation in the closed formulary of the VAHCS.

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fonylurea. The Veterans Administration Health Care System (VAHCS) restricts the use of alternative agents by placing them in a nonformulary status with criteria for use.⁵ With their highest level of evidence, the ADA Standards of Medical Care supports the addition of a second oral agent, a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin if metformin alone does not achieve or maintain the glycated hemoglobin (A1C) target.

The VA/DoD and ADA standards encourage providers to consider the needs of individual patients when determining appropriate therapy, recognizing the lack of evidence for the “one size fits all” approach.^{4,5} Glycemic control targets should be determined based on individual patient characteristics in the context of comorbidities, life expectancy, risk of hypoglycemia, pre-existing microvascular complications, and patient preferences.^{4,5}

According to the VA/DoD guidelines, all patients with diabetes should have a target A1C <9% (75 mmol/mol).⁵ Patients with advanced microvascular disease, major comorbid illness, and/or life expectancy less than 5 years should have a target A1C 8% to 9% (64-75 mmol/mol). Patients who have had diabetes for more than 10 years, and/or have comorbid conditions, and have a combination diabetes regimen including insulin should have a target A1C <8% (64 mmol/mol). A patient without significant microvascular complications, who is free of major concurrent illnesses and has a life expectancy of at least 10 years, should have a target A1C <7% (53 mmol/mol).

In 2012, the ADA and the American Geriatric Society (AGS) published a consensus report on diabetes in older adults.⁶ Their report creates a framework for establishing glycemic goals in adults with diabetes aged over 65 years. This framework, similar to that of the VA/DoD, considers patient characteristics, health status, life expectancy, hypoglycemia vulnerability, and fall risk.⁶ Establishing a target A1C does not restrict patients and providers from discussing the benefits of a lower goal, but implies there are reduced benefits of intensifying treatment.⁵

The addition of insulin is an effective method for lowering A1C. The ADA recognizes that the progressive nature of T2D eventually results in the need for insulin therapy for many patients.⁴ Evidence supports early insulin initiation, or intensification in patients with significant hyperglycemia (defined by plasma blood glucose >300 mg/dL, A1C >10% [86 mmol/mol], and/or symptoms of hyperglycemia), although treatment with insulin is often delayed.⁷

Take-Away Points

In 2014, it was estimated that more than 29 million Americans had type 2 diabetes, and the estimated total cost for diabetes in the United States was \$245 billion in 2012. Diabetes-related costs can decline by 4.2% for each percentage point reduction in glycated hemoglobin (A1C). In our study, initiating insulin after 1 or 2 glucose-lowering agents (GLAs) reduced A1C by 2.5 percentage points in approximately 14 months.

- Guidelines recommend intensifying patients' diabetes regimens to achieve A1C goals.
- A closed formulary resulted in two-thirds of patients starting insulin after trials on 1 or 2 GLAs.
- Trials of 3 or more GLAs further delayed insulin initiation and prolonged hyperglycemia.

The purpose of this retrospective study was to determine if the addition of multiple glucose-lowering drug classes is associated with a difference in A1C at insulin initiation in the closed formulary of the VAHCS.

METHODS

Data Source

The electronic VA Informatics and Computing Infrastructure national database was utilized for data extraction. The study was approved by the University of Iowa Institutional Review Board and the Iowa City VA Health Care System Research and Development Committee. Age and region were determined on the day insulin was initiated, and body mass index (BMI) was calculated using the height and weight closest to the insulin initiation date.

Patient Selection

The study population included veterans with T2D (determined according to *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes) who had their insulin prescription first filled in the VA system between January 1, 2009, and August 28, 2013. Data were analyzed for veterans who refilled their insulin prescriptions within the first year, had an A1C >7% (53 mmol/mol) within 60 days prior to insulin initiation, and received a prescription for a GLA within 6 months prior to insulin initiation.

