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Optimizing treatment goals for long-term health outcomes among patients with type 2 diabetes mellitus

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ABSTRACT

Introduction Considerable confusions on treatment target have resulted from recent changes in guidelines. Evidence in medical guidelines came from clinical trials with highly selected patients, whereas treatment goals may differ in some subgroups. This study aimed to assess optimal treatment goals (A1C, blood pressure, low-density lipoprotein cholesterol (LDL-C)) for patients with type 2 diabetes mellitus (T2DM), which lead to optimal health outcomes by different treatment strategies.

Research design and methods A retrospective longitudinal study was conducted for veterans with T2DM by using US Veterans Affairs Administrative Database (2005–2015). Medical records were prepared for repeated evaluation performed at 6-month intervals and multivariate longitudinal regression was used to estimate the risk of microvascular and macrovascular complication events. Second-degree polynomial and splines were applied to identify the optimal goals in their associations with lowest risk of clinical outcomes, controlling for demographic characteristics, medical history, and medications.

Results A total of 124 651 patients with T2DM were selected, with mean of 6.72 follow-up years. In the general population, to achieve the lowest risk of microvascular and macrovascular complication, the optimal goals were A1C=6.81%, LDL-C=109.10 mg/dL; and A1C=6.76%, LDL-C=111.65 mg/dL, systolic blood pressure (SBP)=130.60 mmHg, respectively. The optimal goals differed between age and racial subgroups. Lower SBP for younger patients and lower LDL-C for black patients were associated with better health outcomes.

Conclusions Optimal treatment goals were identified and multi-faceted treatment strategies targeting hyperglycemia and hyperlipidemia and hypertension may improve health outcome in veterans with T2DM. In addition to guidelines' recommended goals, health systems may examine their own large diverse patients with T2DM for better quality of care.

Significance of this study

What is already known about this subject?

⇒ Medical societies have changed their guidelines in treatment targets of hemoglobin A1c, blood pressure (BP), and low-density lipoprotein cholesterol (LDL-c) in diabetes management.

What are the new findings?

⇒ The study estimated the three diabetic management goals (A1C, BP, and LDL-C) in relation to diabetes complications in veteran populations and subpopulations.

⇒ Optimal treatment goals of A1C, LDL-C, and BP were identified for diabetes management in US veterans with T2DM.

How might these results change the focus of research or clinical practice?

⇒ Multi-faceted treatment strategies targeting hypertension, hyperglycemia, and hyperlipidemia may reduce microvascular/macrovascular complication risk and improve health outcomes in the population with T2DM.

INTRODUCTION

Controls for hemoglobin A1c (A1C), blood pressure (BP), and low-density lipoprotein cholesterol (LDL-C) are associated with lowering risk of diabetes complications among patients with type 2 diabetes mellitus (T2DM).[1] Optimizing long-term health outcomes is meaningful for decision-making for health providers and patients with T2DM. For managing T2DM and preventing complications, medical guidelines have been developed with specifications on A1C, BP, and LDL-C treatment goals. The American Diabetes Association (ADA) recommends an A1C less than 7% for most non-pregnant adults with T2DM, but this goal should be 'individualized' to a more stringent goal of 6.5%, or less stringent goal of 8%, based on patients' health conditions.[2] The recommendation leaves flexibility to the healthcare providers with unclear instruction of selecting explicit goal for patients with specific demographic and medical characteristics. The American Heart Association (AHA) in 2013 recommended that specific numerical goals for lipids should be abandoned.[3] ADA recommended regular monitoring of lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) but only left recommendation of triglyceride and HDL cholesterol goal for blood lipid management.[4]

ADA and JNC 8 loosened the general goal of systolic blood pressure (SBP) from less than 140 mmHg to less than 150 mmHg, and additionally increased the goal of DBP from less than 80 mmHg to less than 90 mmHg due to no confirmed benefit found from lowering BP ≤140/80 mmHg in clinical trials.[5–7] Before the updates, the goal of lower than 130/80 mmHg was commonly recommended for adults with diabetes and hypertension in JNC 7 report 2003.[8]

