INDIVIDUALIZED TREATMENT GOALS FOR OPTIMAL LONG-TERM HEALTH OUTCOMES AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

A DISSERTATION

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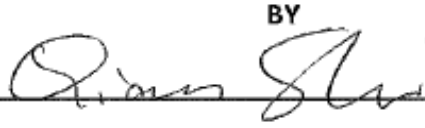

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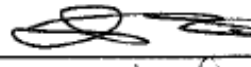

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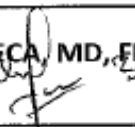

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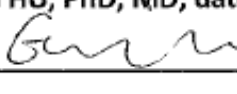

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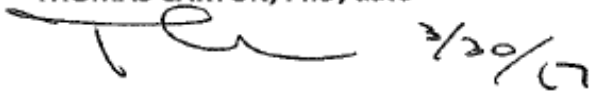

Dissertation Title Page:

Individualized Treatment Goals for Optimal Long-Term Health Outcomes among Patients with Type 2 Diabetes Mellitus

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Abbreviations

Abbreviation	Definition
A1C	Hemoglobin A1c
BP/SBP/DBP	Blood Pressure/ Systolic Blood Pressure/ Diastolic Blood Pressure
LDL-C	Low-Density Lipoprotein Cholesterol
HDL-C	High-Density Lipoprotein Cholesterol
DM	Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
CVD	Cardiovascular Disease
ASCVD	Atherosclerotic Cardiovascular Disease
AAE	Atherosclerosis, Aneurysm, or Embolism
CAD	Coronary Artery Disease
CHD	Congenital Heart Disease
MI	Myocardial Infarction
CHF	Congestive Heart Failure
PVD	Peripheral Vascular Disease
VA	Veteran Affairs
EMR	Electronic Medical Record
VINCI	VA Informatics and Computing Infrastructure
CDW	Corporate Data Warehouse
VHA	Veterans Health Administration
NDS	National Data Systems
VIReC	VA Information Resource Center
ADA	American Diabetes Association
PPC	Professional Practice Committee
AHA	American Heart Association
ACC	American College of Cardiology
JNC	Joint National Committee
CDC	Centers for Disease Control and Prevention
RCT	Randomized Control Trial
ACCORD	Action to Control Cardiovascular Risk in Diabetes

ADVANCE	Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation
VADT	Veterans Affairs Diabetes Trial
STENO-2	Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria
UKPDS	The UK Prospective Diabetes Study
PROACTIVE	PROspective pioglitAzone Clinical Trial In macroVascular Events
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes
ORIGIN	Outcome Reduction With Initial Glargine Intervention
ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care
BMI	Body Mass Index
AUC	Area Under The Curve
SD	Standard Deviation
HR	Hazard Ratio
RR	Relative Risk
ROC	Receiver Operating Characteristic
AIC	Akaike information criterion
GEE	Generalized Estimating Equation

Table of Contents

Abstract

Study aim: This study aimed to assess the individualized treatment goals (A1C, Blood Pressure, LDL-C) for patients with type 2 diabetes mellitus (T2DM), which lead to optimal health outcomes by different treatment strategies.

Background and significance: The evidences in medical guidelines came from clinical trials with highly selected patients, whereas the treatment goals may differ in some subgroups. Additionally, considerable confusions on treatment target has resulted from recent changes in guidelines. So, there is a critical need to examine heterogeneity in optimal goals that lead to the most efficacious treatment options.

Methods: A retrospective longitudinal study was conducted for veterans with T2DM by using US Veterans Affairs (VA) Administrative Database (Jan 2005 and Dec 2015). Longitudinal medical records were prepared for each 6-month cycle and multivariate longitudinal regression was used to estimate the risk of microvascular and macrovascular complication events and mortality. Second-degree polynomial and splines were applied in the model to identify the optimal goals in their associations with lowest risk of clinical outcomes by controlling the demographic characteristics, medical history, and medications.

Results: 124,651 patients with T2DM were selected, with 62.68 years old (SD=10.96) and 6.72 (SD=6.68) follow-up years at average. In general population, A1C=6.06, LDL-C=106.10 and BP=137.90/98.00 were associated with lowest mortality risk. As of achieving lowest risk of microvascular and macrovascular complication, the optimal goals were A1C=6.81, LDL-C=109.10; and A1C=6.76, LDL-C=111.65, SBP=130.60 respectively. The optimal goals differed between age and racial subgroups. Lower SBP for younger patients and lower LDL-C for blacks were identified with better health outcomes.

Conclusions: Individualized treatment goals were identified and multi-faceted 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.

Background

Based on the result of projection, if the current trends cannot be reverted, one out of three adults in the United States are projected to suffer Diabetes Mellitus (DM) by 2050. (8) And type 2 diabetes mellitus (T2DM) accounts for 90% to 95% of all diagnosed cases of DM in adults. (9) About 30% of people with T2DM have microvascular complications (10) and they suffer a twofold-increased risk of CVD compared to their counterpart without T2DM. (11, 12) Great number of cases of CAD, CVD and other complications were identified among population with T2DM in MarketScan Commercial Claims and Encounters Database too. (13) And evidence indicated that 40% of patients with diabetes who aged over 30 years old presented with acute complications. (14) Due to the high incidence and severity of complications, health utilization and expenditure related to diabetes complications raised followed. Average durations of hospitalization were 15.2, 25.5 and 21.2 days for T2DM-related CAD, CVD and complication episodes respectively. $176 billion in direct medical costs on diagnosed diabetes was estimated in 2012, including 43% of the total medical cost on hospital inpatient care and 18% on prescription medications to treat the complications of diabetes. (13) Diabetes and its complications have placed heavy burden for patients and health system. Average medical cost of patients with DM was 2.3 times higher than the patient absence of diabetes. (15)

Better management of DM and well-controlling complications will tremendously relieve economic burden for both patients with T2DM and society. A1C, BP and LDL-C are the frequently-used measurements for evaluating the health condition, risk of complication and quality of treatment among patients with T2DM.

A1C is routinely used for diabetes initial assessment and continuing management care (16), which reflects average glycemic over past several months and is meaningful for predicting diabetes complications. (17, 18) From CDC report (2003-2006), about 57% adults with diabetes controlled their A1C level under 7%, and 20% patients' were between 7.0% and 7.9%, and 23% of patients failed to control their A1C level (≥8%). Lipid-lowering treatment is recommended in medical guidelines and has been shown positive effect on prevention of CVD for older patients with diabetes (19). More than half of adults with diabetes were reported having high blood cholesterol in 2009 (age-adjusted percentage: 58.4%). Lowering LDL-C by difference therapeutic interventions has been found associated with lower rate of cardiovascular disease. (20) LDL-C level varies by race, ethnicity and gender.

Hypertension is more widely prevalent chronic condition and attracts more attentions among patient with T2DM. Nearly 1 in 3 American adults have high blood pressure and 2 in 3 people with diabetes report having high BP or take prescription medications to lower their BP. Controlling BP at a proper level has been widely accepted for lowering the risk of heart attack or stroke. High BP can lead to and worsen diabetes related complications, including diabetic eye disease and kidney disease. And, diabetes and hypertension are interrelated and predispose patients to other heart and circulation problem with blood vessel damage. Better management of BP among patients with T2DM shows promising benefits.

Multifactorial intervention targeting at controlling A1C, BP and LDL-C by intensive treatment has been demonstrated effective for reducing the risk of major diabetes related complications and death. (21) However, the risk of diabetes related complications may be not homogeneous among populations with different characteristics. Diabetes increased the risk for CHD differently among men and women (hazard ratio 1.99 and 2.93 for men and women, respectively). (22) Customized treatment strategies are needed for lowering the risk of complication event, however, no guidelines provide evidence-based suggestion for setting individualized treatment target.

For managing T2DM and preventing complications, a number of guidelines from medical societies have been developed the treatment goals for patients with T2DM. However, the standards of measurements are not fully consistent and frequently updated based on the latest well-accepted evidences.

In the 2015 version of guideline, 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 more stringent goal of 6.5%, or less stringent goal of 8%, based on patients' health conditions (23). The recommendation leaves flexibility to the healthcare providers with unclear instruction of selecting explicit goal for patients with specific demographic and medical characteristics.

The medical guidelines from different societies updated their guidelines occasionally but not simultaneously, so the goals of same measurement may vary in different guidelines. Diabetes had been listed as equivalent risk factor as coronary heart disease for managing LDL-C, which supports LDL-C lowering is the primary lipid target in guidelines. (24) (25) The American Heart Association (AHA) in 2013 recommended that specific numerical goals for lipids should be abandoned, as there was no trial that had randomized patients to a specific

LDL cholesterol goal (26). Followed with the change in AHA guideline, ADA removed the LDL cholesterol goal after 2014 and only left recommendation of triglyceride and HDL cholesterol goal for blood lipid management (23). Prior to the changing of AHA and ADA, the goal of LDL-C for people with diabetes was less than 100 mg/dl and in addition, those who had overt CV disease, it should be controlled less than 70 mg/dl (27).

The BP target underwent changes in recent year too. ADA and JNC 8 loosed the general goal of SBP from less than 130 mmHg to less than 140 mmHg, and additionally increased the goal of DBP from less than 80 mmHg to less than 90 mmHg (23, 28, 29) due to no confirmed benefit found from lowering BP $\leq$ 130/80 mmHg in clinical trials. (30) 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. (31)

The discordance between guidelines leads to wide controversy about the appropriate treatment targets for the population with T2DM. And the equivocal wording in the discussion about cut-point of management goal brings more difficulties for patients and their health providers. Due to the confusions, healthcare providers may tend to be conservative for avoiding the uncertain risk. So, more explicit targets of A1C, BP and LDL-C are meaningful for clinical practice and daily diabetes management.

It is not clear that how to individualize treatment while guidelines leave the flexibility to physicians for adjusting the treatment goal, and no clear targets for racial/ethnic and age subgroups can be used as references. Among a great number of evidences, the flexibility may confuse health providers and increases the difficulty in decision making and lowering adherence in patients with T2DM. Even worse, some valuable evidences are inconsistent.

Reaching A1C achievement (<= 7%) has been proved to reduce the risk of microvascular complications of diabetes. It also showed the risk reduction in MI, stroke, CVD death occurrences by intensive blood glucose control in long-term follow-up clinical trial study (32). However the ACCORD, ADVANCE and VADT showed the reduction had no significance. (33) The conflict evidence from multicenter clinical trials of highly selected patients infer that the treatment goals may be different in subgroups. Furthermore, the goal of A1C should be considered individually with the evidence that the meaning of A1C level is differentiated for patients with particular demographic characteristics. A1C is substantially determined by genetic factors and fractions of the variance in A1C correlates with diabetes complications were found in a study among nondiabetic twins. (34) The relationship

between the value of plasma glucose and hemoglobin A1C shows inter-person divergent in patients with T2DM. (35) The A1C inherently makes differentiated capacities of showing blood glucose level among patients with T2DM from various populations (e.g. races, ethnicities etc.). It was demonstrated by the ACCORD trial with the evidence that the association between A1C level and the risk of hypoglycemia and mortality was affected by HGI, which was differentiated among racial groups. (1)

Not only should the A1C goal be customized by considering the demographic characteristics, but also the BP target. The less stringent goal of BP was based on that no evidence from RCT demonstrated better primary health outcomes by the intensive treatment with SBP goal lower than 140 mmHg. Although the medical guidelines hold relatively conservative altitude towards the BP target, many evidences pointed out the potential benefits from intensive BP-lowering therapy with stringent BP goal. Reductions in the risk of death from any cause and cardiovascular disease caused death were found in ADVANCE-BP (36), and the lower risk of stroke was detected from the ACCORD too. (30)

Based on the inconsistent results from RCTs, guidelines were tending to be conservative toward BP standard for avoiding possible side effects, even within some specific sub-populations. However, such a recommendation ignores the fact that, even though no significant improvement on primary outcomes (e.g. death) from intensive BP treatment, a reduction in the risk of stroke still could be meaningful to patients under such risk. And lowering BP still has great potential to protect patients with T2DM from complications in relatively longer term than clinical trial follow-up period. Furthermore, it is far from enough to control BP with one standard for all racial/ethnic or age subgroups. In JNC8, BP goal is <150/90 mmHg for elder population aged ≥ 60 years old but no further discussion about the standards for other age or racial subgroups with T2DM. (29) Intensive BP control therapy showed more effects of risk reduction on complications in the elder group aged ≥ 65 years old than the younger group with T2DM. (37) Additionally, the too low and too high SBP were both found increased the risk of stroke but the magnitude of association was differentiated between African American and whites, (38) which implied that gene may play a role in the BP level. (39)

The evidences infer that BP target should be customized by not only health conditions but also demographic characteristics. Additionally, meta-analysis results showed that the benefits of lower BP were associated with baseline SBP, even more than the chosen target. (40) For

improving health outcome in clinical practice, individualized BP treatment target should be clarified in medical guideline.

For most of patients with diabetes, cholesterol-lowering drugs were recommended for controlling blood cholesterol, with statins as first line medication. From the current recommendation, all patients with diabetes have LDL-C >70 mg/dl are recommended moderated or intensity statin therapy. (26) It was widely controversial and may be misunderstood by patients. While it may lead to a significant number of patients being inadequately treated when further treatment is easily available to reduce the risk of CV events, and it may be burdensome for patients with suboptimal LDL-C level but cannot tolerate the recommended statin dose.

Furthermore, hyperlipidemia differentiate prevalent among racial/ethnic groups (Table 1). (41) For patients with diabetes, the unadjusted percentages of LDL >130 mg/dl were varied by races and ethnicities. (African American 69%, non-Hispanic white 61%; Hispanic 62%, non-Hispanic white 54%). (42) Diabetes and high LDL-C are synergistic and the LDL-C levels are not homogeneous among racial/ethnic and gender groups. So, individualized LDL-C management goal is needed for properly controlling blood lipid and filling the gap of customized goal for subgroups.

Table 1: percentages of people with high LDL cholesterol (≥130 mg/dl) in the United States (43)

Racial/Ethnic Group	Men (%)	Women (%)
All	31.0	32.0
Non-Hispanic Whites	29.4	32.0
Non-Hispanic Blacks	30.7	33.6
Mexican Americans	38.8	31.8

From the guidelines and treatment targets for A1C, LDL-C and BP introduced above, the complexity of triple-goal is shown, which implies that single cut-point may be hard to fulfill the needs for all patients with T2DM. Customized goals of A1C, BP and LDL-C may help to provide evidences of adjusting treatment strategy properly. Evidence-based individualized management target should be considered and will be meaningful for better diabetes management, and then reducing the risk of diabetes related complications or death.

Additionally, U-shape relationships have been found between these three T2DM managements of A1C, BP, total cholesterol and all-cause mortality in a retrospective cohort study in Europe, which means monotonically lowering the levels of three measurements, may not be appropriate. (44) This evidence implies that optimal management goals may exist for reaching minimum risk of complication or death. In this study, the lowest risks were associated with levels that differed from current guidelines (3). It left a chance for further study to find the optimal triple-goal by a more representative data.

Furthermore, most of the evidences came from multicenter clinical trials with highly selected patients and intervention aimed on specific management goal. However, very few studies have considered whether long-term clinical outcomes associated with triple-goal in the population with T2DM. Only one small single-center clinical trial (Steno) has attempted to control all the risk factors of diabetes related complications for patients with T2DM. This trial demonstrated that multifactorial treatment significantly reduced the risk of cardiovascular events, microvascular complications and mortality, which has persisted over many years after the trial concluded. (5, 45) However, due to the nature of the trial and the population studied, the applicability to the U.S. population with T2DM is very limited.

Significance

The recommendations of A1C, BP and LDL-C goals in current guidelines are mainly aimed for general population with T2DM, whereas the targets may have different determinants in some subgroups. Although ≤130/80 mmHg has been demonstrated lowering the risk of complications by RCTs, however, no solid evidence to test if the stringent antihypertension therapy aimed on the tight BP target will bring more benefits. And due to not all of patients with T2DM can afford the intensive treatment or control their BP under the stringent target, loose treatment target (130-140 mmHg of SBP, 80-90 mmHg of DBP) may not increase the risk of complications for all of patients with T2DM. Discussion about the flexibility of treatment goal is meaningful and customized goal for specific population is practical.

Evidence from the ACCORD trial demonstrated that high A1C in relation to blood glucose (high glycation) may be associated with more hypoglycemia and higher mortality in some specific age/ethnicity subgroups with T2DM (1), which indicates that A1C is inherently different for patients with various characters. Individualized A1C treatment goal should be considered instead of a universal cut-point too.

What's more, no study was focused on the group of diabetic management goals, which includes blood glucose, blood pressure and blood lipid. Any isolate management or treatment target may ignore the correlations between these three management targets. The synergistic effect of A1C, BP and LDL-C has not been considered into research before.

Valid risk assessment model built upon large-scale dataset can be performed as prediction model and used as backbone of risk assessment tools in clinical practice. By estimating the all of the three diabetic management (A1C, BP and LDL-C), which were associates the risk of complications, patients with T2DM will be provided a comprehensive management targets to approach better long-term control for preventing diabetes related complications. And the triple-goal, which will be customized for specific sub-populations, may be more instructive for clinical practice by explicit guidance.

Adherence to guidelines is challenging for patients with T2DM in clinical practice due to cost, tolerability of medications, side effect, and low long-term adherence to therapy. Confusions in guidelines may bring more difficulties for patients with T2DM to follow. And the inappropriate treatment based on unclear goal may increase the probability of side effect, which will lower the adherence rate too. So, individualized management goals of A1C, BP

and LDL-C may benefit patients with T2DM by potentially reducing the risk of diabetes related complications and optimizing long-term health outcomes.

