Use of Intensive Glycemic Management in Older Adults with Diabetes Mellitus

Suzanne V. Arnold, MD, MHA,[*†] *Kasia J. Lipska, MD,*[‡] *Jingyan Wang, MS,*[*†] *Leo Seman, MD, PhD,*[§] *Sanjeev N. Mehta, MD, MPH,*[¶] *and Mikhail Kosiborod, MD*[*†]

OBJECTIVES: To examine the proportion of older adults with diabetes mellitus treated with tight glucose control and the factors associated with this practice.
DESIGN: Cross-sectional analysis.
SETTING: Outpatient sites in the Diabetes Collaborative Registry (N=151).
PARTICIPANTS: Adults aged 75 and older with type 2 diabetes mellitus (N=42,669).
MEASUREMENTS: Participants were categorized based on glycosylated hemoglobin (HbA1c) and glucose-lowering medications: poor control (HbA1c >9%), moderate control (HbA1c 8–9%), conservative control (HbA1c 7–8%), tight control (HbA1c <7%) with low-risk agents (low risk for hypoglycemia), tight control with high-risk agents, and diet control (HbA1c <7% taking no glucose-lowering medications). We used hierarchical logistic regression to examine participant and site factors associated with tight control and high-risk agents versus conservative or tight control and low-risk agents.
RESULTS: Of 30,696 participants without diet-controlled diabetes, 5,596 (18%) had moderate or poor control, 9,227 (30%) had conservative control, 7,893 (26%) had tight control taking low-risk agents, and 7,980 (26%) had tight control taking high-risk agents. Older age, male sex, heart failure, chronic kidney disease, and coronary artery disease were each independently associated with greater odds of tight control with high-risk agents. There were no differences according to practice specialty (endocrinology, primary care, cardiology) in how aggressively participants were managed.
CONCLUSION: One-quarter of U.S. older adults with type 2 diabetes mellitus are tightly controlled with glucose-lowering medications that have a high risk of hypoglycemia. These results suggest potential overtreatment of a substantial proportion of people and should encourage further efforts to translate guidelines to daily practice. **J Am Geriatr Soc 66:1190–1194, 2018.**

Key words: diabetes mellitus; glucose control; hypoglycemia

The aging of the population has largely driven the epidemic growth of diabetes mellitus in the United States, where it is estimated that 26% of adults aged 65 and older have diabetes mellitus,[1] but glycemic management in older adults has unique challenges. Tight glucose control reduces the risk of microvascular complications,[2] but these benefits are counterbalanced by more hypoglycemia, which is a natural consequence of tight glucose control, particularly with the use of insulin-providing medications, counterbalance these potential benefits. Because older adults are less likely to benefit and more likely to be harmed from tight glucose control, the American Diabetes Association guidelines have suggested, at least since 2004, that treatment targets should be relaxed in older adults with diabetes, with particular attention to minimize hypoglycemia.[3,4] After the Action to Control Cardiovascular Risk in Diabetes trial showed an increase in mortality with intensive glucose control,[5] the Veterans Administration in 2010[6] and the European Diabetes Working Party for Older People in 2011[7] also recommended higher glycosylated hemoglobin (HbA1c) targets in older adults with diabetes, with the American Diabetes Association strengthening their recommendation in 2012,[1] but prior studies have shown that this guidance has not translated effectively to clinical practice, with frequent use of intensive management in older adults with diabetes.[8–10] Over the last decade, there has been a marked increase in the number of glucose-lowering medications that confer

From the *Department of Cardiology, Saint Luke's Mid America Heart Institute; †University of Missouri-Kansas City, Kansas City, Missouri; ‡Section of Endocrinology, Dept of Internal Medicine, School of Medicine, Yale University, New Haven, Connecticut; §Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut; and the ¶Joslin Diabetes Center, Boston, Massachusetts.