Reaching A1C achievement (≤7%) has been a controversy on reducing the risk of myocardial infarction, stroke, and cardiovascular disease (CVD) death occurrences by intensive blood glucose control in long-term follow-up clinical trial study.[9 10] A1C inherently makes differentiated capacities of showing blood glucose level among patients with T2DM such as race/ethnic populations. The ACCORD trial demonstrated that the association between A1C level and the risk of hypoglycemia and mortality differs across racial groups.[11] For the BP target, the less stringent goal of BP was based on that no evidence from randomized controlled trials (RCTs) demonstrated better primary health outcomes by the intensive treatment (SBP <140 mmHg). However, reduction in the risk of stroke was detected from the ACCORD.[7] Furthermore, intensive BP control therapy showed a greater risk reduction on complications in the elder group aged ≥65 years than the younger group with T2DM but no further discussion about the standards for other age or racial subgroups.[12 13] Currently, all patients with diabetes who have LDL-C >70 mg/dL are recommended moderated or intensity statin therapy.[4] However, for patients with diabetes, the unadjusted percentages of LDL >130 mg/dL were varied by races and ethnicities.[14] The discordance between guidelines published by medical societies leads to a wide controversy about the appropriate treatment targets for T2DM. In addition, there are no clear targets for racial/ethnic and age subgroups. All these may confuse health providers and increase the treatment inertia and poor adherence in patients with T2DM. Therefore, individualized goals of A1C, BP, and LDL-C may help to provide evidence of optimizing treatment strategy properly. Finally, very few studies have considered whether long-term clinical outcomes associated with multiple risk factor reduction in the population with T2DM.[15]

This study aimed to examine the optimized goals of blood glucose, BP, and LDL-C control to reduce diabetes complications. By estimating the three diabetic management (A1C, BP, and LDL-C) in relation to the risk of complications in the populations and subpopulations, a comprehensive management program can be implemented for better long-term control for preventing diabetes-related complications.

RESEARCH DESIGN AND METHODS

Data and study design

This study was a retrospective observational study using National Veterans Affairs (VA) electronic medical record data including patient-level records of pharmacy, inpatient, outpatient, and laboratory results from January 1, 2004 to December 31, 2015. Adult patients with T2DM who had at least 2-year enrollment, no history of complications, and at least two measures of A1C, LDL-C, and BP between January 1, 2004 and December 31, 2015 were selected. Index date was defined as the date of first T2DM diagnosis during the study period. The baseline period was defined as the 12 months prior to the index date. Data were prepared with each cycle length of 6 months starting from the index date. The last cycle was allowed for ≤6 months during the follow-up period, which was defined as the time after the index date until the end date of continuous enrollment, death, or the end of study data availability.

Variable definition

The clinical outcomes defined by the ICD-CM codes were classified into macrovascular and microvascular complications (online supplemental appendix A). The clinical outcome was assessed within the cycle. All clinical outcomes can be recurrent.

Age, gender, and race/ethnicity were identified on index date. Body mass index (BMI) and other comorbidities and health conditions including smoking status, mental health, renal disease, hypertension, hyperglycemia, and hyperlipidemia were evaluated at baseline (online supplemental appendix B).

Medications, BP, and laboratory results (A1C, LDL-C levels) were time-varying variables and were specified for each cycle. The use of anti-diabetic medication, antihypertensive medications, and lipid-lowering medications were assessed for each cycle (online supplemental appendix C).

The average of A1C and LDL-C estimates for each cycle were estimated using the area under the curve method.[16] In the multivariate regression analysis, the laboratory results were transformed into splines for model fitting. A1C was cut at 7%, LDL-C at 100 mg/dL, and BP at 130/90 mmHg. The original laboratory results, quadratic laboratory results, and quadratic second spline (original laboratory value – laboratory cut point) were all used for fitting the regression model to explore the potential nonlinear relationship with clinical outcomes.

Interpolation technique was used for data simulation in this study. If the value of patients' demographics or vital signs at baseline was missing, the nearest value after index date was interpolated. 'Unknown' was assigned if the there was no record for the whole study period. A1C, BP, and LDL-C result higher or lower than 5 times of the median were defined as extreme value and interpolated with corresponding study group's median.

Statistical analysis

Descriptive analysis of baseline demographic and medical characteristics, laboratory measurements, clinical outcomes, medication use, and length of follow-up period was presented by mean, median, and SD for continuous variables; and by count and proportion (%) for categorical variables. The correlation between single laboratory measurement at baseline and clinical outcome

was evaluated in univariate analysis to explore the potentially non-linear relationship. The measures of A1C, LDL-C, SBP, and diastolic blood pressure (DBP) were separately examined with the clinical outcomes of microvascular/macrovascular complication. For avoiding the extraordinary influence on the curve, the extreme values were excluded from univariate analysis.