Literature Review

Summary of Medical Guidelines

Standards of Medical Care in Diabetes were published and updated by ADA's Professional Practice Committee (PPC) every year for providing diabetes clinical practice recommendations. A brief summary of the latest 5 years' medical guidelines is provided here for showing the changes of triple-goal in recent years.

In 2011, the A1C target was 7% only for non-pregnant adults with diabetes, though more or less stringent targets were recommended for selected individuals (46). In 2012, beyond the general A1C goal (7%), ADA recommended more stringent A1C goal which was set as < 6.5% for patients can be achieved without significant hypoglycemia or other adverse effects of treatment. This tight goal was appropriate for patients with short duration of diabetes, long life expectancy, and no significant CVD. And less stringent A1C goal, 8%, was suggested for patients with a history of severe hypoglycemia, limited expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and who had difficulties to attain the general goal after well education, monitoring and treatment (47). More specific goals for individuals with particular conditions were added into guidelines from 2012 till the latest version of 2015, which shows more individualized A1C goals were recommended for better adopting (27, 28, 47, 48).

Not only the A1C, were BP targets adapted in the guidelines within the recent five years too. By carefully comparing ADA guideline from 2011 to 2015, the trend of loose BP targets can be found after 2012 due to no solid evidence supported the benefit of tight BP control (26, 27). Since 2013, the SBP goal had been raised to 140 mmHg from 130 mmHg for patients with diabetes and hypertension, but still kept the diastolic blood pressure goal as 80 mmHg in 2013 and 2014 (28, 46). Lower systolic target (130 mmHg) was suggested to be appropriate for younger patients who can afford without burden. But the wording leaves flexibility and confusions at the same time.

In the latest updated 2015 guideline, the blood pressure goals were continuously loosed to 140/90 mmHg for general patients with diabetes and hypertension. The more intensive goals of 130/80 mmHg were recommended to younger patients, who can achieve without undue treatment burden (48). The goals for blood lipid were relatively stable before 2015. From 2011 to 2014, recommended Triglyceride level was <150 mg/dL (1.7 mmol/L), HDL

cholesterol level was > 40 mg/dL (1.0 mmol/L) in men and > 50 mg/dL (1.3 mmol/L) in women, and LDL cholesterol level was < 100 mg/dL (2.6 mmol/L) for individuals without overt CVD while a lower LDL cholesterol goal of less than 70 mg/dL (1.8 mmol/L) for individuals with overt CVD. LDL cholesterol-target statin therapy was preferred strategy for all these years (27, 28, 46, 47). However, statin treatment initiation and initial statin dose were decided primarily by risk status instead of LDL cholesterol level, so the ADA guideline removed the LDL cholesterol goal in 2015 (48).

Beyond the ADA guideline, ACC/AHA blood cholesterol guideline also mentioned about the lipid management goal for patients with T2DM. In the 2013 ACC/AHA blood cholesterol guideline, moderate intensity statin therapy was recommended to all patients with diabetes and aged between 40 to 75 years old as primary prevention from ASCVD. The statin therapy for patients with diabetes, whose LDL-C <70 mg/dL or age <40 or >75 years old, can be customized based on the toleration, side effect and benefit of lowering the risk of ASCVD. Due to the RCTs used fixed dosage for blood lipid control, no solid evidence shows optimal goal of LDL-C in primary and secondary prevention care. (49)

JNC8, as an important reference for BP target, adjusted its goal for patients with T2DM too. In the 2014 hypertension guideline (JNC 8), initiate pharmacologic treatment goals were set to lower BP at SBP >=140 mmHg or DBP >=90mmHg and treat to a goal SBP <140 mmHg and goal DBP <90mmHg in the adult population with diabetes (29). SBP goal of lower than 130 mmHg and DBP goal of lower than 80 mmHg were commonly recommended for adults with diabetes and hypertension from 2003 in JNC 7 report (31). This new update of loose goals of BP control was based on no RCT evidence of better health outcomes from the treatment with SBP goal as lower than 140 mmHg. Although JNC 8 is widely accepted guideline, the VA still provides clinical practice guideline for management of DM. Within the context of VA, the target for patients with hypertension was <140/80 mmHg, which was adopted from JNC 7 and evidenced from UKPDS and HOT trial (50).

Major studies about blood glucose (A1C)

As golden standard, the results from randomized clinical trials were considered the major evidences for making decision in medical guidelines and clinical practice. A summary of the major clinical trials aimed to control blood glucose and set A1C target as treatment goal is

provided here for clearing the association between the goal of diabetes management/treatment and the health outcomes in the previous studies.

In ACCORD glycemic trial, the intensive blood glucose control targeted at A1C <6% and reduced the A1C to 6.4% at the end of study, which was achieved the goal of A1C (7%). While the standard therapy group (A1C= 7.5%) failed to achieve the goal suggested by guidelines, but met the less stringent goal (8.0%) for the patients cannot afford intensive treatment or in relatively worse health conditions. (48) However, the patients received intensive glucose lowering therapy showed no additional benefit on primary outcome of macro- or microvascular complications compared to the routine treatment group (HR=0.9, 95% CI: 0.78 - 1.04, P=0.16). At the same time, the intensive treatment significantly increased the risks of severe hypoglycemia and all cause of death, which made the study halted before scheduled end. (51)

Intensive treatment aimed at A1C level lower than the stringent goal in guidelines has no benefit but may be harmful for patients with T2DM with increased adverse events. This study was widely cited by medical guidelines as major evidence for the abandon of too intensive treatment.

Another large scale clinical trial sampled adults with T2DM global wide, intervened 5 years and post-trial followed up the participants for about 6 more years. In ADVANCE glucose lowering study, the intensive glucose control group which achieved A1C level at 6.5% had significantly effect on reducing the risk of combined major macrovascular and microvascular events (HR=0.9, 95% CI: 0.82 – 0.98, P=0.01) and microvascular event only (HR=0.86, 95% CI: 0.77 – 0.97, P=0.01) than the group with standard control (A1C level at 7.3%). However, the benefit was not shown in major macrovascular events independently. And the risk reduction of microvascular complications was mainly contributed by the significantly decreased incidence of nephropathy (HR=0.79, 95% CI: 0.66 – 0.93, P=0.006), while no significant effect on Retinopathy was detected. No matter all cause death or death from cardiovascular causes were not reduced by intensive treatment. But, consistent with ACCORD, the risk of severe hypoglycemia events was higher with the intensive glucose-control significantly (HR=1.86, 95% CI: 1.42 – 2.40, P<0.001) (52).

As a 6-year post-trial follow-up, ADVANCE-ON reported the results of glucose control for surviving participants from ADVANCE trial. No reduction of risk of death or major

macrovascular events was found, which was consistent with the results in ADVANCE trial (36).

The ADVANCE set the A1C goal as 6.5%, looser than the goal in ACCORD, which can imply that no more benefit come from more stringent goal of A1C, even the real difference of A1C levels between these two trials was minor (6.5% in ADVANCE vs. 6.4% in ACCORD). The major complication, CVD, did not reduce in both studies. Simply chasing stringent blood glucose level (6.5%) was demonstrated no benefit on macrovascular complications. Continuously lowering the target (from 7.0% to 6.0%) did not make the risk of complication lower, but increased the risk of death and severe hypoglycemia.

Beyond the two classic large scales randomized clinical trials above, some more well designed clinical trials in specific population with T2DM also provide valuable evidences. VADT, a clinical trial in military veterans, aimed to treat patients with T2DM intensively and reached 1.5% lower in A1C than patients received standard treatment. Finally, A1C reduced to 6.9% in intensive glucose control group compared to 8.4% in the standard glucose control group. There was no significant effect on risk reduction of composite primary outcome, including CVD, MI, stroke, death, CHF, surgery for vascular disease, inoperable coronary disease and amputation, or death from any cause. And the microvascular complication had no significant difference between the intensive and standard treatment groups either. However, the adverse event of hypoglycemia was increased significantly.

The intensive group reached a proper A1C level (6.9%), which was close to the guidelines suggestion (7%), and the control group was failed to fulfill the A1C goal in this study. The comparison between intensive and standard treatment groups is meaningful to approve the effectiveness of current A1C goal on diabetes related primary complications. However, the results did not support that simply reaching A1C goal can provide any significant benefit than suboptimal glucose control.

There are some issues in this clinical trial needed to be mentioned. The patients in VADT were suboptimal responded to original treatment for T2DM before attending this trial, which means that they might resistant to anti-glucose medication in varying degrees. Intensive therapy may not work normal for this sample and may product severe adverse effects at the same time than other population with T2DM. Male was majority gender also limits the generalizability.

Although some trials did not design for reaching specific A1C target, the intervention (medication, etc.) had the effect of A1C lowering, which can provide us more evidences about how the level of A1C influence the diabetes related complications or death.

UKPDS-33 identified new diagnosed T2DM adults and compared diabetes related endpoints between intensive anti-hyperglycemic therapy group and the control group with diet therapy. With a median 10 years follow-up, the A1C maintained at 7% in the intervention group, compared to 7.9% in control group. The risk of microvascular endpoint was significantly lowered in the intensive therapy group, but no CVD benefit was shown in this study and the adverse event of hypoglycemia increased at the same time. UKPDS-34 compared the effectiveness of Metformin treatment to conventional diet therapy among obesity population with T2DM. The composite diabetes endpoints, stroke and all-cause death were all significantly lower in the group with anti-hyperglycemic medication, which kept the A1C at 7.4%.

Compared to conventional life style change, medication on lowering blood glucose provides benefits on risk reduction on diabetes related complications or death. In the long-term diabetes management, 7% of A1C and intensive treatment with the target of 7% A1C may not be appropriate goal for patients with T2DM if we consider the incremental adverse events.

The trials for comparing the effectiveness of Pioglitazone (PROACTIVE) (53, 54) and Rosiglitazone (RECORD) (55) on patients with T2DM evaluated the cardiovascular outcomes by the oral anti-hyperglycemic agents. PROACTIVE showed lower risk of the composite endpoint (including all-cause mortality, non-fatal MI, or stroke) in the Pioglitazone treatment group, which reached A1C level at 7%. However, weight gain and increasing risk of heart failure were found in the intervention group too. While in the RECORD, no benefits on reducing the risk of cardiovascular disease related death and MI, but the risk of heart failure increased too.

Although it is hard to draw conclusion of lowering A1C to about 7% will increase the risk of heart failure, we cannot confirm better cardiovascular outcome from those oral agents either, even they lowered A1C to the guideline recommended level.

ORIGIN and Kumamoto are two randomized clinical trials compared the intensive insulin treatment to standard therapy. No significant effect on cardiovascular-cause death, non-fatal MI or stroke was detected in the early insulin therapy group in ORIGIN trial compared to the

standard treatment. But the adverse events of hypoglycemia and weight gain significantly increased with the A1C level was reduced to 6.2% at the end of study (56).

The Kumamoto trial compared the effectiveness of multi insulin therapy to conventional insulin on microvascular complications among Japanese with T2DM. The early microvascular complications (retinopathy, nephropathy and neuropathy) were significantly reduced by the intensive insulin treatment with the A1C of 7.1%, compared to 9.4% A1C in the control group.

A retrospective cohort study found both A1C levels of lower than 6.25% or higher than 7.75% can lift the risk of all-cause mortality significantly. (3) The lowest HRs appeared in the A1C intervals of [6.25% - 6.75%], [6.75% – 7.25%] and [7.25% – 7.75%]. The approximate U-shape association presented in this study can be assumed by the evidences from the clinical trials provided above. Compared to A1C level greater than 8.0%, lowering the A1C to 7.4% showed the effect of risk reduction on composite diabetic endpoints, death and stroke among obesity people with T2DM (UKPDS-34). Reaching the A1C at about 7% can produce benefit on reducing microvascular complications (Kumamoto, UKPDS-33), though no benefit of macrovascular complications. Continuously lowering the A1C to 6.5% was found to decrease the risk of both microvascular complication and the composite primary outcomes related to T2DM (ADVANCE-glucose control). Further intensive therapy for stringent goal of A1C <6.0% was dangerous with increasing risk of death and severe hypoglycemia and no any significant benefit on micro- or macrovascular complications (ACCORD-glucose control, ORIGIN). What's more, it is worthy to mention that the severe adverse events, hypoglycemia, appeared to increase significantly from A1C level of 7% (UKPDS-33, VADT) and persistently at lower A1C level of 6.5% (ACCORD, ADVANCE). Above all, lowering blood glucose is not consistently beneficial for all A1C entry levels and targets. The guideline recommended A1C level of <7% may not be appropriate to apply in general non-pregnant adults with T2DM and to desire long-term reduction in macrovascular disease. The stringent goal of 6.5% may be even worse for leading to severe hypoglycemia events. The curve of diabetes related complications by different A1C levels is meaningful for long-term diabetes management and can be complimentary evidence to enhance the medical guidelines. And it should be customized for subgroups with different demographic characteristics to make it more informative and practical.

Major studies about blood pressure

Based on the better long-term clinical health outcomes from epidemiological studies, several well-designed randomized clinical trials were conducted in the last decade.

ACCORD-BP, as the primary evidence of stringent BP control has no significant effect on CVD, has been widely cited. It is critical to support JNC 8 to adjust its recommendation of BP target. From ACCORD results, the group with the treatment targeting SBP at 120 mm Hg had no significant lower risk of death or primary composite outcome (included nonfatal MI, nonfatal stroke, cardiovascular-caused death) compared to the group with SBP targeting at 140 mm Hg (30). Although the participants reached optimal SBP of 119.3 mmHg by intensive treatment, compared to the SBP of 133.5 mmHg in the standard therapy group, only stroke (about 35% reduction of relative risk) was reduced significantly (HR: 0.59, 95% CI: 0.39 – 0.89, P=0.01) in the almost 5 years follow-up period. Targeting too stringent SBP (<120 mm Hg) may not have extra benefit on reducing risk of complications, or even be harmful. The risk of severe adverse events attributed to intensive therapy of lowering BP was found significantly higher in the intensive treatment group.

In ADVANCE-BP, the intensive BP lowering treatment reduced 5.6 mmHg more SBP and 2.2 mmHg more DBP than the standard treatment group ($p<0.0001$). (37) With the entry level SBP of 145 mmHg and DBP of 81 mmHg, the patients received intensive treatment reached the BP at about 135/75 mmHg, while the control group had the BP at around 140/77 mmHg. The intensive blood pressure control decreased the risk of macrovascular or microvascular significantly compared to the control group after a mean of 4.3 years of follow-up (HR=0.91, 95% CI: 0.83 – 1.00, P=0.04). The marginal significance was not approved in the risk reduction of microvascular or macrovascular complications separately. However, the all-cause death (HR=0.86, 95% CI: 0.75 – 0.98, P=0.03) and death from cardiovascular disease (HR=0.82, 95% CI: 0.68 – 0.98, P=0.03) were lower significantly in the intensive treatment group. The effect of BP lowering on micro- or macro-vascular disease did not show significance in the ADVANCE-ON, but it reduced the risk of death at the end of the post-trial follow-up (36).

From the two major clinical trials with BP lowering target as the intervention, we can infer that the benefit of BP control was constricted within a specific range. In the ADVANCE trial, SBP was lowered from >140 mmHg to <140 mmHg and the control group sustained the SBP at 140 mmHg, which was demonstrated that the goal of SBP of 140 mmHg in guidelines is meaningful and beneficial for reducing the risk of death among patients with T2DM.

Although the effect of lowering SBP under 140 mmHg on macro- and macro-vascular complications was not clearly certified by the evidence in ADVANCE, the SBP goal of 140 mmHg is safe from severe adverse events and effective for lowering death risk at least. However, further lowering BP did not provide more advantages for patients with T2DM, but brought side effects at the same time. When the intensive BP therapy aimed to lower the SBP at 120 mmHg, the patients did not benefited from reaching the stringent BP goal compared to the control group with SBP >130 mmHg, except lower risk of stroke.

An epidemiological analysis confirmed the results of too stringent BP goal or reducing BP lower than 120/80 mmHg are even harmful. The blood pressure less than 115/75 mmHg was associated with increased cardiovascular events rates and mortality in people with diabetes, which was additional evidence on the negative effect of too low BP. (48) Additionally, the VADT trial found separated SBP ≥ 140 mmHg and combined SBP ≥ 140 mmHg and DBP < 70 mmHg both raised the risk of CVD significantly. Beyond the intensive glucose lowering treatment, the patients in VADT trial also received BP maintenance treatment for both groups, which targeted BP at 130/80 mmHg. It verified the potential harm by too stringent DBP < 70 mmHg.

Based on all above evidences, the association between BP and primary outcomes can be generated to U-shape, like the A1C. The approximate U-shape relationships had been found between risk of mortality and BP recently (3). Lower than the reference group (SBP: 115-125 mm Hg; DBP: 72.5-77.5 mm Hg) showed the mortality leveraging (3). Especially for SBP, higher SBP than reference has significantly lower risk of mortality (3).

Although the benefit on CVD was not supported by ACCORD result, intensive therapy and lowering SBP caused stroke risk reduction significantly. It was also confirmed by a large retrospective study in Finland too. Every 10 mm Hg incremental of SBP or DBP both significantly increased the risk of stroke incidence and stroke mortality among people with diabetes (57). And a meta-analysis included 31 intervention trial showed that risk of stroke was significantly decreased by each 5 mm Hg reduction in SBP and 2 mm Hg reduction in DBP; while the risk of MI did not correlated with BP reduction (58).

Randomized clinical trials demonstrated that lowering blood pressure to <140 mmHg SBP and <90 mmHg DBP reduced the risk of CHD events, stroke, and diabetic kidney disease (59). But further lower BP on extra benefit has not been confirmed.