Patient Assignment

Veterans were grouped into 4 cohorts according to the number of glucose-lowering classes used prior to insulin (1, 2, 3, or >3 classes). Each ingredient in a combination medication was counted; for example, Janumet (metformin/sitagliptin) was considered as 2 GLA classes.

Outcomes

The primary outcome measure was A1C at insulin initiation. Secondary outcomes included: months from first

Table 1. Glucose-Lowering Drug Classes and Agents Available During Study Period

Drug Class	Agents
Biguanides	Metformin
Sulfonylureas	Glipizide, glyburide, glimepiride, chlorpropamide, acetohexamide, tolazamide, tolbutamide
Meglitinides	Repaglinide, nateglinide
Thiazolidinediones	Rosiglitazone, pioglitazone, troglitazone
Alpha-glucosidase inhibitors	Acarbose, miglitol
GLP-1 receptor agonists	Exenatide, liraglutide
DPP-4 inhibitors	Sitagliptin, saxagliptin, linagliptin, alogliptin
Amylin analogs	Pramlintide
SGLT-2 inhibitor	Canagliflozin

DPP-4 indicates dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose transporter-2.

prescription of a GLA to insulin initiation, lowest A1C after insulin initiation, and consecutive months of poor glycemic control (defined as an A1C >8% [64 mmol/mol]) prior to insulin initiation. The definition of poor glycemic control was based on VA/DoD and ADA/AGS recommendations for determining A1C target range. According to the US Census Bureau, in 2010 more than 42% of veterans were aged 65 years or older, so we therefore decided that a greater number of veterans with T2D would meet the criteria for an A1C target <8% (64 mmol/mol) compared with <9% (75 mmol/mol) or <7% (53 mmol/mol).⁸

Statistical Methods

Baseline characteristics for veterans at initiation of insulin following trials of the GLAs were reported as the mean and SD. Descriptive statistics were performed for all outcome variables. To reduce potential bias from extreme values, BMI and lowest A1C post insulin were winsorized at the 99th level in calculating the mean (ie, BMIs below the 1st percentile were set to equal to the 1st percentile BMI, and BMIs above the 99th percentile were set to equal to the 99th percentile). All data were analyzed using SPSS, version 21 (IBM, Armonk, New York).

RESULTS

There were 90,497 veterans with T2D who met the inclusion criteria. **Table 2** describes their demographic characteristics along with GLA classes, type of insulin initiated, and final A1C post insulin for the overall population and each cohort. Most veterans in this study were white males; the mean age was 62.8 years. The mean BMI was 32.9, which matches World Health Organization Obe-

sity Class I. Most veterans included in the study population lived in the South (37%), and the least number of veterans lived in the Northeast (14%).

The number of veterans receiving 1, 2, 3, or >3 GLAs was 10,728, 49,860, 23,747, and 5380, respectively. More than 55% of the study population received a trial of 2 GLAs and 26% received a trial of 3 GLAs before starting insulin. Veterans receiving 3 or more GLAs were, on average, 2 to 3 years older than those receiving 2 or less. Nearly 75% of veterans aged under 60 years started insulin after a trial of 1 or 2 GLAs, while about 35% of veterans 60 years or older were found to start insulin after a trial of 3 or more GLAs.

Insulin was initiated in the total study population at a mean A1C—the most recent measurement within 60 days before starting insulin—of 9.9% (85 mmol/mol). Veterans with only 1 GLA trial started insulin with the highest mean A1C at 10.3% (89 mmol/mol) while veterans receiving trials of 3 or more GLAs started insulin with the lowest A1C at 9.6% (81 mmol/mol). The majority of veterans received 2 GLA trials and started insulin with a mean A1C of 9.9% (85 mmol/mol).

Most veterans were started on a basal-only insulin regimen. However, veterans receiving 1 GLA trial were more likely to initiate bolus, or a combination of basal and bolus insulin, compared with the other 3 cohorts. Months from the first GLA prescription to insulin initiation increased with the number of GLA trials and prolonged the time veterans were exposed to A1C >8% (64 mmol/mol) (**Figures 1 and 2**).