Presented at The American Heart Association Quality of Care and Outcomes Research Scientific Sessions in Washington DC on April 7, 2018

Address correspondence to Suzanne V. Arnold, MD, MHA, Saint Luke's Mid America Heart Institute, 4401 Wornall Rd., Kansas City, MO 64111. E-mail: suz.v.arnold@gmail.com

DOI: 10.1111/jgs.15335

0002-8614/18/$15.00

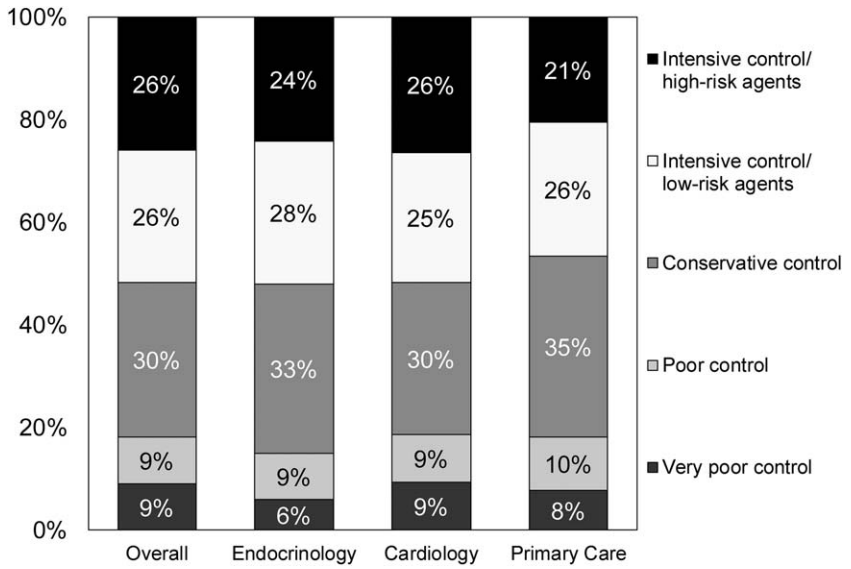

Figure 1. Proportions of older adults treated with different categories of glucose control. Overall and stratified according to site specialty. Poor control: glycosylated hemoglobin (HbA1c) ≥9%; moderate control: HbA1c 8 to <9%; conservative control: HbA1c 7 to <8%; tight control with low-risk agents: HbA1c <7% taking only glucose-lowering medications with low risk of hypoglycemia; tight control with high-risk agents: HbA1c <7% taking ≥1 glucose-lowering medications with high risk of hypoglycemia. Individuals with HbA1c <7% on diet only were not included.

negligible risk of hypoglycemia, expanding the menu of safer treatment options. To investigate whether these newer treatment options, along with updated guideline statements,[4,6,7] have shifted glucose management of older adults, we used a large U.S. outpatient database of adults with diabetes to examine contemporary practice patterns of glycemic control and to examine factors that might contribute to these treatment choices.

METHODS

Patient Population

The Diabetes Collaborative Registry is a U.S. quality improvement registry that was designed to describe the outpatient care of diabetes through the spectrum of primary and specialty care.[11] Data are extracted from electronic health records using an automated system integration solution. For the current study, data were examined from 2014 to 2016, with the most recent visit used for each patient. The present analyses were limited to individuals aged 75 and older with type 2 diabetes mellitus and available HbA1c data. Because participation in the registry requires no data collection beyond that of routine clinical care and all collected data are de-identified, Chesapeake Research Review Incorporated granted a waiver of written informed consent and authorization for this study.

Statistical Analysis

Participants were divided into categories of glycemic management: diet control (HbA1c <7% taking no glucose-lowering medications), tight control with high-risk agents (HbA1c <7% taking insulin, sulfonylurea, or meglitinides), tight control with low-risk agents (HbA1c <7% taking medications with low risk for hypoglycemia: metformin, dipeptidyl peptidase 4 inhibitors, thiazolidinedione, sodium-glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, alpha-glucosidase inhibitors, colesevelam, or bromocriptine only (no high-risk medications)), conservative control (HbA1c 7–8%), moderate control (HbA1c 8–9%), and poor control (HbA1c >9%). We compared demographic and clinical factors of these groups using chi-square tests for categorical variables and one-way analysis of variance for continuous variables.