Only limited pre-specific clinical trial evidence for the benefits of lower SBP or DBP targets (29). Results from meta-analysis of clinical trials showed no significant reduction in risk of death or nonfatal myocardial infarction (MI) among adults with T2DM comparing intensive blood pressure targets (SBP <130 mmHg and DBP <80 mmHg) and standard targets (SBP upper limit to 140-160 mmHg and DBP upper limit to 85-100 mmHg). (11) However, statistically significant 35% reduction of relative risk (RR) in stroke were found in the intensive BP targets group, though the absolute risk reduction was only 1% (40). There is widely controversial on the BP lowering target due to inconsistent results. In the latest published meta-analysis of randomized trials of blood pressure control, every 10-mmHg systolic blood pressure lowering can lead to significantly reduced relative risk (RR) of mortality, cardiovascular events, coronary heart disease, stroke, albuminuria and retinopathy. After stratifying the baseline SBP by the standard of >140 mmHg or >130 mmHg, lowering SBP 10-mmHg was still significantly beneficial for decreasing the RR of mortality, cardiovascular events, coronary heart disease, stroke, heart failure, and albuminuria. For the stratified group with baseline SBP <140 mmHg or <130 mmHg, only stroke and albuminuria can be found significantly affected by SBP lowering. And the associations between lowering SBP and risk of vascular events were not significantly different across classes of medication (60). This meta-analysis places valuable evidence that lowering BP is still considerable and meaningful for controlling diabetic complications, though the JNC8 broadened their BP treatment goal based on the clinical trial results.

Goal of BP in the population with T2DM is still controversial due to the inconsistent and insufficient evidences from clinical trials and observational studies. However, the assumed U-shape relationship between BP and clinical outcomes is still waiting for approval by more analysis. Therefore, individualized assessment of the risk of vascular events by different BP levels is needed and useful for helping patients and physicians to make decision on customized treatment target.

Major studies about blood lipid (LDL-C)

In 2015, ADA removed the goal for LDL-C <100 mg/dl due to no clinical trials compared the 2 LDL-C targets <100 mg/dl or <70 mg/dl and no solid evidence to support the LDL-C goal. (11) The majority of studies only confirmed the single fixed-dose statin to lower LDL-C were effective for improving clinical outcomes. (26) The deficiency of instruction on LDL-C management may cause more confusion during clinical practice.

In the recent published guideline, statin was widely recommended for patient with T2DM to routinely control blood lipid. Discussions about if statin is sufficient for control lipid and if combination of more than one lipid control medicines can improve the lipid management were hot debated.

However, in ACCORD lipid trial, combination therapy of open-label statin with fenofibrate did not reduce the LDL-C significantly (61). LDL-C reduced from 100 mg/dl to 81 mg/dl in the combined therapy group and in the control group LDL-C was dropped from 101 mg/dl to 80 mg/dl, which found the fenofibrate had no significantly additional effect on lowering LDL-C. And no significant differences on CVD or death were detected in the combination therapy groups compared to the standard treatment group either.

The ACCORD lipid trial showed that the statin was effective enough for controlling the LDL-C under the suggested level. The combined therapy with non-statin was redundant and brought no more benefits. But the effectiveness of combined lipid control therapy for the patients with T2DM who failed to control lipid by statin only is still leave unsure. The combination of fenofibrate and statin was not effective, but other kinds of lipid control agents may improve the clinical outcomes potentially.

Current ADA guideline removes the LDL-C goal and suggests widely statin usage for CVD risk prevention. However, in AIM-HIGH study (62), the additional reduction in non-HDL–C levels with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL–C levels of 40 to 80 mg/dL (62). This result demonstrated that intensive therapy for the patients have been under lipid control would not be beneficial.

Furthermore, the results in ACCORD-lipid were diverged in subgroup analysis. The combined treatment may be harmful for women with T2DM and beneficial for men with the risk reduction of complications ($p=0.01$ for interaction). The gender influence was confirmed by another analysis in Finland. (63) The total cholesterol has positive association with stroke among Finnish men, but this association was reversed among women.

However, a positive and consistent association was found between total/HDL cholesterol ratio and stroke in both men and women too, though the associations were attenuated by BMI, BP and history of diabetes adjustment (64). The influence pattern of blood lipid or LDL-C may be different for different kinds of complications or be discrepant in various subgroups. Individualized analysis and goal setting suggestion should be studied.

In summary, evaluating the effect of different LDL-C levels on CVD or identifying the optimal LDL-C goal are both meaningful. For patients with T2DM with various characters, individualized LDL-C goal will be more beneficial for patients and practical for providers.

Multifactorial intervention clinical trial

Steno-2 was well-designed clinical trial, which tried to manage blood glucose, BP, lipid by intensive therapy and caught the long-term death or complication events. However, only DBP and LDL-C level reached the recommended target at end of intervention and end of follow-up among the patients received intensive therapy. SBP was dropped to around 130 mm Hg at the end of intervention but raised to 140 mm Hg at the end of follow-up, which was higher than the standard we used in this study. While A1C levels were all above the standard 7%, no matter at the end of intervention (7.9%) or at end of follow-up (7.7%).

With the total of 13.3 years of multifactorial intervention and follow-up, risks of all-cause and cardiovascular caused death were significantly lower in the intensive treatment group than conventional group (5). At the end of intervention period (7.8 years), the risk of cardiovascular disease and microvascular complications were found significantly lower in intensive treatment group (45).

No matter what kinds of therapy patients with T2DM choose, better management of A1C, BP and LDL-C has significantly effect on risk reduction of all-cause death and micro- or macro-vascular complications. The therapy targeting at hyperglycemia, hypertension and dyslipidemia was demonstrated effective to reduce mortality and comorbidity rates in randomized clinical trial.

As another randomized clinical trial with multifactorial therapy, ADDITION-Europe was failed to reach better performance of diabetes management. (65) The A1C, BP and cholesterol did not significantly improve in the intensive treatment group. And the complications of CVD and mortality did not show significant change. No significantly increased hypoglycemia appeared either. It may imply that minor improvement or change of A1C, BP and lipid levels cannot affect the risk of diabetes related complications or mortality.

This study tried to find the individualized and optimized goals of blood glucose, BP and LDL-C control has positive correlation with less diabetes related complications, which is meaningful for decision making for health providers and patients with T2DM.

Summary of predictive models

Risk factors associated with diabetes related complications and mortality have been examined thoroughly, which provide valuable evidence about the biological processes underlying diabetes. And risk factors are crucial part of risk assessment model and determine the validity and capacity of a complication risk predictive model. The classic risk assessment models for predicting the long-term risk of T2DM complications are identified and summarized. (Appendix 3)

For building up predictive model, relatively large sample size and long follow-up time are needed. The shortest study (Sweden) from my summary was 5-year long, while the longest one lasted about 14 years (UKPDS) (66-70). UKPDS and Japan were collected data from randomized clinical trials (71). The sample sizes were limited by the nature of design, but were still reached 4,540 and 1,748 respectively. And other prospective or retrospective observational studies were all large-scale, which had 2,300,000 patients in QRISK, 33,067 patients in Cleveland and 11,646 patients in Sweden study (72, 73). Only Cleveland study was taken place in U.S (74). And all other studies were in Europe or Asia. Cox regression is classic and widely accepted model for predicting the risk of complication or death. Except UKPDS, all other studies were used Cox regression model.

QRisk employed both Cox proportional hazard models to estimate coefficients and fractional polynomials to model non-linear risk relations with continuous variables for predicting the risk and 10-year risk of cardiovascular disease. Cox regression was used for predicting the risk of death in Cleveland study and risk of CVD in Sweden study. And major macro- and micro-vascular complications and death (CHD, stroke, non-cardiovascular mortality, nephropathy and retinopathy) were predicted in Japan study by models built up by Cox regression. UKPDS applied different methods for various outcomes, e.g. ad hoc model (CHD, stroke), logistic function (MI, stroke), and parametric survival models (major diabetes related complications).

For model validation, QRisk used validity dataset to validate internally and applied Framingham equation as external validity. Cross-validation was widely used in those studies. UKPDS, Cleveland, Sweden and Japan predictive models all adopted this method for validating internally. External validity of UKPDS models was evaluated by different methods, including comparison with survival probabilities from nonparametric (life table)

methods, comparison the predicted risk with modified Framingham score, comparison with other study results, and using the excluded data as validation data set. And Japan study used UKPDS engine as comparison for assessing external validity.

And received higher values of Receiver Operating Characteristic (ROC) curves, BIC and R^2 were considered as better model performances in QRisk study. Cleveland applied Concordance Index and calibration curve to evaluate model performance. Kolmogorov-type Supremum test and Goodness of fit (Hosmer-Lemeshow test) were chose in Sweden study, while the UKPDS engines applied diagnostic plots and permutation testing for testing the prediction performance.

SBP and A1C were important predictors for all of the models mentioned above and only Cleveland study considered DBP at the same time. Only Sweden study did not include any kinds of blood lipid measures into its model. And all other models added at least one of lipid measures in and Total Cholesterol and HDL-C were most frequent used. Due to LDL-C cannot be tested directly years ago and was calculated by total cholesterol, HDL-C and triglycerides, it was not well accepted for using as major predictor in the predictive models. Only Cleveland study input it into model and HDL-C, Triglycerides at the same time.

Age, race/ethnicity and gender are widely used demographic characteristics as controlled variables in predictive model. Except Sweden and Japan studies did not include ethnicity, all other studies added these three variables into their models. BMI was considered by all models except UKPDS. Smoking status or history and duration of diabetes were significant predictors and used in all models. Social deprivation was only involved in QRisk models and physical activity was used as predictor in the Japan study.

Previous related complication events were critical for those models too. CHD, MI, stroke and AF were used in QRISK and UKPDS models a lot. Retinopathy, kidney disease or Rheumatoid arthritis were not common. Only one of UKPDS engine considered them. Diabetes treatment was controlled in the Cleveland and Sweden predictive models too.

Methods

Study design

A retrospective study was designed to build up predictive model for estimating the optimal triple-goal for patients with T2DM, aiming to lower complications incidence and reaching better clinical health outcomes in the long-term healthcare management. Longitudinal data was used for estimating the risk of certain complication event. The optimized group of triple diabetes management goals (A1C, BP and LDL-C) was estimated for different age, racial groups, BMI by the risk predictive model.

Data source

This study was a retrospective observational study based on National Veteran Affairs (VA) electronic medical record (EMR) data including patients' records of pharmacy, inpatient, outpatient, and lab results from January 01, 2004 to December 31, 2015.

The Veterans Health Administration is the largest integrated health care system in the United States, providing care for veterans across the country. According to US Census Bureau, there were approximately 19 million living US veterans in 2014.

VA EMR is named as VA Informatics and Computing Infrastructure (VINCI) data database, which is a nation-wide view of high value VA patient data. VINCI is a research and development partnership and operational platform for health services research, epidemiology, decision support, and business intelligence. VINCI databases are stored in several servers within VINCI workspace. Data was operated on the VINCI system only.

The veterans administration's corporate data warehouse (CDW) is a national repository comprising data from several Veterans Health Administration (VHA) clinical and administrative systems, which includes VHA National Data Systems (NDS), VA Information Resource Center (VIReC), and others authorize research access to patient data. The data from multiple data sets throughout the VHA was incorporated into one standard database structure.

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

Sample selection

All patients with T2DM records (ICD-9-CM: 250.x0 and 250.x2) were selected. Index date was set as the date of first T2DM diagnosis between January 1, 2004 and December 31, 2015.

1. Inclusion Criteria:
    - Patients had at least two T2DM records (ICD-9-CM: 250.x0 and 250.x2) between January 1 2004 and December 31 2015
    - Enrollment period: eligible patients were enrolled at least 12 months before the first T2DM record (index date) and continuously enrolled at least 12 months after index date
    - Patients aged >=18 and age <=80 years old on the Index date
    - Patients with at least one lab measurements of A1C, BP and LDL-C during baseline period (included the index date)
    - Patients had at least one lab measurements of A1C, BP and LDL within 12 months after the index date
2. Exclusion criteria:
    - Patients had type 1 diabetes mellitus diagnosis (ICD-9-CM: 250.x1 or 250.x3)
    - Patients had records of microvascular complication and macrovascular complication at baseline period

Time Frame

Study period: The study period was defined as time from baseline to study endpoint (Jan 1st 2004, Dec 31st 2015).

Index date: The index date for T2DM patients was defined as the date of the first diagnosed as T2DM during the entire data period available

Baseline period: The baseline period was defined as the 12 months prior to the index date.

Follow-up period: Follow-up period was defined as the continuous enrollment time after the index date till anyone of endpoint appeared.

Endpoint: Study endpoint was defined as the first record of the following events:

- Death
- End of patient enrollment
- End of data availability

Variable definition

1. Outcome definition

The clinical outcomes were defined by the ICD-9-CM and ICD-10-CM codes recorded between the index date and the data endpoint. The clinical outcomes were classified into three major outcomes (**Appendix B**: macrovascular complication, microvascular complication, death) and subcategorized into atherosclerosis, aneurysm, or embolism (AAE), coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease (PVD) for macrovascular complication; retinopathy, nephropathy, neuropathy for microvascular complication. If at least one date of diagnosis for the clinical outcome was located within the beginning and ending of cycle, then this cycle was considered as having the clinical outcome (set as 1). Otherwise, if within the 6 months of the cycle, there was not any diagnosis found, then this cycle was considered as free of the clinical outcome. Except death, other clinical outcomes can be recurrent.

2. Covariate definition

Baseline Demographics:

• Age: patient's age at index date (round up of the year of index date minus birth date)

• Gender: the gender reported as 'M' was male, 'F' was female

• Race: the race reported as 'WHITE' or 'CAUCASION', and ethnicity was not 'HISPANIC' was defined as white; the race reported as 'BLACK' and ethnicity was not 'HISPANIC' was defined as black; and the race reported as 'ASIAN', 'AMERICAN INDIAN', 'NATIVE AMERICAN' or ethnicity reported as 'HISPANIC' was defined as other races

• Ethnicity: the ethnicity reported as 'HISPANIC' was defined as Hispanic; and reported as 'NOT HISPANIC' was defined as non-Hispanic; reported as 'UNKNOWN' or 'OTHERS' was defined as others

• BMI: patients' weight and height at baseline period were identified and used for calculating BMI. The average value was calculated for the patients had more than one weight or height measurements at baseline. If there was no record at baseline, the nearest value of height or weight after index date was used for imputation.

Comorbidities and health condition at baseline:

The ICD-9-CM codes of smoking status, mental health, renal disease, hypertension, hyperglycemia and hyperlipidemia at baseline period were identified (Appendix 2).

Comorbidities was defined as binary variables, which 1 represented having the specific condition.

3. Medication at follow-up period

The agents in use for treatment of T2DM were identified and classified as insulin and oral anti-diabetic medication, which included subgroups of Alpha-Glucosidase Inhibitors, Biguanides, DPP-4 inhibitor, Glucagon-Like Peptides agonist, Meglitinides, SGLT2 Inhibitors, Sulfonylureas, and Thiazolidinediones. The anti-hypertensive medications, which included beta-blockers, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, and diuretics, and the medications to treat hyperlipidemia, which included statins, niacin, bile-acid resins, fabric acid derivatives and cholesterol absorption inhibitors were identified (Appendix 3).

Having medication at each cycle or not was measured by the medication name and prescription date. If at least one date of prescription for the medication was found within begin and end of cycle, then this cycle was considered as having the medication (set as 1). Otherwise, if within the 6 months of the cycle, there was not any selected medication found, then this cycle was considered as free of the medication (set as 0). The percentage of coverage for medication was calculated by the total prescription days over the total follow-up days. The total prescription days was sum up by all of the fill days of supply for the selected medications.

Data preparation for lab measurements

1. Cycle building

Longitudinal data was prepared with each cycle length of 6 months starting from the index date. The last cycle was $\leq$ 6 months, which ended at the date of the end of data availability, the end of enrollment, or date of death.

2. Outcomes and lab results estimation for cycles

Lab results (A1C, BP and LDL-C levels), clinical outcomes and medication (anti-diabetic medication, anti-hypertension medication, and lipid lowering medication) were time varied variables and were specified for each cycle. The average of A1C and LDL-C estimates for each cycle were estimated using the area under the curve (AUC) method: for each patient, any two adjacent A1C or BP, LDL-C readings were connected by straight lines over time, irrespective of whether they were in the same cycle or different cycles; then trapezoidal areas

under each curve were determined, added together, and divided by the time of cycle (182 days).

3. Splines of lab results

In the multivariate regression analysis, the lab results were transformed into splines for model fitting. There is no gold standard for creating splines. One knot for two segments and second degree were used for building the splines. A1C was cut at 7, LDL-C at 100 mg/dL, BP at 130/90 mmHg. The original lab results, the quadratic lab results and the quadratic second spline (original lab value – lab cut point) were all put in the regression model for exploring the potential non-linear relationship with clinical outcomes.

4. Missing data imputation

Interpolation technique was used for data simulation in this study. If the value of patients' demographics and 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.

5. Define extreme values and data clean

A1C, BP and LDL-C result higher or lower than the 5 times of median were defined as extreme value, and interpolated with corresponding study group's median.

Statistical analysis

1. Descriptive analysis

Patient demographic characteristics and medical history at baseline were described by mean, median and standard deviation (SD) for continuous variables; and by count and proportion (%) for categorical variables.

The time to event (clinical outcomes or death) was measured by the date of first diagnosis of the specific outcome minus the index date. And the time to the end of study was measured by the date of death or data availability minus the index date. The durations were calculated for whole population, population with microvascular complications, population free from microvascular complications, population with macrovascular complications, population free from macrovascular complications, and the population died during the study period. Mean, standard deviation and median were presented with year as unit.