Veterans who received 1 GLA trial started insulin after a mean of 28 months. On average, their A1C was >8% (64 mmol/mol) for 5 months prior to starting insulin. Time to insulin from first GLA prescription increased considerably—to a mean of 60 months—for veterans who received 2 GLAs. The A1C in these veterans was >8% (64 mmol/mol) for 11 consecutive months prior to insulin initiation. After 84 months, veterans in the 3-GLA cohort started insulin, but an additional 10 months lapsed before veterans in the >3-GLA cohort were started. For veterans receiving 3 or >3 GLAs, their A1C was >8% (64 mmol/mol) for 14 and 15 consecutive months, respectively, prior to insulin initiation. In all study patients, the addition of insulin improved the A1C to its lowest value of 7.4% (57 mmol/mol) in 14.5 months. However, it took an additional month to reach the lowest value in veterans with >3 trials of GLAs.

Table 2. Characteristics of Veterans With Type 2 Diabetes Starting Insulin

	Overall Population, N = 90,497	1 GLA Class, n = 10,728	2 GLA Classes, n = 49,860	3 GLA Classes, n = 23,747	>3 GLA Classes, n = 5380
Age, years ± SD	62.8 ± 10	61.8 ± 11.3	61.9 ± 9.9	64.5 ± 9.5	65.2 ± 9.2
Age category, %					
<50 years	8.8	12.6	10	5.8	4.3
50-59 years	23.1	25.1	25.1	19.3	18.1
60-69 years	46.9	41.7	46.9	48.5	49.8
≥70 years	21.2	20.6	18	26.4	27.8
Gender					
Male, %	96.2	96.1	95.8	96.8	96.7
BMI winsorized	32.9 ± 6.5	32.9 ± 6.8	32.9 ± 6.5	32.9 ± 6.4	32.8 ± 6.3
Region, % ^a					
West	18.5	18.4	17.9	19.1	21.5
Midwest	25.8	23.9	25.5	26.8	28.4
South	36.9	38.3	38.6	34.7	28.3
Northeast	14	14.6	13.7	14	16.2
NR	4.8	4.8	4.3	5.4	5.6
Race, %					
Black	16.3	20.7	17	13.7	12.9
White	69.6	66.8	69.4	71	71.3
Other ^b	14.1	12.5	13.6	15.3	15.8
GLA class prior to insulin, %					
Metformin	93.3	58.9	97.3	99.2	99.7
Sulfonylurea	92.1	40.1	98.7	99.7	99.9
Thiazolidinedione	27.8	0.6	2.7	76.4	94.6
Alpha-glucosidase inhibitors	9.24	0.2	0.8	17	70.3
Other ^c	5.15	0.2	0.5	7.7	46
A1C at insulin initiation % (mmol/mol) ± SD	9.9 (85) ± 1.9	10.3 (89) ± 2.3	9.9 (85) ± 1.9	9.6 (81) ± 1.7	9.6 (81) ± 1.7
Type of insulin ^d initiated, %					
Basal	83.3	74.2	84.2	85.1	85.3
Bolus	6	11	5.7	4.6	4.9
Both	10.7	14.8	10.1	10.3	9.8
Lowest A1C post insulin % (mmol/mol) ± SD winsorized	7.4 (57) ± 1.2	7.2 (55) ± 1.4	7.4 (57) ± 1.2	7.4 (57) ± 1.1	7.4 (57) ± 1.1
Months to lowest A1C post insulin	14.5 ± 11.8	13.2 ± 11.1	14.2 ± 11.7	15.4 ± 12.2	15.1 ± 12.1

A1C indicates glycated hemoglobin; BMI, body mass index; GLA, glucose-lowering agent; NR, no region specified.

^aAssignment of Veterans Integrated Service Networks (VISNs) by US census geographic region: Northeast, VISNs 1-5; Midwest, VISNs 10-12, 15, and 23; South, VISNs 6-9, 16, and 17; West, VISNs 18-22; and NR indicates not reported.