We used multivariable hierarchical logistic regression to examine factors associated with tight control with high-risk agents. For this analysis, we excluded individuals with diet control and moderate or poor control. Covariates in the model included age, sex, heart failure, chronic kidney disease (glomerular filtration rate <30 mL/min per 1.83 m^2, dialysis, or (if glomerular filtration rate unavailable) a chart diagnosis of chronic kidney disease), coronary artery disease, and site specialty (endocrinology, cardiology, primary care). Site was included as a random effect to account for participant clustering within sites. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Of 42,669 individuals with type 2 diabetes mellitus aged 75 and older, 11,973 (28.1%) had diet-controlled diabetes, 15,873 (37.2%) had tight control, 9,227 (21.6%) had conservative control, 2,750 (6.4%) had moderate control, and 2,846 (6.7%) had poor control. Of individuals with tight control, half were taking medications with a high risk of hypoglycemia (26% of all patients not diet controlled). Individuals treated by endocrinologists were less likely to have poor glycemic control, and those treated by

Table 1. Participant Characteristics Stratified According to Glycemic Control

Characteristic	Poor Control, n = 2,750	Moderate Control, n = 2,846	Conservative Control, n = 9,227	Tight Control with Low-Risk Agents, n = 7,893	Tight Control with High-Risk Agents n = 7,980	Diet Control, n = 11,973
Age, mean ± SD	81.3 ± 5.0	80.8 ± 4.7	81.2 ± 4.9	80.7 ± 4.7	81.7 ± 5.0	81.9 ± 5.1
Female, %	47.3	46.0	44.9	46.8	43.4	51.1
White, %	89.4	89.0	89.8	89.4	89.1	90.3
Body mass index, kg/m^2, mean ± SD	29.6 ± 6.1	30.4 ± 6.1	29.8 ± 5.7	29.1 ± 5.6	29.6 ± 5.9	28.3 ± 5.5
Smoking history, %	47.1	47.6	47.6	47.7	49.5	46.5
Hypertension, %	91.5	92.3	90.9	91.5	91.6	92.0
Systolic blood pressure, mmHg, mean ± SD	129.1 ± 18.9	130.8 ± 18.7	130.3 ± 17.9	129.9 ± 17.5	129.4 ± 18.2	130.5 ± 17.9
Diastolic blood pressure, mmHg, mean ± SD	69.9 ± 10.4	69.8 ± 10.0	70.0 ± 10.0	71.0 ± 9.9	69.2 ± 10.1	71.5 ± 10.0
Chronic kidney disease, %	12.8	10.8	9.4	4.1	12.1	7.4
Coronary artery disease, %	71.9	71.1	69.2	62.4	70.7	59.4
Peripheral arterial disease, %	28.7	26.4	24.8	20.2	26.6	22.5
Prior stroke, %	16.7	13.9	12.6	12.0	13.9	13.1
Heart failure, %	41.1	36.2	33.4	25.6	38.1	29.4
Atrial fibrillation, %	41.2	36.9	35.0	33.1	38.8	34.6
Glycosylated hemoglobin, %, mean ± SD	10.6 ± 1.2	8.5 ± 0.3	7.4 ± 0.3	6.2 ± 0.4	6.3 ± 0.4	6.0 ± 0.4
Number of glucose-lowering medications, mean ± SD	1.6 ± 1.3	1.9 ± 1.2	1.7 ± 1.1	1.2 ± 0.5	1.9 ± 0.9	0.0 ± 0.0
Insulin, %	42.2	47.0	29.5	0.0	30.9	NA
Metformin, %	45.1	52.2	54.8	86.2	47.9	NA
Sulfonylurea, %	39.2	49.7	44.4	0.0	76.5	NA
Thiazolidinedione, %	11.0	11.1	9.9	11.1	10.9	NA
Dipeptidyl peptidase-4inhibitor, %	17.2	21.0	18.7	17.6	16.4	NA
Glucagon-like peptide-1 receptor agonist, %	3.3	4.6	2.8	1.6	2.0	NA
Sodium-glucose co-transporter 2 inhibitor, %	2.0	3.6	2.0	1.4	0.9	NA
other glucose-lowering medications, %	4.3	4.7	4.3	2.8	6.6	NA

P<.001 for all comparisons except white race (p = .11) and hypertension (p = .05).
SD = standard deviation; NA = not applicable.