The counts and values of lab tests at baseline, follow-up period, and 1 to 5 years of post-index period were measured. The number of count (with standard deviation) and mean of lab results (with standard deviation) were presented.

The numbers and percentages of patients had clinical outcomes during the whole follow-up period were measured for death, microvascular/macrovascular complications and their subtypes. And the numbers and proportions of outcomes happened in first year after index date, second year after index date, third year after index date, and after 3 years of post-index date were presented too. Survival plot was used for showing the percentage surviving from clinical outcomes versus follow-up time. The survival function was estimated by Kaplan-Meier method (product-limit estimator).

Anti-diabetic, anti-hypertension and lipid lowering medications were classified by drug generic name in the prescription data. The number and percentage of patients were prescribed during the follow-up period were calculated. The percentage of treatment coverage time for each drug was presented.

2. Univariate analysis

The correlation between single lab measurement at baseline and clinical outcome was evaluated in univariate analysis. For exploring the potentially non-linear relationship between lab results and the risk of clinical outcome, local regression model was applied. The lab results of A1C, LDL-C, SBP and DBP were separately examined with the clinical outcomes of mortality, microvascular complication and macrovascular complication.

Local polynomial regression (LOESS regression) was used for fitting the potential non-linear relationship by weighted least square estimation at each lab value. The default degree ($\lambda = 2$) was used and smoothing parameter was set as 0.1 in this study. A group of smoothing parameters were used for estimating the bias corrected Akaike information criterion (AIC). The minimized AIC provided supportive information for finding the appropriate smoothing parameter. The smoothing parameter was determined by clinical meaning, smallest AIC and the smoothness of the curve. Repeating the method for every lab measurement with each clinical outcome, the smoothing parameter was determined for each LOESS model between one lab test and one of clinical outcome.

From the regression, the fitted value for the clinical outcome was calculated for lab result and was plotted on the scatterplot. The fitted values were connected, producing the local polynomial nonparametric regression curve. Due to there are no coefficient estimates from local regression, so the relationship between lab result and clinical outcome was only displayed as graph.

For avoiding the extraordinary influence on the curve, the extreme values were excluded from univariate analysis. The aim of this study was to estimate the optimal diabetes management targets, so the lab result, which was clinically too large or too low, does not contribute to the regression model. Even worse, it may distort the relationship due to some number of unusual lab results. In this study, A1C>15% or A1C<5%; LDL-C>200 mg/dL or LDL-C <40 mg/dL; SBP>200 mmHg or SBP<90 mmHg; DBP >100 mmHg or DBP<50 mmHg were excluded from the univariate local regression.

3. Multivariate analysis

Logistic regression with repeated measures and splines of lab results was used for estimating the relationship between time-varying outcome and lab measurements. For better approaching the possible non-linear relationship, splines of the lab results were created by starting with 1 knot and second degree (polynomial). Model building was based on clinical meanings, literature review and the results of model fitting. The distribution of clinical outcome in the model was set as binomial (DIST=BIN) and the link function was defined as logit.

The lab measurements, medication and clinical outcomes were all repeated measured for each cycle. Within-patient measurements were likely to be correlated between cycles, whereas between-patient measurements were likely to be independent. For such discrete correlated data, Generalized Estimating Equation (GEE) was used for analyzing such data by specifying REPEATED in PROC GENMOD. In the model, the clinical outcome was correlated binary response, which was modeled using the same link function and linear predictor setup (systematic component) as the independence case. The random component was described by the same variance functions as in the independence case, but the covariance structure of the correlated measurements were also modeled. The setting of the working correlation matrix, which was used to model the correlation of the clinical outcome from selected patients, was specified as autoregressive for correlation type (CORR=AR) and as exchangeable or

compound symmetric structure for correlation structure (TYPE=EXCH). The non-linear relationships between lab results (included A1C, LDL-C, SBP, and DBP) and predicted risk of clinical outcomes were displayed by smooth surface.

4. Finding the optimal lab results

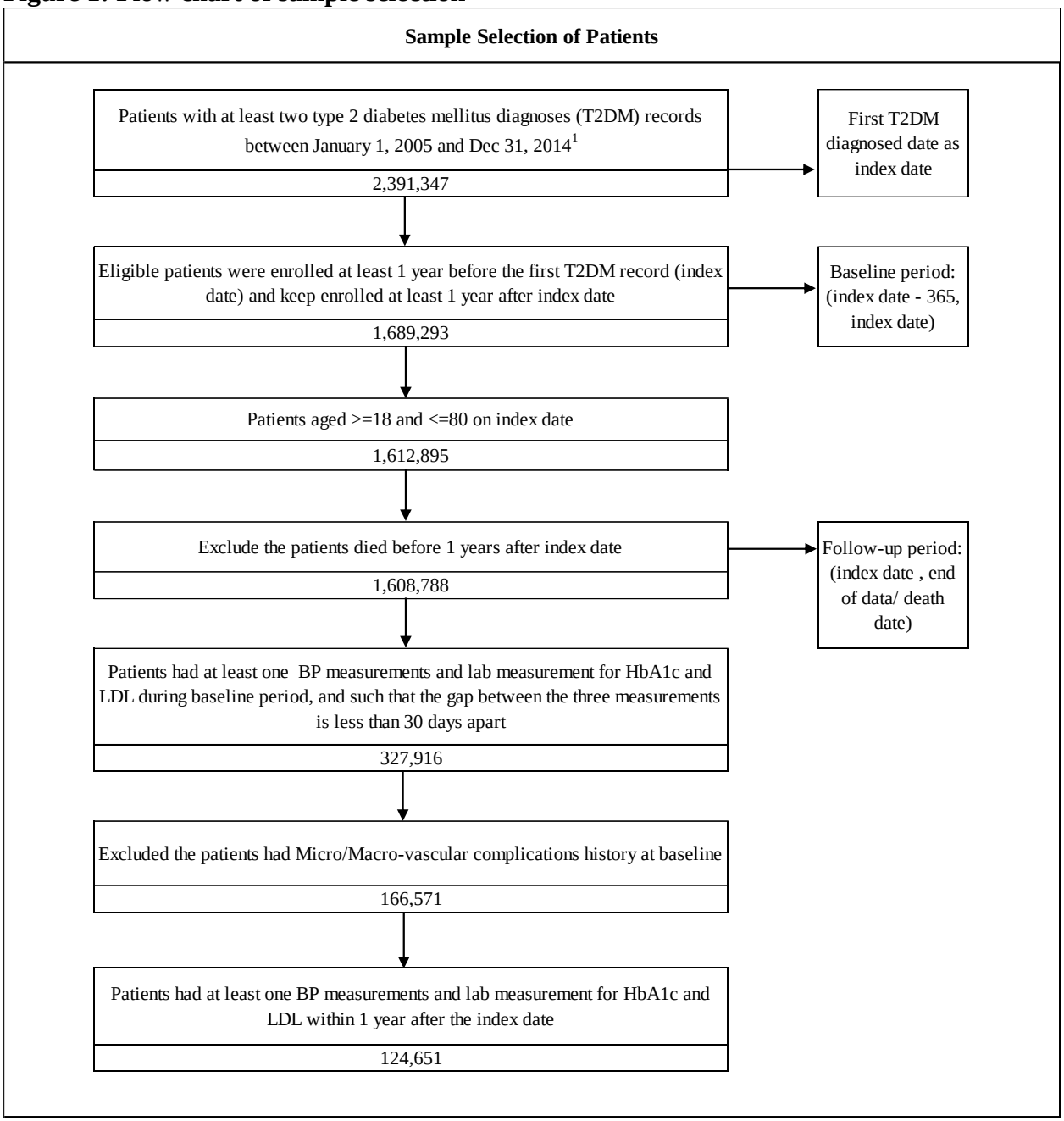
By logistic regression, the predicted probability of getting clinical outcome was calculated for each patient. All predicted values were sorted by ascending order and the lowest probability was found. The lab results with the lowest probability of having clinical outcome were identified. For reducing the bias from one-time estimation, the estimation procedure were duplicated by 100 times by the bootstrapped samples (sampling with replacement, and resampling by the patient ID). Mean of the lab results corresponding to lowest predicted probability of clinical outcome were determined as the optimal lab results. And the 95% confidence interval was determined by the 95% percentile method.

Results

Sample Selection

From January 1st 2005 to December 31st 2014, total 2,391,347 patients with at least two T2DM diagnoses were identified. After checking the eligibility, 1,689,293 patients were retained with at least 12 months continuous enrollment before the index date, and kept enrolled at least 12 months after the index date. Out of them, 1,612,895 adults aged between 18 and 80 years old were selected and 1,608,788 patients were retained after excluding the patients who died within the first year after the index date. Furthermore, at baseline period, 327,916 selected patients had at least one BP measurement and lab test results of A1C and LDL-C, and only 166,571 patients left after excluded the patients with microvascular or macrovascular complication history at baseline. Finally, patients with at least one BP measurement and lab test result of A1C and LDL-C within 1 year after the index date were selected and the medical records of 124,651 patients were used for analysis in this study. (**Figure 1**)

Figure 1: Flow chart of sample selection



Demographic characteristics at baseline

A total of 124,651 patients with T2DM were selected in the study sample with average age of 62.68 years old (SD=10.96) on the index date, which included 15,819 (12.69%) patients younger than 50 years old, 36,539 (29.31%) patients aged between 50 and 60 years old, 47,867 (38.40%) patients aged from 60 to 70 years old, and 24,426 (19.60%) patients were between 70 and 80 years old. 96.01% (119,677) of patients were male. White was major race with 67.41% (84,028) of patients, while 19.91% (24,817) of patients were black. Native

American, Asian, Indian American and Hispanic were all categorized to other race, which was represented only 3.75% (4,673) of patients, while 8.93% (11,133) of patients reported race/ethnicity as 'unknown' or the race/ethnicity was left as missing. At baseline period, the average of BMI was 33.32 kg/m^2 (SD=6.44) of selected patients, with mean weight of 223.13 lbs. (SD=46.76) and mean height of 69.38 inches (SD=3.07). 30,084 (24.13%) patients were normal or underweight (BMI<25), while 24,989 (20.05%) patients were overweight (25≤BMI<30) and 69,578 (55.82%) patients were classified as obesity by BMI. However, only 23.07% (28,757) of patients had diagnosis of obesity at baseline period. 15.85% (19,757) of patients had records of tobacco usage history. 65.63% (81,808) of patients had hypertension, while 56.15% (69,992) of them were diagnosed with dyslipidemia. Only 1.07% of patients had medical records of hypoglycemia during the 1 year of baseline period. And there were 7.88% (9,822) patients with diagnosis of renal disease, and 25.44% (31,711) patients were identified with mental disease. (**Table 1**)

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	15,819	12.69%
[50,60)	36,539	29.31%
[60, 70)	47,867	38.40%
[70,80]	24,426	19.60%
BMI		
<25	30,084	24.13%
[25,30)	24,989	20.05%
≥30	69,578	55.82%
Male	119,677	96.01%
Race		
White	84,028	67.41%
Black	24,817	19.91%
Others*	4,673	3.75%
Unknown	11,133	8.93%
Comorbidity		
Obesity	28,757	23.07%
Tobacco	19,757	15.85%
Hypertension	81,808	65.63%
Hypoglycemia	1,334	1.07%
Dyslipidemia	69,992	56.15%
Mental disease	31,711	25.44%
Renal disease	9,822	7.88%

*Others: included Native American, Asian, Indian American, Hispanic and patients who reported as 'others'

Counts of lab measurements and results

During the 1 year of baseline period, 1.47 times of A1C were taken on average (SD=0.70). While for the study follow-up period, an average of 11.01 times of A1C tests was detected, with standard deviation of 7.77 times. And the mean A1C value was 7.08% (SD=1.05) at baseline, and was 6.89% (SD=1.05) at follow-up period. The numbers of A1C test in the first five years after index date were fluctuated between 1.89 and 2.08 times per year with SD around 1. The mean value of A1C test was dropped at the first year of post-index to 6.76% (SD=1.15), and then slightly increased to 7.01% (SD=1.41) at the fifth year of post-index.

Similar with A1C test, selected patients had an average of 1.64 LDL-C tests (SD=0.84) at baseline, and 10.01 tests (SD=6.90) during follow-up period. The mean LDL-C value was 105.11 mg/dL (SD=34.88) at baseline, while it was 91.23 mg/dL (SD=26.89) during follow-up period. From the first to fifth year after index date, patients received 1.94 (SD=1.01) to 1.76 (SD=0.93) times of LDL-C tests on average. The mean value of LDL-C decreased to 96.34 mg/dL (SD=31.11) at the first year of post-index, and then slightly declined year over year to 87.29 mg/dL (SD=30.63) at the fifth year of post-index.

BP was more frequently measured, which was 4.08 times (SD=8.08) at baseline period and 35.95 times (65.32) during the follow-up years at average. The times of BP measurement fluctuated between 5.43 and 6.18 during the first five years after index date. The BP were 136.08/78.53 mmHg (SD=14.35/9.55) at baseline, and it dropped to 132.77/75.94 mmHg (SD=10.30/7.52) during follow-up period. The BP values kept stable during the first five year of post-index. (**Table 2**)

Table 2: Numbers of Lab Measurements and Lab Results at Baseline and Five Follow-up Years

	Baseline		Follow-up		1-year Post-index		2-year Post-index		3-year Post-index		4-year Post-index		5-year Post-index	
A1C														
n, SD	1.47	0.7	11.01	7.77	2.08	1.01	1.9	0.94	1.89	0.94	1.9	0.97	1.91	0.98
mean, SD	7.08	2.5	6.89	1.05	6.76	1.15	6.8	1.18	6.88	1.27	6.94	1.27	7.01	1.41
LDL-C														
n, SD	1.64	0.84	10.01	6.9	1.94	1.01	1.83	0.95	1.8	0.92	1.78	0.91	1.76	0.93
mean, SD	105.11	34.88	91.23	26.89	96.34	31.11	93.11	30.97	90.84	30.68	88.89	30.57	87.29	30.63
SBP														
n, SD	4.08	8.08	35.95	65.32	6.18	10.17	5.43	10.6	5.47	11.07	5.64	11.75	5.78	12.21
mean, SD	136.08	14.35	132.77	10.3	132.77	12.19	132.58	12.93	132.54	13.16	132.47	13.23	132.5	13.31
DBP														
mean, SD	78.53	9.55	75.94	7.52	76.47	8.39	76.13	9.79	75.85	9.05	75.59	9.08	75.33	9.12

For the population with specific clinical outcome, the lab results were estimated for the cycle of the clinical outcome initially happened and the pre-outcome cycle. Among the patients had microvascular complication, the mean value of lab tests were 7.10% (SD=1.26) for A1C, 88.94 mg/Dl (SD=28.53) for LDL-C and 133/75.14 mmHg (12.21/8.38) for BP at the cycle of first microvascular complication was diagnosed, while it was 7.17% (SD=1.74) for A1C, 93.03 mg/dL (SD=32.11) for LDL-C and 134.01/76.18 mmHg (SD=14.06/9.44) for BP at the pre-outcome cycle. Patients who had their first macrovascular complication diagnosis with an average of A1C at 6.98% (SD=1.17), LDL-C at 85.97 mg/Dl (SD=27.66), and BP at 132.54/73.47 mmHg (SD=12.25/8.31) at the cycle of diagnosis, and the mean value was 7.02% (SD=1.66), 92.35 mg/dL (SD=31.81) and 134.66/75.05 mmHg (SD=14.81/9.71) respectively at the previous cycle. For the population died at the end of study, the average A1C of 6.92% (SD=1.21), LDL-C of 88.18 mg/dL (SD=29.73), and BP of 130.36/71.36 mmHg (SD=14.96/9.15) at the cycle of death occurred, while it was 6.92% (SD=1.30), 86.81 mg/dL (SD=30.59), and 131.18/71.47 mmHg (SD=15.29/9.49) at the cycle before death, respectively. (**Table 3**)

Table 3: Lab Results at the Cycle of First Event Occurrence and the Cycle Before Event Occurred

	1st Microvascular complication (N=43,889)				1st Macrovascular complication (N=40,798)				Death (N=22,524)			
	Outcome occurred cycle		Pre-outcome cycle		Outcome occurred cycle		Pre-outcome cycle		Outcome occurred cycle		Pre-outcome cycle	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
A1C	7.1	1.26	7.17	1.74	6.98	1.17	7.02	1.66	6.92	1.21	6.92	1.3
LDL-C	88.94	28.53	93.03	32.11	85.97	27.66	92.35	31.81	88.18	29.73	86.81	30.59
SBP	133	12.21	134.01	14.06	132.54	12.25	134.66	14.81	130.36	14.96	131.18	15.29
DBP	75.14	8.38	76.18	9.44	73.47	8.31	75.05	9.71	71.36	9.15	71.47	9.49

Out of total 124,651 patients, 43,890 (35.21%) patients had at least one microvascular complications during the follow-up period, which included 12,615 (10.12%) retinopathy, 8,863 (7.11%) nephropathy, and 32,833 (26.34%) neuropathy. 10.68% of patients had the first diagnosis of microvascular complication at the first year after index date, while 6.34% happened at second year, 4.66% at third year, and 13.54% happened after 3 year of post-index.

Out of 124,651 patients, 40,798 (32.73%) patients had at least one macrovascular complications during the follow-up period, which included 25,504 (20.46%) patients with CAD, 13,138(10.54%) patients with cerebrovascular disease, 12,066 (9.68%) patients with PVD, and 8239 (6.61%) AAE. 10.78% of total patients had the first diagnosis of macrovascular complication at the first year after index date, while 5.55% happened at second year, 4.17% at third year, and 12.24% happened after 3 year of post-index.