^bOther indicates American Indian, Asian, unknown.

^cOther indicates amylin analog, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and meglitinides.

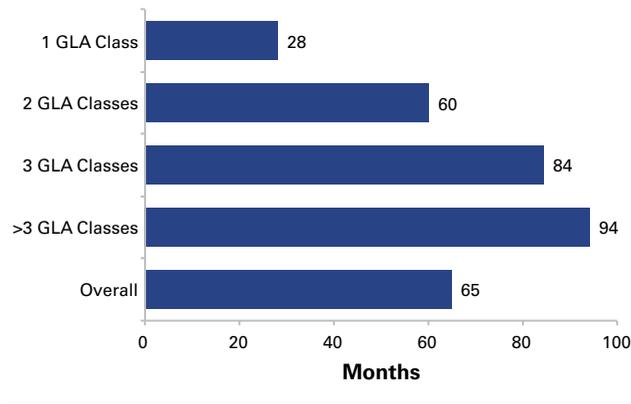
^dBasal insulins include insulin glargine, insulin detemir, neutral protamine Hagedorn, Ultralente, or Lente. Bolus insulins include insulin aspart, insulin lispro, regular, or glulisine; Both: combination of any 2 or more of the above insulins or Humulin 70/30, Humalog Mix 50/50, NovoLog 70/30, Humalog Mix75/25.

DISCUSSION

Analysis found the use of multiple GLAs did not clinically impact A1C at insulin initiation. On average, vet-

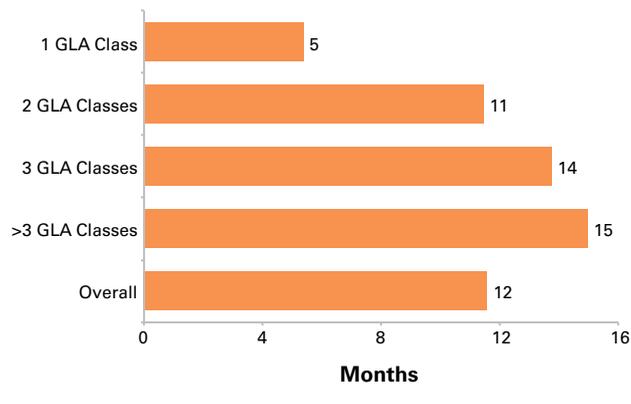
erans delayed starting insulin for 65 months while A1C remained above treatment goals. Two-thirds of patients started insulin after receiving a trial of 1 or 2 GLAs, whereas the addition of 3 or more GLAs further delayed

Figure 1. Months to Insulin Initiation



GLA indicates glucose-lowering agent.

Figure 2. Consecutive Months With A1C >8% (64 mmol/mol) Prior to Insulin Initiation



A1C indicates glycated hemoglobin; GLA, glucose-lowering agent.

insulin initiation. When compared with the overall mean, patients who received >3 GLAs delayed their use of insulin by an additional 29 months and were exposed to 15 consecutive months of poor glycemic control. In accordance with the VA/DoD practice guidelines, the most common 2-class combination of GLAs, prior to starting insulin, was metformin with a sulfonylurea. The newer agents, dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists, were most commonly prescribed for those veterans in the >3-GLA cohort. It was more common for older veterans (aged >60 years) to receive a trial on 3 or more GLAs compared with younger veterans. This finding may reflect implementation of recommendations from the ADA/AGS consensus statement.