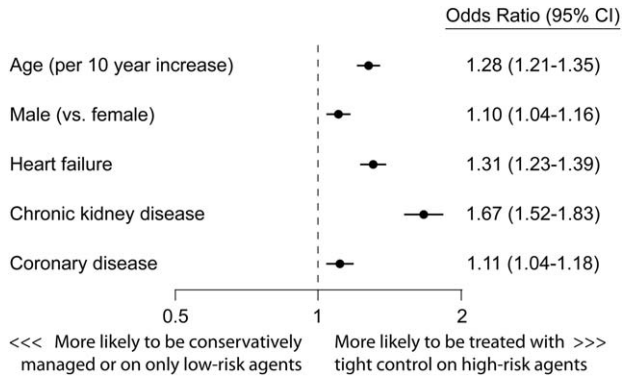

Figure 2. Factors associated with tight glycemic control in individuals taking high-risk agents. Individuals with diet control, moderate control, or poor control were not included in this analysis.

primary care physicians were more likely to be conservatively managed (Figure 1).

Individuals with tight control taking high-risk agents were older and had a high burden of comorbidities (Table 1). They were treated with an average of 1.9±0.9 glucose-lowering medications, and mean HbA1c was 6.3±0.4%. Individuals with tight control taking low-risk agents were taking an average of 1.2±0.5 glucose-lowering medications, which was most often metformin (86.2%). In the multivariable model, older age, male sex, heart failure, chronic kidney disease, and coronary artery disease were each independently associated with greater odds of tight control with high-risk agents (Figure 2). After adjusting for these factors, there were no differences between specialties in how aggressively individuals were managed (p=.40).

DISCUSSION

In a large U.S. outpatient cohort, one-quarter of older adults with type 2 diabetes that was not controlled with diet alone were managed with tight control with medications that have a high risk of hypoglycemia. Contrary to expectations, older age and comorbidities were associated with greater likelihood of tight glucose management with high-risk agents, which runs counter to guideline recommendations for more conservative management in these individuals.[4,6,7] Despite greater availability of agents that do not typically cause hypoglycemia, insulin or insulin secretagogues continue to be used at high rates in older adults, even when HbA1c levels are low. These results suggest potential overtreatment of a substantial proportion of older adults with diabetes.

When managing risk factors, physicians often focus on achieving particular targets (e.g., HbA1c, blood pressure, cholesterol), but older adults may not derive the same benefits from risk factor control as younger individuals—especially when the risk factor takes years to exert its influence on outcomes, whereas treatment of the risk factor has immediate potential for harm. It is for this reason that most risk factor quality metrics do not apply to individuals aged 75 and older, although many providers are unaware of this distinction or are fearful of causing harm or even being exposed to liability if they de-escalate therapy in older adults.[12] Tight glucose control reduces the risk of microvascular (and perhaps macrovascular) events, but it is likely that it takes over 10 years of tight glycemic control to realize any benefit.[2] Tight glucose control markedly increases the risk of hypoglycemia—a risk that is even greater in older adults who have defective glucose counter-regulation, multiple comorbidities, and polypharmacy.[13] Hypoglycemia is not just a benign nuisance, but is also associated with greater risk of myocardial infarction, heart failure, stroke, cardiovascular death,[14] falls, fractures, and dementia, in addition to its adverse effects on quality of life and higher healthcare costs.[13,15]

Our data show that efforts are needed to more efficiently transfer the guideline recommendations to daily practice. Busy healthcare providers may be challenged to identify optimal diabetes treatment strategies in older adults with multiple comorbidities, given the need to address numerous, frequently revised evidence-based guidelines and quality metrics. This is even more challenging when de-escalation is the evidence-based recommendation, because guidelines often use vague or cautionary language (e.g., "glycemic goals for some older adults might be reasonably relaxed, using individual criteria"). Furthermore, although quality metrics for risk factor management often do not apply to older adults, there are no incentives or specific metrics to cut back on therapy. Future work should focus on generating better evidence on when, how, and in whom to de-intensify and on ensuring that incentives align with these recommendations.

There are potential limitations to our work that should be considered. First, because all Diabetes Collaborative Registry sites participate voluntarily in the registry, which is designed for quality improvement, our results may not represent general care of individuals with diabetes in the United States. Second, other factors might have justified tight control in some of the older adults in this study, including longer life expectancy despite the presence of comorbidities and individual values and preferences about treatment. Third, the greater use of insulin and sulfonylureas in individuals with comorbidities may reflect concerns about cardiac or renal safety with metformin and the emerging medications (even though several of these medications have demonstrated cardiovascular and nephroprotective benefits across the range of age, comorbidity burden, and moderate chronic kidney disease). Nevertheless, although providers might be uncomfortable using these classes of medications in older adults with comorbidities, this does not explain why these individuals are treated to a low HbA1c target. In individuals who may be eligible only for glucose-lowering medications with higher risk of hypoglycemia, conservative glycemic targets are even more important. Finally, we were unable to identify harms of tight control with high-risk agents, because hypoglycemia events are poorly captured in outpatient electronic health records.