Logistic regression with repeated measurements and splines of laboratory results was used for estimating the relationship between time-varying outcome and laboratory measurements. For better approaching the possible non-linear relationship, splines of the laboratory results were created by starting with 1 knot and second degree (polynomial). Model specification was based on clinical knowledge, literature review, and the results of model fitting. The distribution of clinical outcome in the model was considered as binomial and the link function was determined as logit.

Since the laboratory measurements, medication, and clinical outcomes were all measured separately for each cycle, within-patient measurements were likely to be correlated between cycles, whereas between-patient measurements were likely to be independent. Generalized estimating equation was selected for analyzing such discrete correlated data.

The predicted probability of getting clinical outcome was calculated for each patient. All predicted values were sorted by ascending order and the lowest probability was found. The laboratory results associated with the lowest probability of having clinical outcome were identified. To reduce the bias from one-time estimation, the estimation was bootstrapped 100 times. Mean of the laboratory results corresponding to lowest predicted probability of clinical outcome were determined as the predicted optimal laboratory results. Also, the 95% CI was determined by the 95th percentile method.

This observational study was conducted under the provisions of Privacy Rule 45 CFR 164.514(e), and was expedited for Investigational Review Board review and approval since there was no collection or use of personally identifiable information in the conduct of this study.

RESULTS

Baseline characteristics

A total of 124,651 patients with T2DM were selected as the study population (online supplemental appendix D). For the whole population, the mean follow-up time was 6.72 years (SD 3.21) and the median was 6.68 years. The average age is 62.68 years (SD 10.96) on the index date. The group aged 60–70 years has the largest proportion, 38.40% (47867), of patients. Also, 96.01% (119677) of patients were male. White race represented 67.41% (84028) of patients. The average BMI was 33.32 kg/m^2 (SD 6.44). Moreover, 15.85% (19757) of patients had tobacco usage history; 65.63% (81808) of patients had hypertension, 56.15% (69992) of patients had dyslipidemia, and 1.07% of patients had hypoglycemia at baseline.

Table 1 Demographic characteristics at baseline

Number of patients: 124 651	Mean±SD	Median
Age (years)	62.68±10.96	62.56
BMI* (kg/m^2)	33.32±6.44	32.47
Weight (lb)	223.13±46.76	217.5
Height (in.)	69.38±3.07	69.5
	N	**%**
Age		
<50	15819	12.69
(50,60)	36539	29.31
(60, 70)	47867	38.40
(70,80)	24426	19.60
BMI		
<25	30084	24.13
(25,30)	24989	20.05
≥30	69578	55.82
Male	119677	96.01
Race		
White	84028	67.41
Black	24817	19.91
Others*	4673	3.75
Unknown	11133	8.93
Comorbidity		
Obesity	28757	23.07
Tobacco	19757	15.85
Hypertension	81808	65.63
Hypoglycemia	1334	1.07
Dyslipidemia	69992	56.15
Mental disease	31711	25.44
Renal disease	9822	7.88

*Others included Native American, Asian, Indian American, Hispanic, and patients who reported their race as 'others'.
BMI, body mass index.

Also, 7.88% (9822) and 25.44% (31 711) patients were identified with renal disease and mental disease, respectively (table 1).

Multivariate analysis

For microvascular complication, A1C as 6.81% (SD 0.32) and LDL-C as 109.10 mg/dL (SD 12.03) were associated with achieving the lowest estimated risk for total population. Lower or higher values in A1C and LDL-C would increase the risk of microvascular complication, while BP had a unidirectional (not U-shaped) effect that lower SBP and higher DBP were associated with lower risk of microvascular complication for all patients. In the subgroup analysis, lower SBP and higher SBP were associated with lower risk of microvascular complication for all patients aged younger than 70 years. Lower A1C and LDL-C at 105.78 mg/dL (SD 20.31), A1C at 6.88% (SD 0.35) and LDL-C at 98.90 mg/dL (SD 10.85), and A1C at 6.58% (SD 0.22) and LDL-C at 110.12 mg/dL (SD

Table 2 Optimal laboratory measurements associated with lowest risk of microvascular complication