During the whole follow-up period, 22,524 patients died (18.07%). Patients died at the first year of post-index have been excluded from this study. 2456 (1.97%) patients were found died at the second year after index date, while 2630 (2.11%) death occurred at the third year of post-index, and 17,439 (13.99%) patients died after three years of post-index. (**Table 4**)

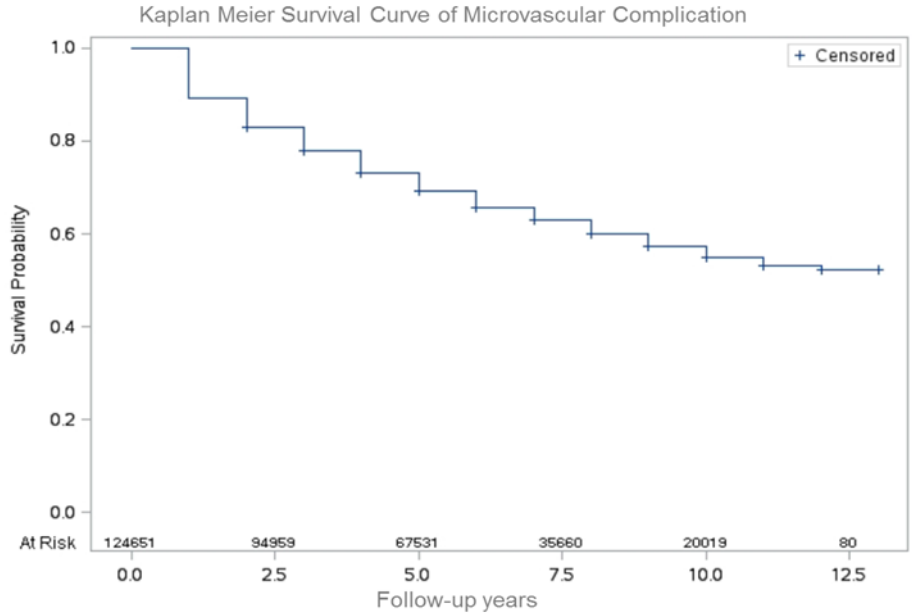
Table 4: Prevalence of Clinical Outcomes and the Proportions of First Event Occurrence Year

	Whole follow-up period		1-year Post-index		2-year Post-index		3-year Post-index		>3-year Post-index	
N=124651	n	%	n	%	n	%	n	%	n	%
Microvascular Complications	43890	35.21%	13313	10.68%	7903	6.34%	5809	4.66%	16878	13.54%
Retinopathy	12615	10.12%	4276	3.43%	2306	1.85%	1683	1.35%	4350	3.49%
Nephropathy	8863	7.11%	3041	2.44%	1633	1.31%	1147	0.92%	3041	2.44%
Neuropathy	32833	26.34%	10346	8.30%	6046	4.85%	4325	3.47%	12116	9.72%
Macrovascular Complications	40798	32.73%	13437	10.78%	6918	5.55%	5198	4.17%	15257	12.24%
CAD	25504	20.46%	9685	7.77%	4363	3.50%	3129	2.51%	8327	6.68%
Cerebrovascular disease	13138	10.54%	4575	3.67%	2194	1.76%	1658	1.33%	4712	3.78%
PVD	12066	9.68%	4450	3.57%	2082	1.67%	1458	1.17%	4076	3.27%
AAE	8239	6.61%	2879	2.31%	1433	1.15%	1060	0.85%	2879	2.31%
Death	22524	18.07%	n/a	n/a	2456	1.97%	2630	2.11%	17439	13.99%

*Follow-up time= 1st diagnosed date-index date; Years of follow-up was rounded up

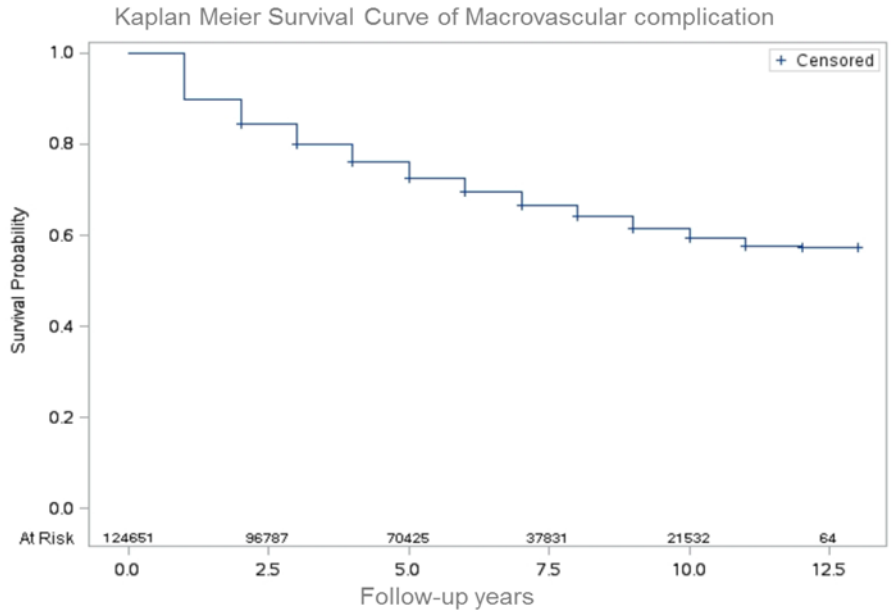
From the Kaplan Meier survival analysis (**Figure 2**), the 5-year survival rate of microvascular complication was 69.25% and 10-year survival rate dropped to 55.02%. More than 10% of patients had their first diagnosis of microvascular complication during the first year of follow-up (1-year survival rate=89.26%). With the longer follow-up years and more loss of 'very sick' patients, the incidence rates decreased year by year due to patients.

Figure 2: Kaplan-Meier Survival Curve for Microvascular Complication



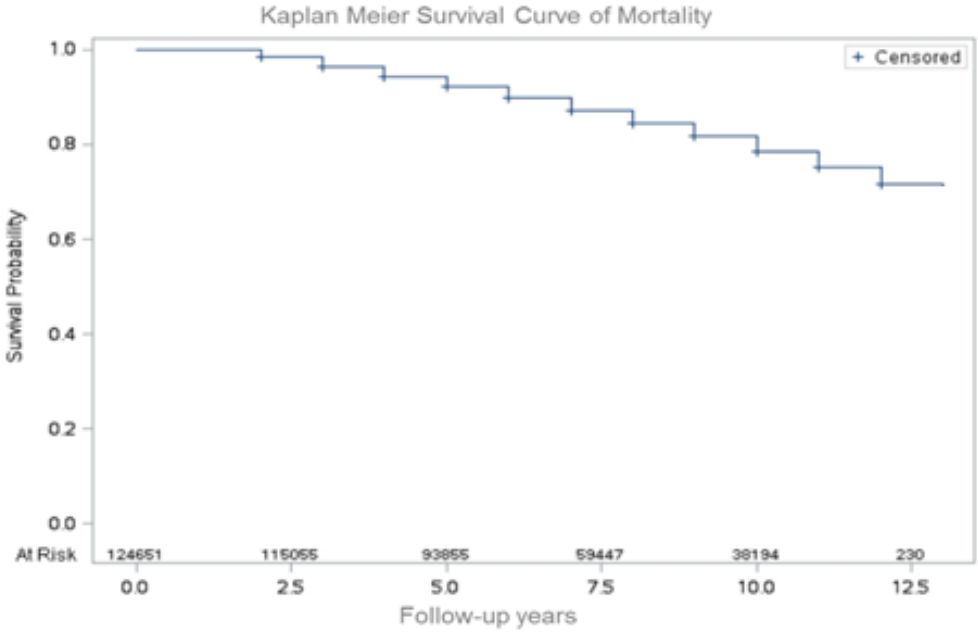
From the Kaplan Meier survival analysis (**Figure 3**), the 5-year survival rate of macrovascular complication was 72.65% and 10-year survival rate dropped to 59.49%. About 10% of patients had their first diagnosis of macrovascular complication during the first year of follow-up (1-year survival rate=89.75%).

Figure 3: Kaplan-Meier Survival Curve for Microvascular Complication



The mortality rate grew with longer time of follow-up. Due to the patients died within the first year of follow-up had been excluded, the survival rate was estimated from second year after index date. 1.64% patients died in the second year of follow-up. The 5-year survival rate was 92.17% and 10-year survival rate was 78.59%. Till the end of study, 71.61% of patients survived. (**Figure 4**)

Figure 4: Kaplan-Meier Survival Curve for Mortality



Follow-up years for selected population

For the whole population, the mean of follow-up time was 6.72 years (SD=3.21) and the median was 6.68 years. The patients who died during the study period had an average 5.71 follow-up years (SD=2.95) and the median was 5.43 years. (**Table 5a**)

Table 5a: Follow-up Years of Whole Population and Population Died at the End of Study

	Whole population		**Death**	
	Mean ± SD	Median	Mean ± SD	Median
Time to end of study	6.72 years ± 3.21	6.68 years	5.71 years ± 2.95	5.43 years

After sub-grouping population by if diagnosis of microvascular complication was found during follow-up period, average 2.86 years (SD=2.56) were from the index date till their first microvascular complication, and total 7.89 years of follow-up time for population who had microvascular complication. Patients who were free from microvascular complication were followed 6.08 years (SD=3.15) on average. (**Table 5b**)

Table 5b: Follow-up Years of the Patients Had Microvascular complication and Microvascular Complication Free Population

	Microvascular Complication		**Micro-free**	
	Mean ± SD	Median	Mean ± SD	Median
Time to first event	2.86 years ± 2.56	2.11 years	N/A	N/A
Time to end of study	7.89 years ± 2.99	8.34 years	6.08 years ± 3.15	5.77 years

During follow-up period, patients were followed 2.81 years (SD=2.01) before they diagnosed as macrovascular complication, and were totally followed 7.88 years (SD=3.04) averagely. The patients who were free from macrovascular complication had a mean follow-up time of 6.15 years (SD=3.15). (**Table 5c**)

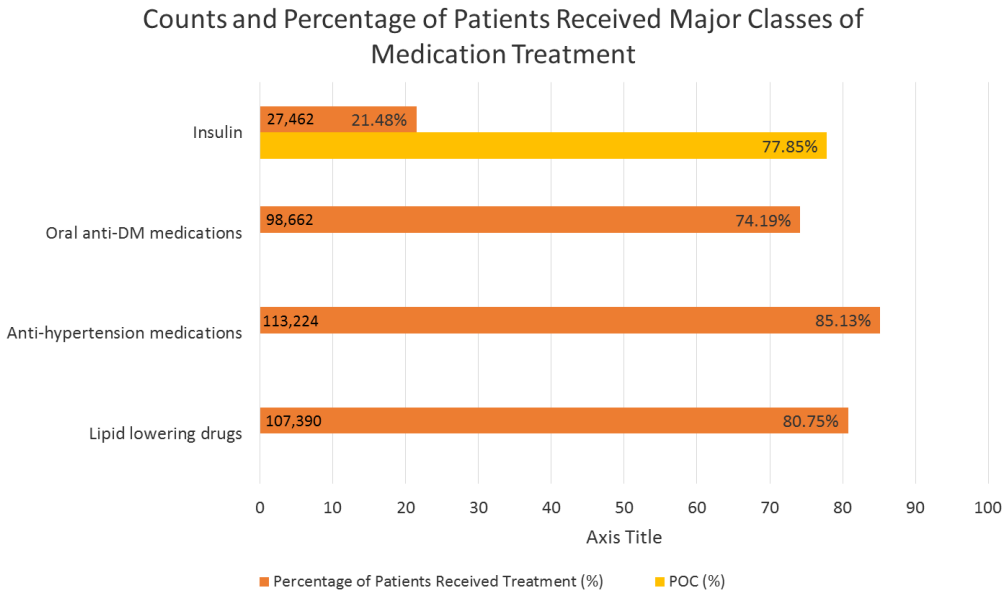
Table 5c: Follow-up Years of the Patients Had Macrovascular complication and Macrovascular Complication Free Population

	Macrovascular Complication		**Macro-free**	
	Mean ± SD	Median	Mean ± SD	Median
Time to first event	2.81 years ± 2.58	2.01 years	N/A	N/A
Time to end of study	7.88 years ± 3.04	8.35 years	6.15 years ± 3.15	5.86 years

Medications

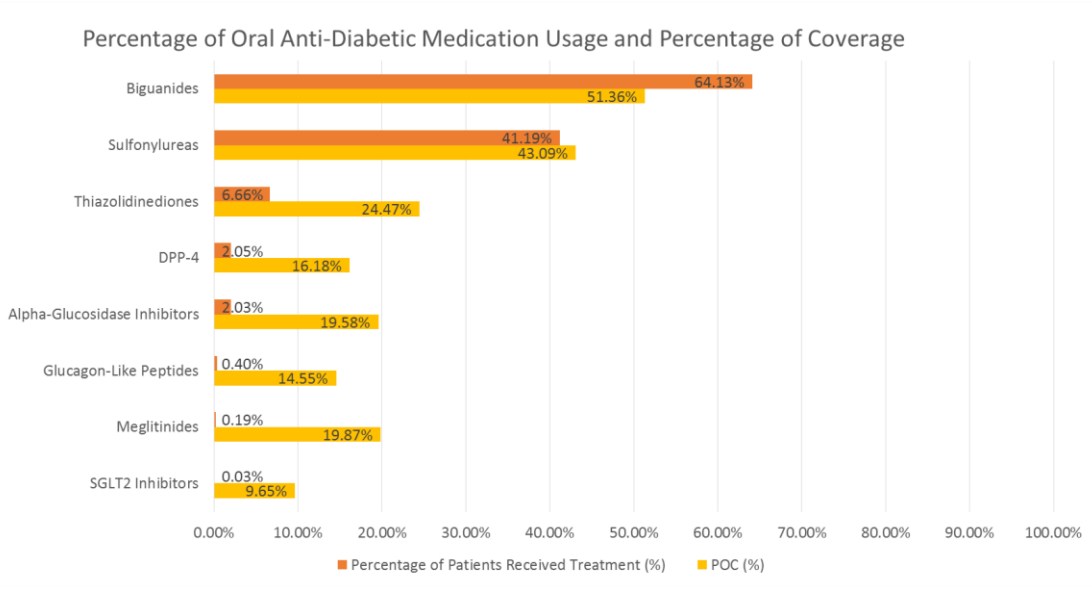
In the follow-up period, 21.48% of patients (27,462) were identified as insulin users and the average percentage of coverage was 77.85%, while 74.19% (98,662) used at least one oral anti-diabetic medication. 85.13% (113,224) of patients had received anti-hypertension medication and 80.75% (107,390) had had lipid lowering drugs. (**Figure 5**)

Figure 5: Prescription Rates of Major Classes of Medication Treatments and Percentage of Coverage of Insulin



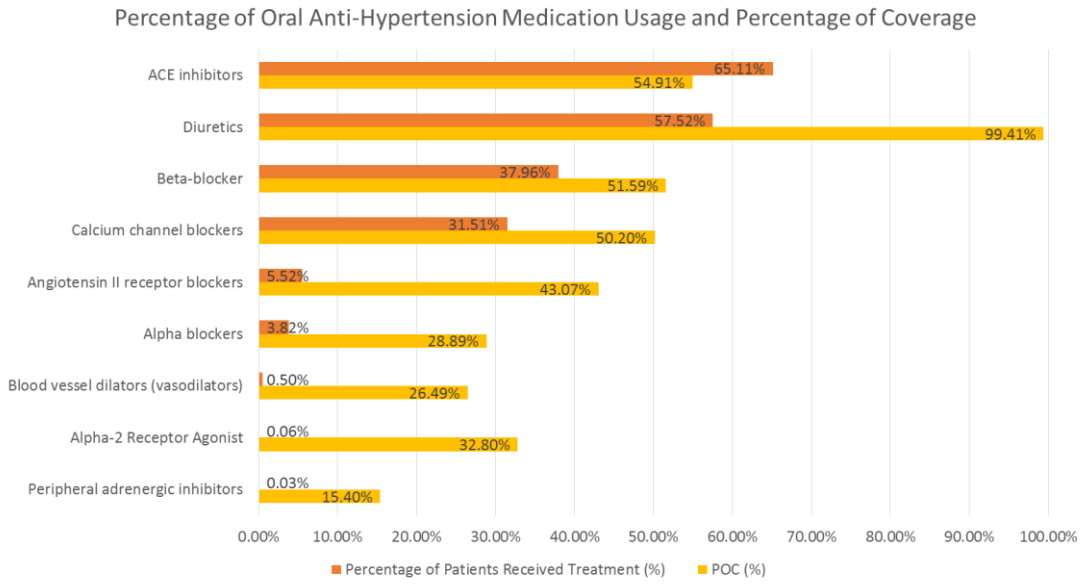
This figure (**Figure 6**) was shown the ranking the oral anti-diabetic medication use rate. The biguanides was most widely used (64.13%) and patients who received biguanides were covered 51.35% time of follow-up period averagely. Sulfonylureas and thiazolidinedione were the second and third frequently used anti-diabetic medications. 41.19% and 6.66% of patients were prescribed, and covered 43.09% and 24.47% of follow-up period respectively. Only about 2% patients used DDP-4 and Alpha-Glucosidase Inhibitors, while the less than 1% patients were prescribed Glucagon-Like Peptides agonists, meglitinides and SGLT2 Inhibitors.