Previous large-scale studies have shown similar findings on delaying insulin therapy. Kostev and colleagues

examined data in the United Kingdom and Germany to determine whether time to insulin therapy had changed from 2005 to 2010⁹; they found that the median time to insulin initiation significantly increased in both countries. In addition, there was a significant increase in the A1C measured prior to insulin initiation in 2010 compared with in 2005 (8.4% [68 mmol/mol] vs 8.2% [66 mmol/mol]; $P < .001$ in Germany; and 9.8% [84 mmol/mol] vs 9.5% [80 mmol/mol]; $P < .001$ in the United Kingdom). The authors speculated that the decision to use new diabetes medications instead of starting insulin may have contributed to these higher A1Cs and delayed insulin initiation.⁹

Khanti and colleagues studied the time to treatment intensification in individuals with T2D treated with 1, 2, or 3 oral antidiabetes drugs, and the associated levels of glycemic control. For patients taking 1, 2, or 3 oral antidiabetic agents, median time to intensification with insulin was 7.1, 6.1, or 6.0 years, respectively.¹⁰ A retrospective study involving 14,824 people with T2D between 1995 and 2005 observed that the median time to insulin initiation for people prescribed multiple oral antidiabetic agents was 7.7 years, and the mean A1C before insulin was 9.85% (84 mmol/mol).¹¹

The costs associated with T2D are significant, as several studies have reported a strong association between costs and diabetes control.^{3,12} Between 1998 and 2003, annual diabetes costs increased 24% when comparing patients with an A1C $\leq 7\%$ with patients with an A1C $> 9\%$.¹² More recently, a trial reported by Aagren and Luo of 34,469 patients with T2D found that a 1 percentage point increase in A1C corresponded to a 4.4% increase in diabetes-related costs, whereas a 1 percentage point drop in A1C was associated with a 4.2% reduction in costs.¹³ Levin and colleagues reviewed 51,771 patients to examine both efficacy and costs when patients added a third agent to their regimen of 2 oral antidiabetic drugs.¹⁴ They found that patients who added insulin had the greatest reduction in A1C, and after 2 years, they saw an 11% reduction in their diabetes-related healthcare costs. Costs increased for patients who delayed insulin initiation by adding a noninsulin agent (oral agent or GLP-1). After 2 years, patients on 3 oral agents saw their diabetes-related healthcare costs increase by 46%, whereas the costs for patients who added a GLP-1 increased 72%.¹⁴

This study did not report on the cost burden associated with T2D in the VAHCS; however, there is a known association between improved diabetes control and lower healthcare costs. In this study, patients who started insulin after 2 GLAs experienced a 2.5 percentage point drop in A1C over an average of 14 months.

The report from Aagren and Luo indicates this improvement in A1C would result in substantial cost savings.¹³ Delaying insulin for a third GLA resulted in 3 more consecutive months of poorer glucose control, a 24-month delay in insulin initiation, and a 15-month lapse before patients achieved their lowest A1C post insulin initiation. This duration of prolonged hyperglycemia would be expected to increase diabetes-related healthcare costs for the VAHCS.

Limitations

This study has several limitations. First, poor glycemic control was defined as an A1C >8% (64 mmol/mol), but providers could have established higher glycemic targets for their patients. This may especially be true for the 21% of veterans 70 years or older in the analysis. Second, the date of first GLA trial was determined by provider entry of VA electronic prescription. Veterans may have started therapy prior to entering the VAHCS. To control for this, only veterans with a documented A1C in the VAHCS lab package 60 days prior to the date of first GLA prescription were included. Third, the ability of veterans to receive prescriptions outside the VAHCS might have influenced the analysis in multiple ways. A veteran may have requested to purchase a GLA outside the VA system, especially if the non-VA cost was less expensive. In addition, the accuracy of the date of insulin initiation and corresponding A1C level were dependent on VA prescription data. To overcome this, the study population was limited to those veterans who received a prescription for a GLA within 6 months prior to first VA insulin prescription. Fourth, the analysis did not report duration of diabetes because of concerns with timely ICD-9-CM coding in relation to ADA diagnostic criteria for T2D. Despite these limitations, the veterans with T2D in the analysis comprise a good representation of clinical practice and diabetes control within a closed formulary system.