		A1C		LDL-C		SBP		DBP	
	n	Estimate	SD	Estimate	SD	Estimate	SD	Estimate	SD
Whole population	124651	6.81	0.32	109.10	12.03	Positive linear		Negative linear	
Subgroup									
Age									
<50	15819	Positive linear		105.78	20.31	Positive linear		Negative linear	
(50, 60)	36539	6.88	0.35	98.90	10.85	Positive linear		Negative linear	
(60, 70)	47867	6.58	0.22	110.12	17.01	Positive linear		Negative linear	
(70, 80)	24426	6.87	0.48	108.39	16.59	121.50	3.99	98.90	2.08
Race									
White	84028	6.78	0.31	118.30	18.36	Positive linear		Negative linear	
Black	24817	7.11	0.29	104.70	6.27	119.30	5.82	Negative linear	
Others	4673	9.94	1.19	Negative linear		Positive linear		Negative linear	
BMI									
<25	30084	6.69	0.33	106.95	11.61	Positive linear		Negative linear	
(25, 30)	24989	6.85	0.23	110.50	12.96	Positive linear		Negative linear	
≥30	69578	6.86	0.37	109.2	11.63	Positive linear		Negative linear	

BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

17.01) were shown with the lowest risk of microvascular complication in the model for patients in the age group of <50, 50 to 60 years old, and 60 to 70 years old, respectively. For patients aged between 70 and 80 years, A1C 6.87% (SD 0.48), LDL-C 108.39 mg/dL (SD 16.59), and BP 121.50/98.90 mmHg (SD 3.99/2.08) were associated with optimal microvascular outcome.

For white patients, A1C as 6.78% (SD 0.31), LDL-C as 118.30 mg/dL (SD=18.36), lower SBP, and higher DBP were associated with the lowest risk of microvascular complication. The optimal values were 7.11% for A1C (SD 0.29), 104.70 mg/dL (SD 6.27) for LDL-C, and 119.30 mmHg (SD 5.82) among black patients.

For the patients with BMI <25 (normal weight) to achieve lowest risk of microvascular complication, the optimal A1C was 6.69% (SD 0.33) and LDL-C was 106.95 mg/dL (SD 11.61). Also, the optimal estimation of A1C was 6.85% (SD 0.23) while LDL-C was 110.50 mg/dL (SD 12.96) for the overweight patients (25≤BMI<30). Among the obese patients, the A1C and LDL-C values with lowest risk of microvascular complication were 6.86% (SD 0.37) and 109.20 mg/dL (SD 11.63). Across all BMI groups, lower SBP and higher DBP were associated with better outcome when the specific optimal values of A1C and LDL-C were achieved (table 2)

For achieving the lowest risk of macrovascular complication (table 3), A1C at 6.76% (SD 0.24), LDL-C at 111.65 mg/dL (SD 6.78), and SBP at 130.60 mmHg (SD 6.64) were estimated as the optimal values for general T2DM population. Patients younger than 50 years were estimated to have lowest risk of macrovascular complication with A1C as 6.96% (SD 0.23), lower LDL-C, SBP as 121.1 mmHg (SD 4.75), and higher DBP. For the subgroup aged between 50 and 60 years, optimal A1C as 6.80% (SD 0.23), LDL-C as 124.25 mg/dL (SD 9.83), SBP as 124.20 mmHg (SD 5.11), and higher DBP were associated with better macrovascular outcome. Among patients aged between 60 and 70 years, A1C as 6.71% (SD 0.19), LDL-C as 131.55 mg/dL (SD 8.49), BP as 136.95 mmHg (SD 6.62), and higher DBP were associated with the lowest risk of macrovascular complication. The optimal laboratory values were 6.56% (SD 0.27) for A1C, 104.60 mg/dL (SD 6.46) for LDL-C, 134.30 mmHg (SD 6.11) for SBP, and higher DBP for patients aged between 70 and 80 years.

For white patients, the optimal laboratory values of 6.67% (SD 0.22) for A1C, 130.05 mg/dL (SD 8.42) for LDL-C, 138.85 mmHg (SD 5.77) for SBP, and higher DBP were found associated with the lowest risk of macrovascular complication. The optimal values were 6.96% (SD 0.24) for A1C, 119.80 mg/dL (SD 9.02) for LDL-C, and 122.95 mmHg (SD 5.02) for SBP for the black subgroup.