Figure 6: Prescription Rates of Classes of Anti-Diabetic Medication and Percentages of Coverage



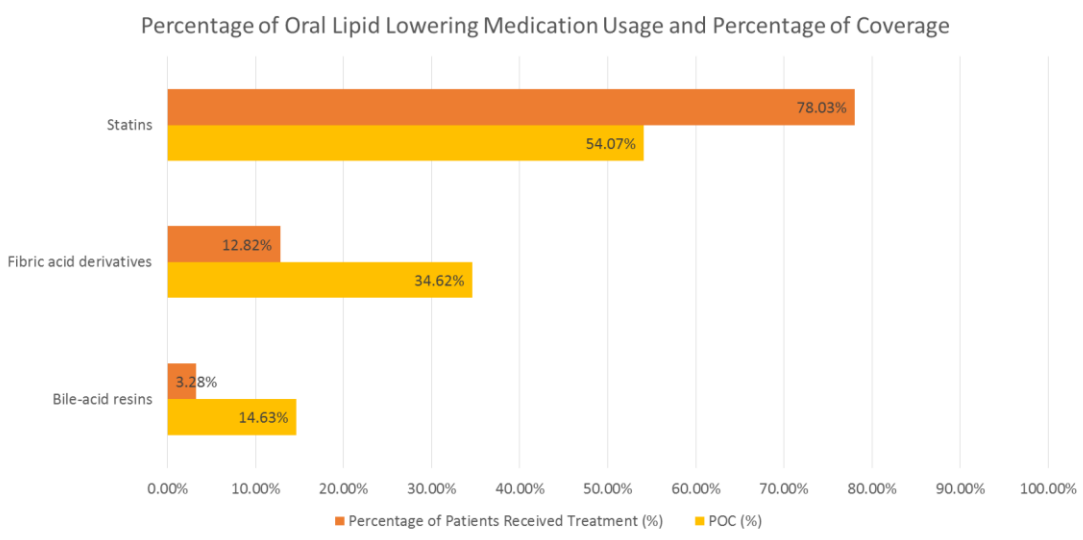
ACE Inhibitors, Diuretics, Beta-blocker and Calcium channel blockers were top 4 most frequently used anti-hypertension medications, which were used among 65.11%, 57.52%, 37.96% and 31.51% respectively. The percentage of coverage of patients who have ever been prescribed Diuretics reached 99.41%, while all the other three drug were between 50.20% and 54.91%. Small percentage of patients used Angiotensin II receptor blockers or Alpha blockers, which were 5.52% and 3.82% respectively. And less than 1% patients were prescribed blood vessel dilators, Alpha-2 receptor agonist and or peripheral adrenergic inhibitors (0.50%, 0.06%, and 0.03% respectively). (**Figure 7**)

Figure 7: Prescription Rates of Classes of Anti-Hypertension Medications and Percentages of Coverage



78.03% of patients used statins and the treatment covered 54.07% of follow-up period. And 12.82% and 3.28% of patients used fabric acid derivatives and bile-acid resins as lipid lowering medication, and were covered by the treatment 34.62% and 14.63% time of whole follow-up period respectively. (Figure 8)

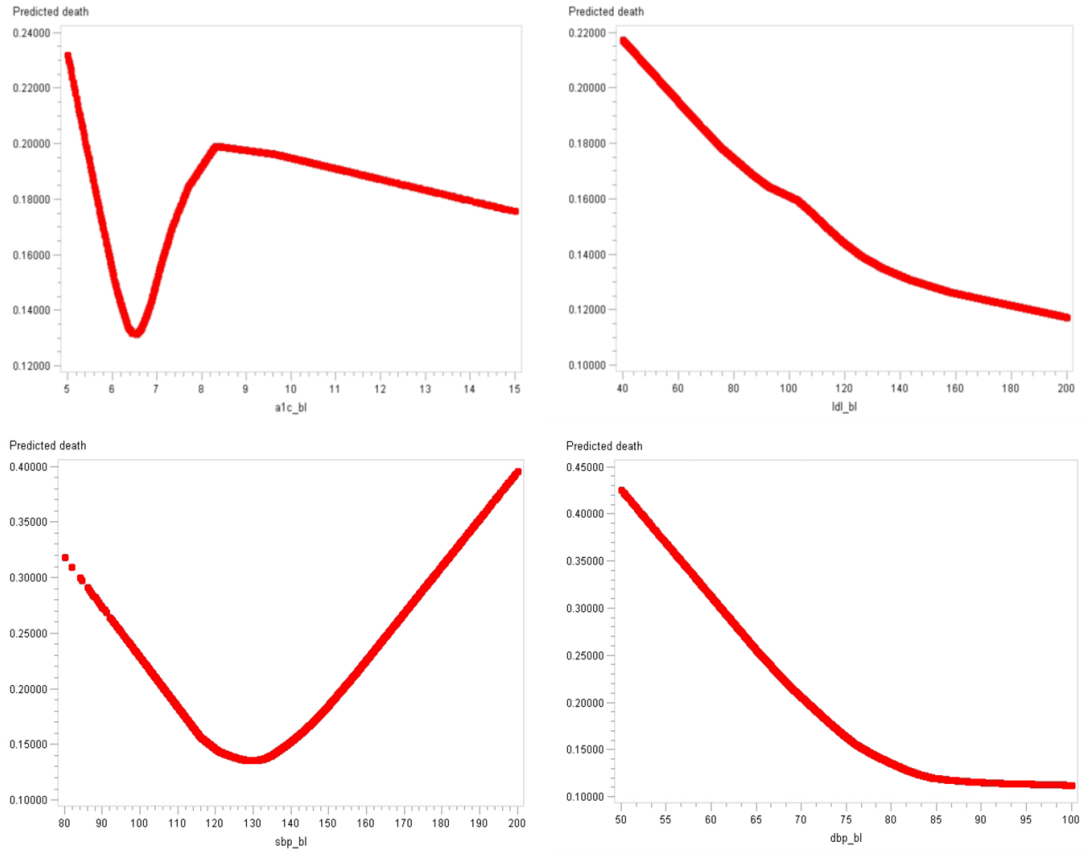
Figure 8: Prescription Rates of Classes of Lipid Lowering Medications and Percentages of Coverage



Univariate analysis

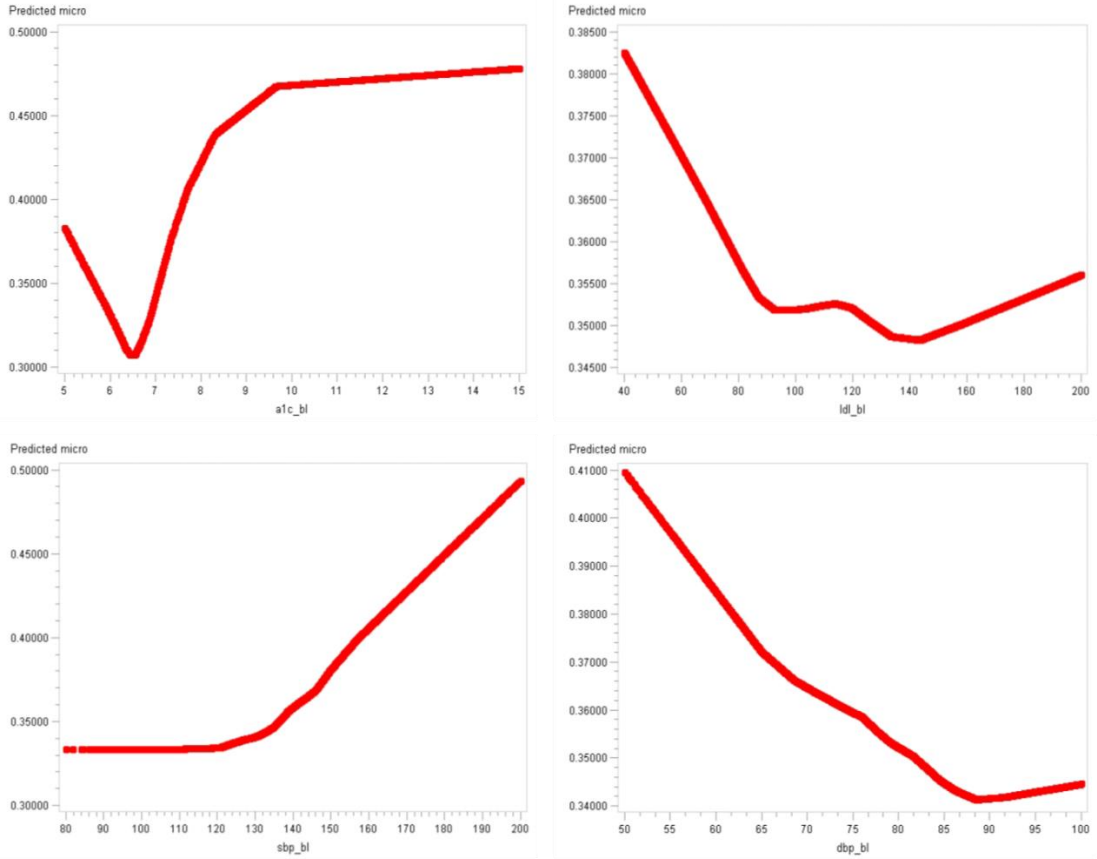
Each lab measurement at baseline period was used for univariate analysis by LOESS regression. The smooth curves (**Figure 9**) were shown the visualized potential non-linear relationship between each lab test and a specific clinical outcome. From Figure 9, the predicted risk of death was dropping with the A1C increased till around 6.5%. Then the risk started to raise up with the increase of A1C after about 6.5%. However, risk stopped rising when the A1C reached about 8.5%. The relationship between LDL-C and the risk of death was close to linearity. The patients had higher LDL-C at baseline were found with lower risk of death during follow-up. The SBP showed U-shape relationship with the risk of death. SBP between 120-135 mmHg was associated with lowest risk intuitively. Lower or higher than this range were associated elevated risk. While the DBP was not found similar relationship with the predicted risk of death. Observed by the curve, the risk decreased with the DBP increased from 50 to 85 mmHg, and it kept constant when the DBP was higher than 85 mmHg.

Figure 9: Plots of Predicted Risk of Mortality and Lab Measurements at Baseline from Local Regression



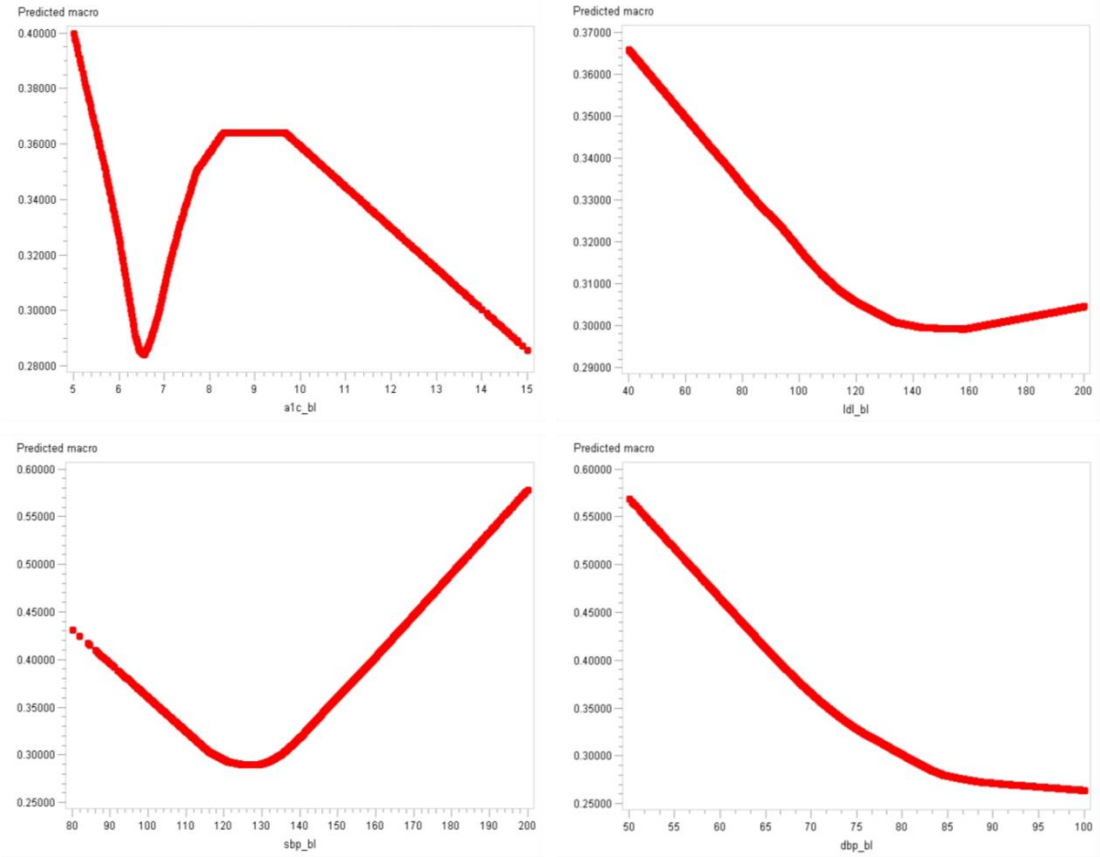
From **Figure 10**, the lowest predicted risk of microvascular complications happened at round 6.5 of A1C. Lower than 6.5%, the risk decreased with the increased A1C. However, after the A1C reached 6.5%, the predicted risk sharply went up with increasing A1C. The rate of growth turned to be very small after A1C reached 10%. The relationship between the predicted risk of microvascular complications and LDL-C value at baseline was close to U-shape. The range of 90 to 140 mg/dL was shown relatively lower risk. Lower or higher LDL-C than this range were both associated with elevated risk. The growth of SBP was related to increasing risk of microvascular complications. But the rate of growth was very low when SBP was lower than 130 mmHg. The risk rose up quickly with increasing SBP while SBP was >130 mmHg. The risk was monotonic decreased with growth of DBP till it reached around 85 mmHg. When DBP was higher than 85 mmHg, the risk slightly increased with the DBP grew.

Figure 10: Plots of Predicted Risk of Microvascular Complication and Lab Measurements at Baseline from Local Regression



The lowest predicted risk of macrovascular complications was associated with A1C of 6.5% too. Lower than 6.5%, the risk decreased with increasing A1C. While the A1C between 6.5% and 8%, the increasing predicted risk was associated with larger A1C. However, the risk decreased with increasing A1C when A1C was higher than 8%. The increasing LDL-C was related to growth of risk of macrovascular complications. However, the trend changed when LDL-C reached around 140 mg/dL. The predicted risk stopped growing, and start to increase slightly with increasing LDL-C when LDL-C was larger than 160 mg/dL. Intuitively, the SBP between 120 and 130 mmHg was associated with lowest risk of macrovascular complications. The risk was elevated if SBP higher or lower than this range. Not like the quadratic relationship of SBP, the risk was monotonically decreased with SBP increasing. The rate of reduction was much lower while the DBP reached around 85 mmHg. (**Figure 11**)

Figure 11: Plots of Predicted Risk of Macrovascular Complication and Lab Measurements at Baseline from Local Regression



Multivariate analysis

Estimated the risk of death for whole study population (**Table 6**), A1C at 6.06% (SD=0.21), LDL-C at 106.10 mg/dL (SD=9.28), SBP 137.90 mmHg (SD=2.86) and DBP at 98.00 mmHg (SD=2.46) were found to associated with lowest risk of mortality in the regression model. Not all lab results were shown quadratic relationship with the risk of mortality in the subgroup analysis. Among the patients aged younger than 50 years old, the optimal A1C value was 6.15% (SD=0.28), LDL-C was 81.45 mg/dL (SD=11.47), SBP was 131.40 mmHg (SD=3.41), while a higher DBP was associated with lower risk of death. For patients age between 50 and 60 years old, the optimal lab results were 6.32% (SD=0.28) for A1C, 98.30 mg/dL (SD=8.83) for LDL-C, 130.80/99.75 mmHg (SD=3.87/1.10) for BP, which were associated with lowest risk of mortality. increasing A1C, LDL-C and DBP values were found associated with lower risk of death among patients aged between 60 and 70 years old, while optimal SBP was 146.50 mmHg (SD=6.22). For patients of 70 to 80 years old, the optimal lab values associated with lowest risk of death were 6.15% for A1C (SD=0.18), 101.80 mg/dL for LDL-C (SD=8.95), 147.85/93.15 mmHg for BP (SD=3.64/2.43).

The optimal A1C, LDL-C and BP were 6.02% (SD=0.23), 112.70 mg/dL (SD=11.86) and 139.50/95.20 mmHg (SD=3.59/0.98) for whites. For black patients, LDL-C was managed at 90.50 mg/dL (SD=7.67), SBP at 136.70 mmHg (SD=3.91), and the A1C lower and DBP higher, the risk of death was lower.

For patients with normal weight (BMI<25), A1C at 5.95% (SD=0.20), LDL-C at 99.65 mg/dL (SD=7.08), SBP at 140.40 mmHg (SD=3.74) and higher DBP value were associated with the lowest risk of death. Overweight patients who managed A1C at 6.29% (SD=0.18), BP at 137.10/88.00 mmHg (SD=2.48/2.46), and had higher LDL-C value were estimated with lowest mortality risk. For obesity patients, the optimal lab values were 5.98% (SD=0.27) for A1C, 99.25 md/dL (SD=12.32) for LDL-C, SBP as 136.55 mmHg, with the higher DBP associated with lowest risk of mortality.