CONCLUSIONS

In this study, the decision to use multiple GLAs delayed the escalation to insulin and resulted in prolonged months of hyperglycemia. Reluctance to start insulin (“clinical inertia”) is influenced by both patient and provider factors.¹⁰ Patients may be reluctant to start insulin due to fears of hypoglycemia, weight gain, and the pain of self-injections. Conflicting literature on the benefits of insulin treatment may contribute to a provider’s inertia surrounding insulin initiation. The landmark United Kingdom Prospective Diabetes Study (UKPDS) trial

showed a reduced risk of microvascular complications and nonfatal myocardial infarction in patients with T2D receiving metformin, a sulfonylurea, or insulin to achieve A1C goals early in the disease process.¹⁵ This trial clearly demonstrates the benefit in achieving glycemic control prior to prolonged periods of hyperglycemia.

More recently, large-scale studies—including Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE), and the Veterans Affairs Diabetes Trial—showed reduced benefit with intensification in patients with longstanding T2D and poor glycemic control. The ADVANCE trial reported that tight glucose control in T2D resulted in no significant reduction in the incidence of retinopathy or macrovascular complications. In the ACCORD trial, the glycemic control arm was halted early after an increased mortality rate in the intensive group was observed. The difference in benefits between UKPDS and the more recent large-scale trials suggests maximal benefit results when glycemic control is achieved prior to prolonged periods of hyperglycemia.¹⁵

The use of multiple glucose-lowering drug classes was associated with a numerical, but not a clinical, difference in A1C at insulin initiation. This delay in initiating insulin in veterans with T2D results in prolonged periods of poor glycemic control, which may lead to increased negative health and economic outcomes.

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REFERENCES

1. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. CDC website. <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>. Accessed March 16, 2016.
2. Close to 25 percent of VA Patients have diabetes. Veterans Health Administration website. <http://www.va.gov/health/NewsFeatures/20111115a.asp>. Accessed March 16, 2016.
3. The cost of diabetes. American Diabetes Association website. <http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html>. Published October 2013. Updated June 22, 2015. Accessed March 16, 2016.

4. American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.
5. VA/DoD clinical practice guideline for the management of diabetes mellitus. US Department of Veterans Affairs website. http://www.healthquality.va.gov/guidelines/CD/diabetes/DM2010_FUL-v4e.pdf. Published 2010. Accessed March 16, 2016.
6. Kirkman MS, Briscoe VJ, Clark N, et al; Consensus Development Conference on Diabetes and Older Adults. Diabetes in older adults: a consensus report. *J Am Geriatr Soc*. 2012;60(12):2342-2356. doi: 10.1111/jgs.12035.
7. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364-1379. doi: 10.2337/dc12-0413.
8. American Indian and Alaska Native servicemembers and veterans. Department of Veteran Affairs website. http://www.va.gov/TRIBALGOVERNMENT/docs/AIAN_Report_FINAL_v2_7.pdf. Published September 2012. Accessed March 13, 2016.
9. Kostev K, Rathmann W. Changes in time to insulin initiation in type 2 diabetes patients: a retrospective database analysis in Germany and UK (2005-2010). *Prim Care Diabetes*. 2013;7(3):229-233. doi: 10.1016/j.pcd.2013.03.003.
10. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care*. 2013;36(11):3411-3417. doi: 10.2337/dc13-0331.
11. Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. *Br J Gen Pract*. 2007;57(539):455-460.
12. Banerji MA, Dunn JD. Impact of glycemic control on healthcare resource utilization and costs of type 2 diabetes: current and future pharmacologic approaches to improving outcomes. *Am Health Drug Benefits*. 2013;6(7):382-392.
13. Aagren M, Luo W. Association between glycemic control and short-term healthcare costs among commercially insured diabetes patients in the United States. *J Med Econ*. 2011;14(1):108-114. doi: 10.3111/13696998.2010.548432.
14. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. *J Manag Care Spec Pharm*. 2014;20(5):501-512.
15. Skyler JS, Bergenstal R, Bonow RO, et al; American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care*. 2009;32(1):187-192. doi: 10.2337/dc08-9026. ■

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