For all BMI groups, a higher DBP was associated with better outcome of macrovascular complication, while

Table 3 Optimal laboratory measurements associated with lowest risk of macrovascular complication

		A1C		LDL-C		SBP		DBP	
	N	Estimate	SD	Estimate	SD	Estimate	SD	Estimate	SD
Whole population	124651	6.76	0.24	111.65	6.78	130.6	6.64	Negative linear	
Subgroup									
Age									
<50	15819	6.96	0.23	Positive linear		121.1	4.75	Negative linear	
(50,60)	36539	6.8	0.23	124.25	9.83	124.2	5.11	Negative linear	
(60, 70)	47867	6.71	0.19	131.55	8.49	136.95	6.62	Negative linear	
(70,80)	24426	6.56	0.27	104.6	6.46	134.3	6.11	Negative linear	
Race									
White	84028	6.67	0.22	130.05	8.42	138.85	5.77	Negative linear	
Black	24817	6.96	0.24	119.8	9.02	122.95	5.02	Negative linear	
Others	4673	8.57	1.13	104.1	7.23	Positive linear		Negative linear	
BMI									
<25	30084	6.64	0.28	108.5	5.84	113.15	6.73	Negative linear	
(25,30)	24989	6.43	0.25	132.5	9.44	123.5	4.63	Negative linear	
≥30	69578	6.85	0.22	114.75	7.47	148.35	6.71	Negative linear	

BMI, body mass index; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

the A1C at 6.64% (SD 0.28), LDL-C at 108.50 mg/dL (SD 5.84), and SBP at 113.15 mmHg (SD 6.73) were estimated as the optimal values for patients with normal weight (BMI <25). For patients with BMI between 25 and 30, their optimal A1C was 6.43% (SD 0.25), LDL-C was 132.50 mg/dL (SD 0.44), and SBP was 123.50 mmHg (SD 4.63). The laboratory results associated with lowest risk of macrovascular complication for obese patients (BMI ≥30) were 6.85% (SD 0.22) for A1C, 114.75 mg/dL (SD 7.47) for LDL-C, and 148.35 mmHg (SD 6.71) for SBP.

DISCUSSION

This large-scale retrospective study with a total of 124651 patients with T2DM was selected for predicting the optimal values of major laboratory measurements with the best long-term clinical outcomes. The four risk factors (A1C, LDL-C, SBP, and DBP) as a combination associated with lowest predicted risks of clinical outcome were identified from regression models. The estimated optimal laboratory results were further analyzed for subgroups with various age, race, and BMI levels.

Most guidelines have actually moved toward 'individualized goals'. The guidelines were vague in guidance to picking a particular number of A1C, BP, and LDL-C for each individual based on some kind of decision support system, which we think is needed. This is particularly true of A1c goals where ADA, American Association of Clinical Endocrinology (AACE), and American College of Physicians had different general goals but emphasized individualization.[2 17 18] The goal setting is perhaps a bit easier in very high-risk patients such as the AACE 'extreme risk' group which may comprise individuals with diabetes following an event, or BP goals in those with nephropathy.[17] However, it is harder in people with early diabetes, no complications, and treated in primary care, such as those included in our study. Our study attempted to report what we have observed as the best outcomes, as the optimal values among the subgroup population who achieved the levels seen may be useful as a guide (without being prescriptive) for such subgroups. When it comes to individualization, there is a still long way to go.

A1C control and its optimal value

In our findings, the optimal A1C was associated with lowest risk of microvascular/macrovascular complications. There is a U-shape relationship between A1C and microvascular/macrovascular complication. Explicit evidence has been found to support that lowering A1C by proper treatment can reduce the complication rates (online supplemental appendix E). However, studies rarely talked about how low the A1C should be. In this study, for lowering the risk of microvascular and macrovascular complications, A1C between 6.5% and 7.0% was optimal for the general population with T2DM. In addition, there is no one-for-all A1C target. Also, one more crucial finding is that too tight glycemic control (<5.8%) may be harmful for patients' long-term clinical outcomes.