Table 6: Optimal Lab Measurements Associated with the Lowest Risk of Death

		A1C		LDL-C		SBP		DBP	
	n	Estimate	SD*	Estimate	SD	Estimate	SD	Estimate	SD
Whole population	24,651	6.06	0.21	106.10	9.28	137.90	2.86	98.00	2.46
Subgroup									
Age									
<50	15,819	6.15	0.28	81.45	11.47	131.40	3.41	Negative linear	
[50,60)	6,539	6.32	0.28	98.30	8.83	130.80	3.87	99.75	1.10
[60, 70)	7,867	Positive linear		Negative linear		146.50	6.22	Negative linear	
[70,80]	4,426	6.15	0.18	101.80	8.95	147.85	3.64	93.15	2.43
Race									
White	4,028	6.02	0.23	112.70	11.86	139.50	3.59	95.20	0.98
Black	4,817	Positive linear		90.50	7.67	136.70	3.91	Negative linear	
Others	4,673	6.27	0.43	Negative linear		159.65	11.94	Negative linear	
BMI									
<25	30,084	5.95	0.20	99.65	7.08	140.40	3.74	Negative linear	
[25,30)	24,989	6.29	0.18	Negative linear		137.10	2.48	88.00	2.46
≥30	69,578	5.98	0.27	99.25	12.32	136.55	3.31	Negative linear	

For achieving the lowest estimated risk of microvascular complication, A1C as 6.81% (SD=0.32) and LDL-C as 109.10 (SD=12.03) were found associated with optimal outcome for total population, while BP had unidirectional effect. 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 old. At the same time, 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), A1C at 6.58% (SD=0.22) and LDL-C at 110.12 mg/dL (SD=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 old, A1C at 6.87% (SD=0.48), LDL-C at 108.39 mg/dL (SD=16.59), BP at 121.50/98.90 mmHg (SD=3.99/2.08) were associated optimal outcome.

For whites, the optimal lab measurements were A1C as 6.78% (SD=0.31), LDL-C as 118.30 (SD=18.36), lower SBP and higher DBP, which were associated with the lowest risk of microvascular complication. While the optimal values of 7.11% for A1C (SD=0.29), 104.70 mg/dL (SD=6.27) for LDL-C, 119.30 mmHg (SD=5.82) for SBP, and higher DBP were estimated for blacks.

For 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). And the optimal estimation of A1C was 6.85% (SD=0.23) while LDL-C was 110.50 mg/dL (SD=12.96) for patients overweight (25≤BMI<30). For obesity 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). No matter with BMI, lower SBP and higher DBP were estimated to associate with better outcome when the specific optimal values of A1C and LDL-C were achieved. (**Table 7**)

Table 7: Optimal Lab Measurements Associated with Lowest Risk of Microvascular Complication

		A1C		LDL-C		SBP		DBP	
	n	Estimate	SD	Estimate	SD	Estimate	SD	Estimate	SD
Whole population	124,651	6.81	0.32	109.10	12.03	Positive linear		Negative linear	
Subgroup									
Age									
<50	15,819	Positive linear		105.78	20.31	Positive linear		Negative linear	
[50, 60)	36,539	6.88	0.35	98.90	10.85	Positive linear		Negative linear	
[60, 70)	47,867	6.58	0.22	110.12	17.01	Positive linear		Negative linear	
[70, 80]	24,426	6.87	0.48	108.39	16.59	121.50	3.99	98.90	2.08
Race									
White	84,028	6.78	0.31	118.30	18.36	Positive linear		Negative linear	
Black	24,817	7.11	0.29	104.70	6.27	119.30	5.82	Negative linear	
Others	4,673	9.94	1.19	Negative linear		Positive linear		Negative linear	
BMI									
<25	30,084	6.69	0.33	106.95	11.61	Positive linear		Negative linear	
[25,30)	24,989	6.85	0.23	110.50	12.96	Positive linear		Negative linear	
≥30	69,578	6.86	0.37	109.2	11.63	Positive linear		Negative linear	

For achieving the lowest risk of macrovascular complication (**Table 8**), the A1C at 6.76% (SD=0.24), LDL-C at 111.65 mg/dL (SD=6.78), SBP at 130.60 mmHg (SD=6.64) were estimated as the optimal values for whole population.

Patients, who were younger than 50 years old, were estimated to have lowest risk of macrovascular complication with A1C at 6.96% (SD=0.23), lower LDL-C, SBP at 121.1 mmHg (SD=4.75), and higher DBP. For patients aged between 50 and 60 years old, optimal A1C was 6.80% (SD=0.23), LDL-C was 124.25 mg/dL (SD=9.83), SBP was 124.20 mmHg (SD=5.11) and higher DBP value. For patients aged between 60 and 70 years old, A1C at 6.71% (SD=0.19), LDL-C at 131.55 mg/dL (SD=8.49), BP at 136.95 mmHg (SD=6.62) and higher DBP were associated optimal outcome. The optimal lab 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 old.

Sub-grouped by races, the optimal lab values of were 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 lowest risk of macrovascular complication. While the values were 6.96% (SD=0.24) for A1C, 119.80 mg/dL (SD=9.02) for LDL-C, 122.95 mmHg (SD=5.02) for SBP for patients whose race as black.

No matter which BMI groups patients were in, a higher DBP was associated with better outcome of macrovascular complication. While 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 lab results associated with lowest risk of macrovascular complication for obesity patients (BMI≥30) were 6.85% (SD=0.22) for A1C, 114.75 mg/dL (SD=7.47) for LDL-C, 148.35 mmHg (SD=6.71) for SBP.

Table 8: Optimal Lab Measurements Associated with Lowest Risk of Macrovascular Complication

		A1C		LDL-C		SBP		DBP	
	n	Estimate	SD	Estimate	SD	Estimate	SD	Estimate	SD
Whole population	124,651	6.76	0.24	111.65	6.78	130.60	6.64	Negative linear	
Subgroup									
Age									
<50	15,819	6.96	0.23	Positive linear		121.1	4.75	Negative linear	
[50,60)	36,539	6.80	0.23	124.25	9.83	124.2	5.11	Negative linear	
[60, 70)	47,867	6.71	0.19	131.55	8.49	136.95	6.62	Negative linear	
[70,80)	24,426	6.56	0.27	104.60	6.46	134.30	6.11	Negative linear	
Race									
White	84,028	6.67	0.22	130.05	8.42	138.85	5.77	Negative linear	
Black	24,817	6.96	0.24	119.80	9.02	122.95	5.02	Negative linear	
Others	4,673	8.57	1.13	104.10	7.23	Positive linear		Negative linear	
BMI									
<25	30,084	6.64	0.28	108.50	5.84	113.15	6.73	Negative linear	
[25,30)	24,989	6.43	0.25	132.50	9.44	123.50	4.63	Negative linear	
≥30	69,578	6.85	0.22	114.75	7.47	148.35	6.71	Negative linear	

Discussion

This large-scale retrospective study was designed for predicting the optimal values of major lab measurements with the best long-term clinical outcomes. The estimated optimal lab results were estimated for patients with various age, race and BMI level. The non-linear relationships between lab results (A1C, LDL-C, SBP and SBP) and clinical outcomes (mortality, microvascular and macrovascular complications) were assessed by smooth curves and surfaces. The four lab values as a combination associated with lowest predicted risks of clinical outcome were identified from regression models.

Large sample size was applied in this analysis. A total of 124,651 patients with T2DM were selected with median 7 years of follow-up time. 5-year survival rate was 92.17%, which was lower than patients with T2DM from Sweden (94.4%) (75).

The non-linear relationships between lab measurements (A1C, BP and Lipid) and clinical outcomes were identified in this study. Similar studies were examined in UK and Taiwan population too (3) (76). By Cox model, the UK study mentioned that the categories of A1C 7.25–7.75% (56–61 mmol/mol), total cholesterol 3.5–4.5 mmol/l (135.3 mg/dL-174.0 mg/dL), systolic BP 135–145 mmHg and diastolic BP 82.5–87.5 mmHg were associated with relatively lower risk of death. While optimal values of A1C 7.0–8.0%, SBP 130–140 mmHg, and LDL-C 100–130 mg/dL were detected with lowest risk of all-cause mortality in Taiwan population with T2DM. The categories higher or lower than these ranges may increase the risk and implied the existence of optimal lab values, which confirmed the findings in this study. Due to the method's limitation, the curve was lack of flexibility to accurate describe the potential relationship. Cox can only produce relative risk by comparing with reference level, so the lab values have to be categorized into intervals. In our research, the potential non-linear relationship can be precisely described.

A1C control and its optimal value

Explicit evidences have been found to support that lowering A1C as a results of proper treatment can reduce the complication mortality rates. However, studies rarely talked about how low the A1C should be. In ADA guideline, the A1C goal is tiered

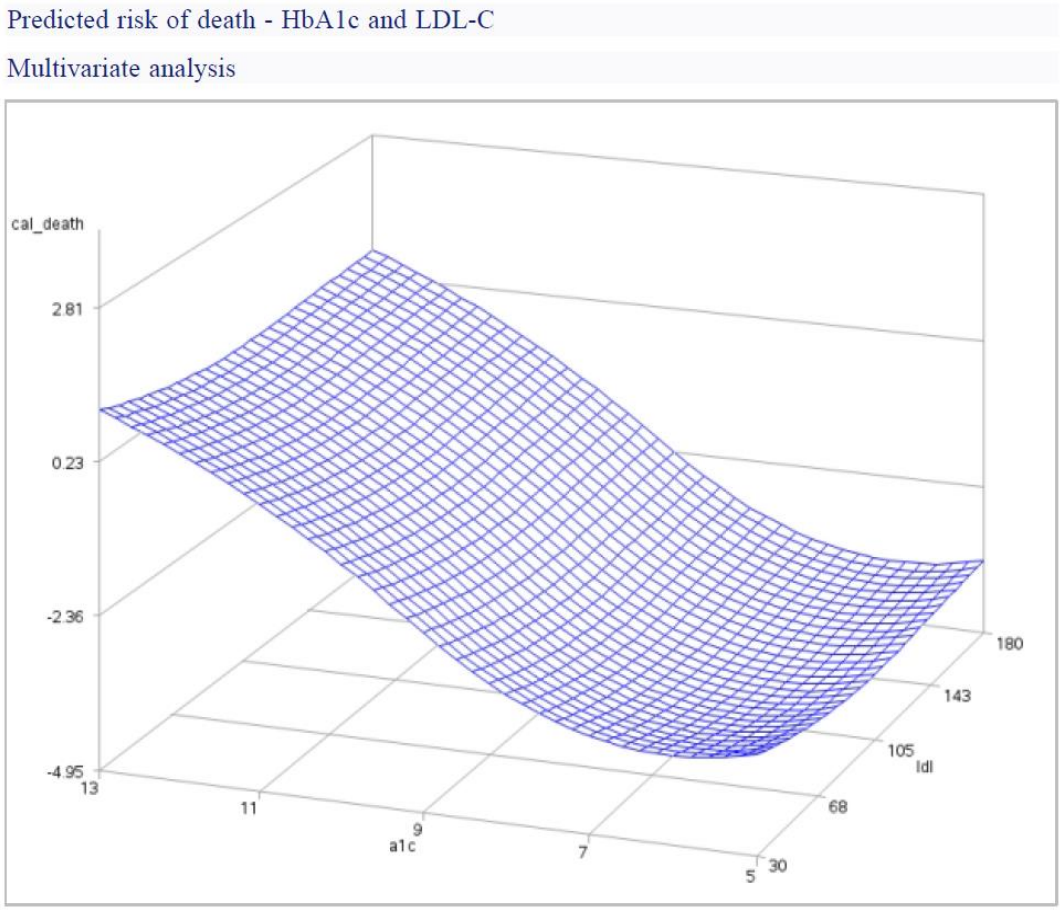
into 3 levels, general goal of <7%, more stringent goal of <6.5%, and less stringent goal of <8%, but does not mention about the lower bond of A1C control. In other words, unless patients complain about intolerable side effects (e.g. hypoglycemia etc.), A1C can be close to the level of DM-free patients (<5.7 %).

In this study, for lowering the risk of microvascular and macrovascular complications, A1C between 6.5% -7.0% was optimal for general population with T2DM. For minimizing the risk of death, 5.8% - 6.3% of A1C was found to be optimal. It confirmed that appropriate glycemic control is meaningful for long-term all kinds of clinical outcomes, not only associated with less microvascular and macrovascular complications but also lowered the mortality rate. Additionally, there is no one-for-all A1C target. The optimal A1C for death is lower than the optimal point for best outcome of microvascular and macrovascular complications. And one more crucial finding is too tight glycemic control (<5.8%) may be harmful for patients' long-term clinical outcomes.

1. Glycemic control and risk of mortality

In this study, A1C controlled at about 6% was associated with the lowest risk of mortality. It is within the range of the more stringent goal (<6.5%), but even lower. The guidelines are tended to be conservative for safety consideration and leave flexibility to physicians.

Figure 12: Smooth Surface of A1C and LDL-C with Risk of Mortality from Multivariate Analysis



The flexibility and conflict evidences induce a lot of debates about if tight glycemic control should be recommended. ACCORD study found the intensive treatment (A1C reached 6.4%) was associated with higher mortality rate in patients with mean age of 62 years old and preexisting cardiovascular disease (51). It implied that intensive treatment is not suitable, at least not suitable for every patient with DM. The population in this study was at similar age (mean age 63 years old) but microvascular and macrovascular complications free at baseline. In general, patients in this study had better health condition than ACCORD. Even in the elder group (70-80 years old), optimal A1C was still as low as 6.15% (SD=0.18). The finding is consistent with the current guideline. Stringent A1C goal (<6.5%) can be recommended for the tolerable patients without severe hypoglycemia or vascular complications.

Furthermore, the A1C target achieved in RCT with designed intensive treatment is different from the A1C level reached in the natural environment. In clinical practice, medication or other glycemic control is designed with comprehensive consideration,

including patient's toleration. Reaching the A1C goal is not mandatory in real world. Patients who controlled their A1C at around 6% with routine care represented the population who received appropriate and effective care and achieved glycemic control. The STENO-2 study demonstrated that all-cause mortality and cardiovascular mortality decreased with intensive treatment, which lowered the A1C from 8.4% to 7.9% (45, 77). It confirmed that lowering A1C can reduce the risk of mortality, but it provided limited information. The sample size of STENO-2 was small (N=160) and the A1C in both cohort were relatively high (7.9% vs 9%). If further lowering A1C carries additional benefit or harm on mortality was unknown in STENO-2. Our study provided valuable information that the risk of mortality may be potentially reduced by better A1C control until it reaches 6% in real world practice. For A1C lower than 6%, the risk of mortality increased. It confirmed that too stringent A1C increased mortality rate in ACCORD study.

Appendix table 1: A1C Targets of intensive and standard glycemic control groups in major RCTs

	Intensive treatment	Standard treatment
UKPDS-33	7% -> 7%	7.9%
UKPDS-34	7% ->7.4%	8%
ACCORD	Target at 6.0% 8.1% -> 6.4% (3.5 yrs follow-up) 8.1% -> 7.2% (5 yrs follow-up)	7.5% 7.6%
ADVANCE	Target at 6.5% 7.5% -> 6.5%	7.3%
STENO-2	8.4% -> 7.9%	8.8% -> 9.0% (received intensive treatment at 2nd stage)
VADT	9.4% -> 6.9%	9.4% -> 8.4%
ORIGIN	6.4% -> 6.5%	6.2%
ADDITION-Europe	Target at <7%	Routine care

2. A1C control and risk of vascular complication

In our findings, the optimal A1C of 6.81% (SD=0.32) was associated with lowest risk of microvascular complications. Higher than 6.81%, the risk dropped with A1C lowering, however, further reducing A1C (e.g. <6.5%) led to increase the risk of microvascular complications from our analysis. From 6.8% to 5%, the trend of risk reduction was averted. The U-shape relationship between A1C and microvascular complication was shown in **Figure 13**. Similar result was found for macrovascular complication and the optimal A1C was estimated as 6.76% (SD=0.24). (**Figure 14**)

Figure 13: Smooth Surface of A1C and LDL-C with Risk of Microvascular Complication from Multivariate Analysis