We found that 26% of older adults with diabetes that was not controlled with diet alone had HbA1c levels lower than 7% while being treated with medications that have a high risk for hypoglycemia. Despite evidence of greater risk of harm without substantial clinical benefit, it appears that tight glycemic control with high-risk agents remains prevalent in older adults with multiple comorbidities. Further efforts are needed to provide more specific

guidance on how to safely treat older adults with diabetes (through targeting treatment with low-risk agents and de-escalation of glucose control) and then to translate that guidance efficiently into busy clinical practice.

ACKNOWLEDGMENTS

Financial Disclosure: The Diabetes Collaborative Registry is funded by AstraZeneca (founding sponsor) and Boehringer Ingelheim. Corporate sponsors had no role in data analysis or interpretation, manuscript development, or in publication review or approval for this study.

Conflict of Interest: LS: Employee of Boehringer Ingelheim Pharmaceuticals; MK: Research grants from AstraZeneca, Boehringer Ingelheim; other research support from AstraZeneca; consulting honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi, Amgen, GSK, Merck (Diabetes), Eisai, Intarcia, Novartis,Glytec and ZS Pharma. KL: Research grants from National Institutes of Health, support from Centers for Medicare and Medicaid Services to develop and maintain publicly reported quality measures. The remaining authors report no relevant disclosures to the current manuscript.

Author Contributions: SVA and JW had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. SVA conceived of the study idea, developed the analytic framework, and directed the analysis. SVA, SNM, and MK acquired the data. JW performed statistical analysis. SVA, KJL, JW, LS, SNM, and MK made important intellectual contributions to analytic design and interpretation of the results. SVA drafted the manuscript. KJL, JW, LS, SNM, and MK provided critical revision of the manuscript for important intellectual content.

REFERENCES

1. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–2664.
2. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589.
3. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: Implications of recent clinical trials. Ann Intern Med 2011;154:554–559.
4. American Diabetes Association. Standards of medical care in diabetes: Pharmacologic approaches to glycemic treatment. Diabetes Care 2017;40:S64–S74.
5. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559.
6. VA/DOD Clinical Practice Guidelines: Management of Diabetes Mellitus in Primary Care. U.S. Department of Veterans Affairs. 2017. Available from www.healthquality.va.gov/Diabetes_Mellitus.asp Accessed 28 December 2017
7. Sinclair AJ, Paolisso G, Castro M et al. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. Executive summary. Diabetes Metab 2011;37 Suppl 3:S27–S38.
8. Lipska KJ, Ross JS, Miao Y, Shah ND, Lee SJ, Steinman MA. Potential overtreatment of diabetes mellitus in older adults with tight glycemic control. JAMA Intern Med 2015;175:356–362.
9. Tseng CL, Soroka O, Maney M, Aron DC, Pogach LM. Assessing potential glycemic overtreatment in persons at hypoglycemic risk. JAMA Intern Med 2014;174:259–268.
10. Sussman JB, Kerr EA, Saini SD, et al. Rates of deintensification of blood pressure and glycemic medication treatment based on levels of control and life expectancy in older patients with diabetes mellitus. JAMA Intern Med 2015;175:1942–1949.
11. Arnold SV, Inzucchi SE, McGuire DK, et al. Evaluating the quality of comprehensive cardiometabolic care for patients with type 2 diabetes in the U.S.: The Diabetes Collaborative Registry. Diabetes Care 2016;39:e99–e101.
12. Caverly TJ, Fagerlin A, Zikmund-Fisher BJ et al. Appropriate prescribing for patients with diabetes at high risk for hypoglycemia: National survey of Veterans Affairs health care professionals. JAMA Intern Med 2015;175:1994–1996.
13. Boulin M, Diaby V, Tannenbaum C. Preventing unnecessary costs of drug-induced hypoglycemia in older adults with type 2 diabetes in the United States and Canada. PLoS One 2016;11:e0162951.
14. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: Systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533.
15. Lipska KJ, Ross JS, Wang Y et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med 2014;174:1116–1124.