The microvascular complication was reduced significantly by intensive glycemic control in the ADVANCE and STENO-2 studies.[15 19] ADVANCE study demonstrated the effect of tight A1C control on microvascular complication reduction with the A1C achievement of lowering from 7.5% to 6.5%, consistent with part of our results. The STENO-2 showed only <20% patients with intensive glycemic control reached the goal of A1C<6.5%. It implied that too stringent A1C level may not have a strong correlation with better clinical outcome of vascular complications. Part of our findings were inconsistent with epidemiological analyses of the

DCCT and UKPDS studies.[1 20] The relationship between A1C and microvascular complications was curvilinear in the epidemiological studies. Lowering A1C from 7% to 6% was associated with further reduction in the risk of microvascular complications, and the absolute risk reductions became much smaller. Also, in our findings, lowering A1C even after it reached 6.8% was inversely associated with higher risk of microvascular complications. Furthermore, the UKPDS study found that intensive glycemic control contributed to lower microvascular risk, mostly reduced retinopathy. As the UKPDS study aimed at lowering fasting blood glucose, A1C of the group with intensive treatment (7%) was lower than the control group (7.9%).

While A1C is the dominant determinant in microvascular complications, glycemic control remains important in macrovascular complications. Buse *et al* have demonstrated that HbA1c lowering explains most of the reduction in events in the LEADER trial.[21] The ACCORD trial results led to confusion in some respects. Intensive glycemic control did reduce macrovascular events to a moderate degree, but this were overshadowed by the increase in mortality. The very low goals in ACCORD with aggressive medication titration, beyond what would have been done in clinical practice, may have contributed to the increase in mortality.[10 11]

In the subgroup analysis, black patients had higher optimal A1c level than white patients for achieving lowest risk of microvascular/macrovascular complication. Our findings were consistent with previous studies that higher A1C level has been found in African Americans than in white patients.[22–24] The race differences in optimal A1C levels for controlling vascular complications between black and white patients have significant clinical implications on diabetes management.[25 26] Our study also demonstrated that stringent A1C control is less appropriate for black patients with T2DM than white patients for the consideration of lowering risk of microvascular and macrovascular complications.

LDL-C control and its optimal value

This study identified the optimal LDL-C values for the veteran population with T2DM, and optimal LDL-C values were slightly higher than the commonly used goal (<100 mg/dL) and much higher than the stringent goal (<70 mg/dL). It implied that the risk of vascular complication might increase if patients achieved the old LDL-C target. White patients had higher optimal LDL-C value than black patients for achieving the lowest risk of microvascular/macrovascular complications.

The ADA guideline removed the LDL-C goal since 2015 and statin is recommended for all patients aged >40 years at different intensities.[27] The shift in blood cholesterol management followed the changing in the ACC/AHA blood cholesterol guideline, which mentioned that statin treatment can be decided by risk evaluation instead of LDL-C level.[28] Diabetes is considered as a Congenital Heart Disease (CHD) equivalent for lipid management. Therefore, patients with T2DM were widely recommended with lipid control treatment, without evaluating the level of LDL-C.

There was limited evidence from RCTs on cholesterol-lowering effects. In the ACCORD lipid trial, LDL-C had no significant difference between treatment and control groups, and no significant CVD benefits were found either.[29] In STENO-2, the risks of cardiovascular disease caused by microvascular and macrovascular complications were all reduced by multifactorial intensive intervention.[30 31] However, the isolated effect of LDL-C lowering was unclear in the STENO-2. The ADDITION-Europe was another randomized trial with intensive multifactorial therapy but found no significant effect on clinical outcomes.[32 33] Based on our findings and literatures, widely used statin (or other lipid-lowering agents) without careful examination of LDL-C is potentially harmful to patients and may increase the risk of long-term clinical outcomes. These inconsistences may be due to the fact that no large microvascular outcome trial has been done with microvascular events as the primary outcome, despite preliminary observations showing a benefit on nephropathy and retinopathy. In addition, researchers have not figured out all the answers yet and continued to grapple with the pathophysiology as to how diabetes and high cholesterol are related. One study found that blood sugar, insulin, and cholesterol all interact with each other in the body, and are affected by each other.[34] However, our study was not suggesting these LDL-C levels as targets/goals. What we have observed is the best outcomes in people who achieved these levels and may be useful as a guide (without being prescriptive) for such people.

Previous studies showed African Americans had lower LDL-C test rate and lower proportion of achieving LDL-C goal, but no significant difference in LDL-C level across races has been found,[35 36] while our study showed that white patients had higher optimal LDL-C value than black patients for achieving the lowest risk of macrovascular/microvascular complications.

BP control and its optimal value

Optimal value was only detected for SBP in the models fitting for macrovascular complication. Lower SBP was correlated to lower risk of microvascular complication. To minimize the risk of macrovascular complication, optimal SBP was found at 131 mmHg. Lower SBP may increase the risk of macrovascular complication in our study. BP of 143/82 mmHg was estimated with lowest risk of vascular events. However, the population used in this study was not patients with T2DM. A retrospective study found that an optimal SBP of 128 mmHg was associated with best outcome of diabetic nephropathy.[37] Considering the risk of macrovascular complication, we found that higher SBP might be the best SBP value for the general population with T2DM.

Compared with the targets in guidelines, the optimal SBP values provided more valuable information. SBP <140 mmHg is recommended for the general diabetes population, while the lower target of <130 mmHg is recommended for healthier patients or who can tolerate. In subgroup analysis, to achieve lower risk of macrovascular complication, patients older than 60 years have

higher optimal SBP than younger patients. The optimal SBP was much higher in white than in black patients. Also, the patients with normal weight had lower SBP for risk reduction than the overweight patients. Therefore, SBP target should be adjusted with respect to age group, race, and body weight. Using the SBP target of <140 mmHg may be not be suitable for obese patients. Younger black patients with normal weight can be recommended with SBP at around 120 mmHg. However, patients who are older, white, and/or with obesity should have less intensive SBP control plan.

Almost all the relationships between DBP and clinical outcomes were negatively associated in the general T2DM population. Higher DBP was associated with lower risk. In the univariate analysis, the risk of vascular complications was monotonic decreased with growth of DBP until it reached around 85 mmHg. When DBP was higher than 85 mmHg, the risk slightly increased when the DBP increased. Our findings were consistent with some other studies. The SPRINT trial found that patients with low DBP showed a significantly higher risk of cardiovascular events and nephrology outcomes.[38 39] The EURODIAB Prospective Complications Study concluded that diastolic blood pressure less than or equal to 83 was an important predictor for progression to proliferative diabetic retinopathy.[40] The diastolic J-shape phenomenon was still in debate.[41–43] However, the diastolic J-shape phenomenon was observed in this study that either too low DBP or too high DBP is harmful.

Limitations

The study has some limitations. There is a lack of information about diabetes duration in our data. To minimize this problem, the patients with a history of microvascular and macrovascular complication at baseline period were excluded. This exclusion can reduce severity of hyperglycemia and complications, both of which are associated with DM duration. Due to the nature of the VA population, more than 90% of patients are male in our sample. Thus, the results should not be generalized to both genders. The optimal blood glucose, blood pressure, and lipid control levels may vary between genders, but unfortunately it cannot be assessed in this study. Although risk prediction is not the primary objective in this study, predicted risk was used for comparison and determination the relative optimal value of diabetes management by applying the splines on the predicted risks. The numbers of knots and degree of these splines may still have estimation errors from the true optimal values.

Finally, this study is based on data that were collected before the results of recent cardiovascular and renal outcome trials were known and subsequent changes in guidelines. However, those trials compared newly developed drugs with placebo, and none of them had optimization of risk factor goals in either the drug or placebo groups, with somewhat better control of glucose and BP in the drug group over a prolonged period, and the trials were done mainly in a population outside the USA with less impressive results in subgroups in this country.[44] Indeed, the analyses have suggested that risk factor differences may explain the benefits of the drugs.[21 45] A comparative effectiveness study between these drugs and optimized goals, and even further subgroup analyses among different races (white vs black patients) and biomarker levels, as in our data is needed. It is noteworthy that at least one analysis has demonstrated less of a benefit of these drugs in outcomes in subgroups particularly in the USA.[44] However, such subgroup analyses may not have enough power.

CONCLUSIONS

Optimal treatment goals of A1C, LDL-C, and BP were identified for diabetes management in the US veterans with T2DM. Optimum clinical blood glucose, blood pressure, and blood lipid targets can be used for diabetes management. Multifaceted treatment strategies targeting hypertension, hyperglycemia, and hyperlipidemia may improve health outcome in veterans with T2DM. In addition to general ADA recommended goals, health system may examine their own large, more diverse patients with T2DM for better quality of care and population health management.

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