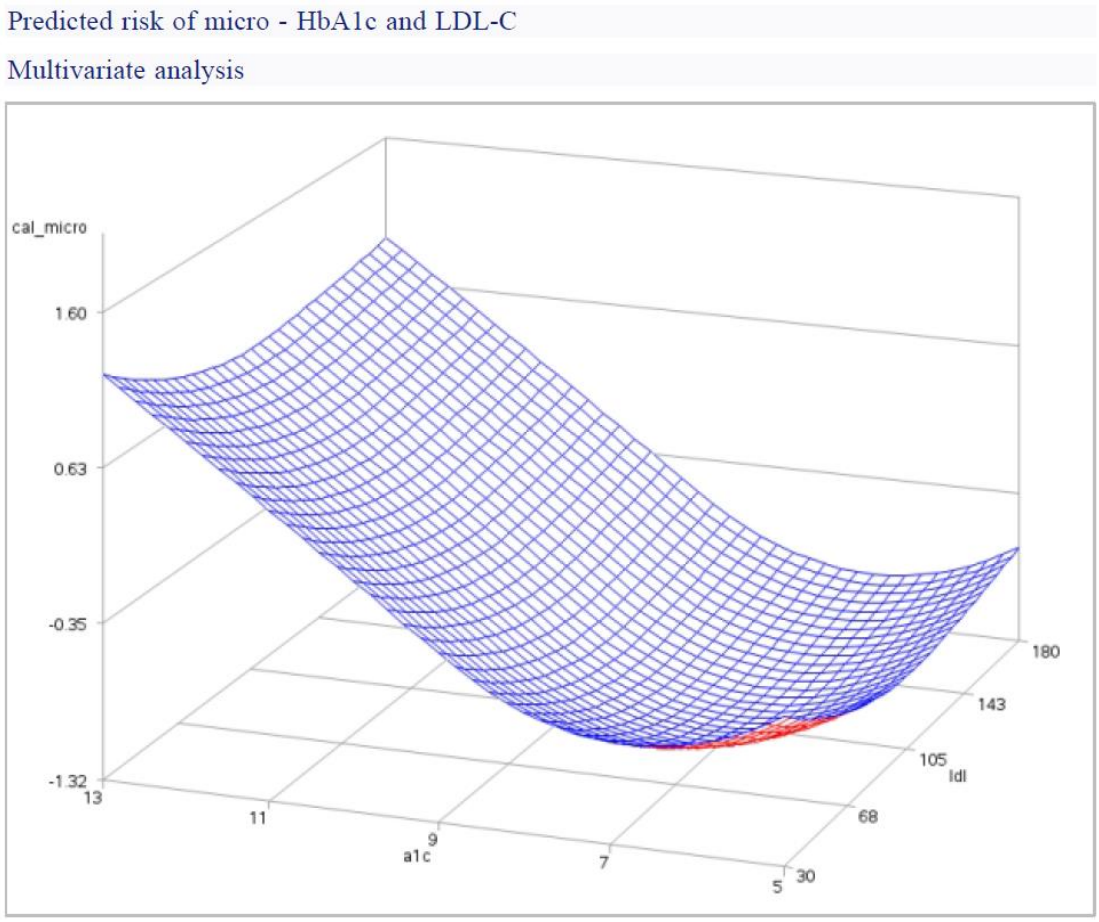
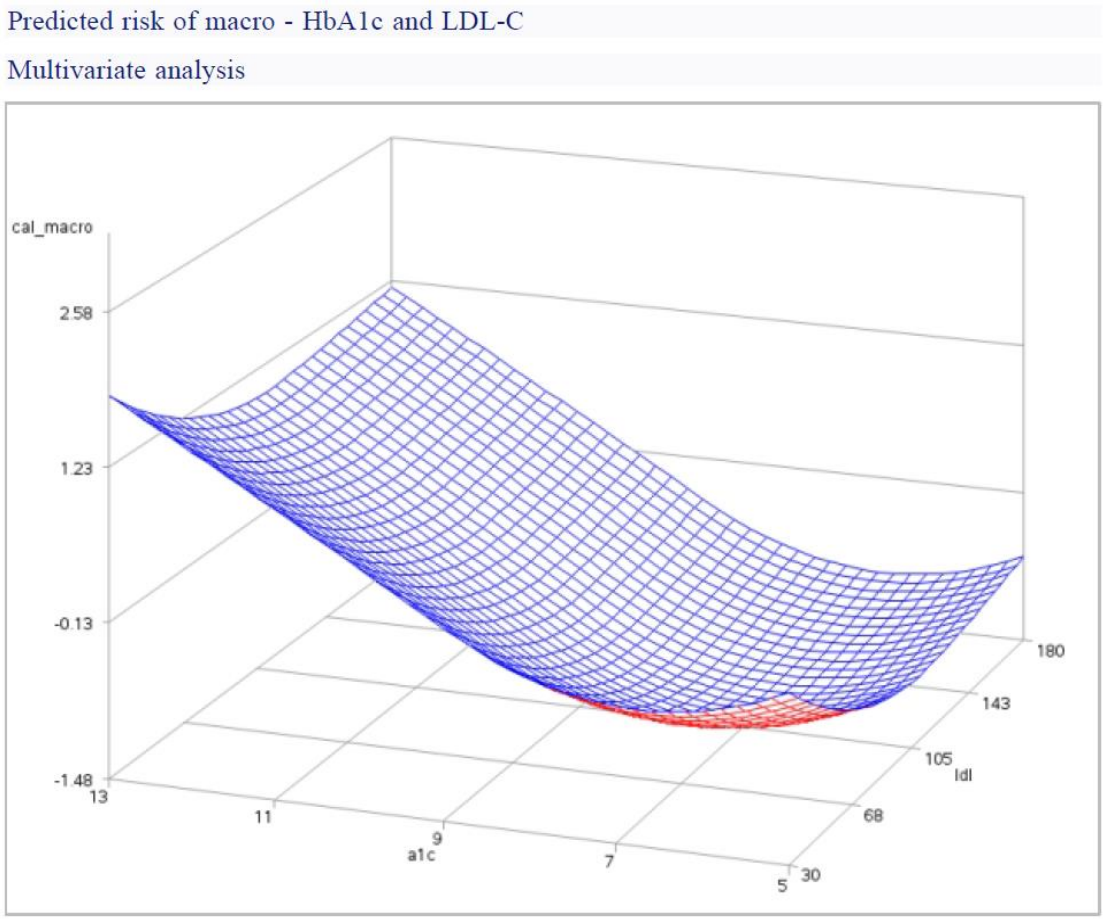


Figure 14: Smooth Surface of A1C and LDL-C with Risk of Macrovascular Complication from Multivariate Analysis



In RCTs, the microvascular complication was reduced significantly by intensive glycemic control in ADVANCE (52) and STENO-2 study. 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%. These findings confirmed part of our results. When the A1C was larger than 6.8%, the risk of microvascular complication reduced with the A1C decreased. The STENO-2 showed the microvascular and macrovascular benefits by multifactorial approach. A1C of 7.9% was achieved with intensive control group, compared to 9.0% of control group. And only <20% patients with intensive glycemic control reached the goal of A1C < 6.5%. It implied that too stringent A1C level may not have strong correlation with better clinical outcome of vascular complications.

Part of results were inconsistent with epidemiological analyses of the DCCT (78) and UKPDS (79). The relationship between A1C and microvascular complications was

curvilinear. Lowering of A1C from 7% to 6% was associated with further reduction in the risk of microvascular complications, and the absolute risk reductions became much smaller. While, in our findings, keep lowering A1C after it reached 6.8% may associated with averted influence on microvascular. Furthermore, UKPDS study found that intensive glycemic control contributed to lower microvascular risk, mostly reduced retinopathy. Though this study aimed at lowering fasting blood glucose, A1C of the group with intensive treatment (7%) was lower than the control group (7.9%).

In the ACCORD study, no significant benefit of microvascular or macrovascular complication was found with tight A1C control (from 8.1% to 6.4%). It may indirectly support out findings that A1C lower than 6.8% was associated with increasing risk of vascular complications. The positive effect of glycemic control achievement from 8% to 6.8% may be offset by the too stringent A1C control (from 6.8% to 6.4%) and made the risk reduction of vascular complication non-significant.

Currently there is a lack of solid evidence about too stringent A1C level may increase the risk of vascular complications. More complicated, the RCTs, like VADT and ADDITION-Europe, with non-significant results of vascular complications brought more uncertainty to the relationship between A1C of lower than 6.5% and risk of vascular complication.

3. Optimal A1C values in subgroup analysis

In the subgroup analysis, the optimal A1C values for lowest risk of mortality did not show significant difference for groups with different age, race and BMI levels. For achieving lowest risk of microvascular complication, the optimal value for black patients (7.11%) was higher than whites (6.78%). And A1C of 6.96% among blacks associated with the lowest risk of macrovascular complication, compared to 6.67% for whites. Higher A1C level has been found in African Americans than in Whites in couple cohort studies with national data source (80-82). However, if the A1C level has differentiated influence on vascular complications between blacks and whites is still controversy (83, 84). From our findings, stringent A1C control is less appropriate for black patients with T2DM than whites for the consideration of lowering risk of microvascular and macrovascular complications. The estimated optimal A1C values associated with lowest vascular complication risks were much higher for patients with other races/ethnicities than whites or blacks. This results was hard to explain by the

current literatures and it contained minorities with all other races and Hispanics. Small proportion of patients with races other than black or white were found in this study. Fitting regression model with smaller sample size produced larger instability, so the optimal A1C was 9.94% with SD=1.19 in the model for microvascular complication and it was 8.57% (SD=1.13) for lowest risk of macrovascular complication.

4. Inconsistent results from other non-linear relationship discussion

Inconsistent results were found from other studies about the non-linear relationship between A1C and clinical outcome. In our study, the optimal A1C was estimated at 6.06 (SD=0.21) for minimizing the risk of death, while the A1C between 7.25 and 7.75 was associated with lowest mortality rate in UK study (3). Even in the subgroup analysis, the optimal point of A1C (varied between 5.95 and 6.32) in our study was significantly lower than 7 for each age, race, or BMI subgroup. Although the A1C estimation in this study was relatively lower, similar trends were found in both studies. The hazard ratios of A1C (6.75-7.25] and (7.25-7.75] had no significant difference with the reference interval [6.25-6.75]. The elevated risk of all-cause mortality was found only when A1C was lower than 6.25 or higher than 7.75 in UK study, similar with the U-shape in this study. Another meta-analysis study found A1C of 7.5% was associated with lowest risk of all-cause mortality. Lower or higher than 7.5% had elevated risk (85). Both studies were detected higher optimal value of A1C than our findings. The inconsistency may be due to the study populations were different. 96% VA population was male.

LDL-C control and its optimal value

Duo to no direct evidence from randomized, controlled clinical trials to support lipid treatment to a specific target, ADA guideline (48) removed the LDL-C goal since 2015 and Statin is recommended for all patients aged >40 years old at different intensity. Before 2015, LDL cholesterol level < 100 mg/dL for patients without overt CVD while aggressive LDL cholesterol goal of < 70 mg/dL for high risk patients were recommended many years. The shift in blood cholesterol management was followed the changing in ACC/AHA blood cholesterol guideline (86) released in 2013, which mentioned that statin treatment can be decided by risk evaluation instead

of LDL-C level. Diabetes is considered as a CHD equivalent for lipid management. Therefore, patients with T2DM was widely recommended with lipid control treatment, without evaluating the level of LDL-C.

Currently lacking of solid evidence does not mean there is a proper LDL-C goal is meaningless. Based on our findings in this study, the optimal LDL-C values exist and vary for different clinical outcomes. In general population, optimal LDL-C values was 106-112 mg/dL for minimizing risk of mortality or vascular complications, which were slightly higher than the old version standard (<100 mg/dL) and much higher than the stringent goal (<70 mg/dL). It indirectly supported the changing of old standard because of the evidence that achieving either general or aggressive LDL-C goal potentially increased the risk of mortality.

1. LDL-C and risk of mortality

The optimal LDL-C value associated with lowest risk of mortality was estimated as 106 mg/dL. Higher or lower LDL-C were both associated with elevated risk of mortality. (**Figure 12**)The U-shape relationship was confirmed by Cleveland retrospective study, which predicted the risk of mortality in patients with T2DM (74). In the Cox model, LDL-C of 150 mg/dL was estimated had highest probability of survival, which was higher than our estimation. The two sides of 150 to 0 and 150 to 450 were both shown increased risk of mortality. Same with our study, Cleveland study had large sample size from EHR with median 8.2 years follow-up time, which was longer than this study (median 6.7 years). Another retrospective study In UK used total cholesterol for estimating the influence of lipid (3). The results are not comparable, but the trend of two sides of extreme values associated with elevated risk of death were alike. Based on literatures, dyslipidemia is the cause for death mainly by increasing cardiovascular disease (87).

2. LDL-C and risk of vascular complications

The estimated LDL-C for lowest risk of microvascular complication was 109 mg/dL, and it was 112 mg/dL for most ideal outcome of macrovascular complication. (**Figure 13, 14**) Compared with the old standard of <100 mg/dL or more stringent goal of <70 mg/dL, the optimal LDL-C was relatively higher and loose. It implied that the risk of vascular complication might increase if patients achieved the old LDL-C target.

The evidences from RCTs were ambiguous. In ACCORD lipid trial, LDL-C had no significant difference between treatment and control groups and no significant CVD benefits was found either (61). The two studies with multifactorial approach, including A1C, lipid and BP control, had diverse results. In STENO-2, the risks of cardiovascular caused mortality, microvascular and macrovascular complications were all reduced by multifactorial intensive intervention (5, 45). With lipid lowering agents, patients in the intensive treatment group achieved significant lower LDL-C level (about 75mg/dL) than conventional therapy (about 140 mg/dL). But the isolated effect of LDL-C lowering was unclear in the STENO-2. The ADDITION-Europe was another randomized trial with intensive multifactorial therapy, which achieved 8 mg/dL lower of LDL-C in the intensive treatment group (81 vs. 89 mg/dL) (65, 88). However, no significant effect on clinical outcomes were found. The LDL-C levels were both much lower than the optimal points found this this study.

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.

3. LDL-C in subgroup analysis

From the results of subgroup analysis, whites had higher optimal LDL-C value than blacks, which were 113 mg/dL for whites compared to 91 mg/dL for blacks for minimized risk of mortality; 118 mg/dL compared to 105 mg/dL for lowest risk of microvascular complications; 130 mg/dL vs. 120 mg/dL for best outcome of macrovascular complications. Previous studies showed African Americans had lower LDL-C test rate and less proportion of patients with diabetes achieving LDL-C goal (89), but the LDL-C level had no significant difference across races been found (90). There was no trend or significant differences of optimal LDL-C found across age or BMI groups.

BP control and its optimal value

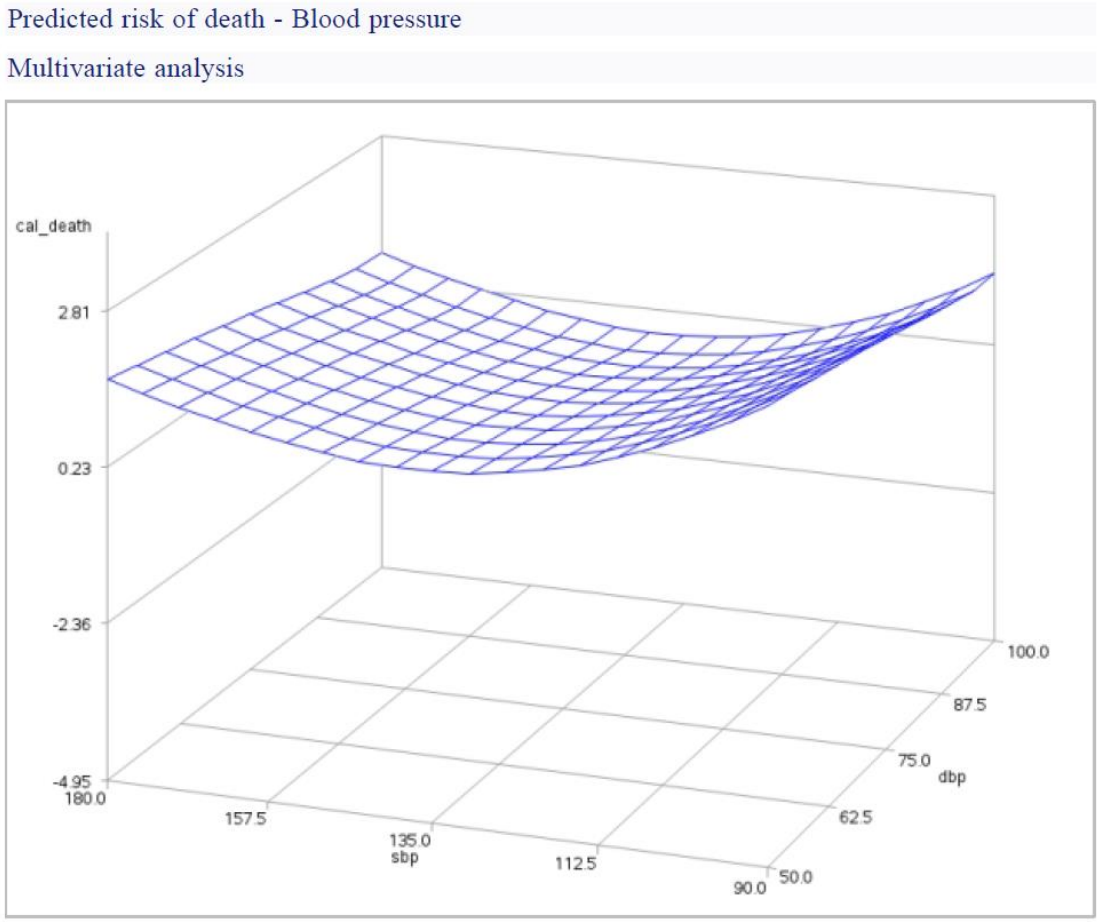
Optimal value was only detected for SBP in the models fitting for mortality and macrovascular complication. Lower SBP was correlated to lower risk of microvascular complication with linear relationship. Almost all of the relationships

between DBP and clinical outcomes were negative linear in the general T2DM population. Higher DBP was associated with lower risk. Compared to the targets in guidelines, the optimal SBP values provided more valuable information. SBP <140 mmHg is recommended for general diabetes population, while the lower target of <130 mmHg for healthier patients or who can tolerate. However, the optimal SBP for lowest risk of mortality was 138 mmHg, which means the risk may be raised up if patients control their SBP lower than this value, like guideline recommended. The current SBP target in guideline potentially misleads patients to achieve a too stringent standard.

1. BP and risk of mortality

In the ACCORD BP trial, SBP target was set at 120 mmHg for the intensive treatment group and 140 mmHg for the control group (30). At the end of study, both groups achieved their targets, reached 119 mmHg and 134 mmHg for intensive treatment and control group respectively. The SBP levels in both groups were lower than the optimal point estimated in our study. The risk of mortality did not show significant reduction with stringent SBP control in ACCORD BP trial. While in the ADVANCE BP (37) study and STENO-2 study (5), the risks of all-cause and cardiovascular-cause death were both significantly lowered by the BP lowering treatment. In ADVANCE BP, the entry SBP was 145 mmHg at average (41% patients <140 mmHg). Patients with placebo kept SBP at around 140 mmHg and patients received treatment lowered SBP to around 135 mmHg. In the STENO-2 study, SBP was reached 140 mmHg among patients with intensive therapy, and 146 mmHg for conventional therapy group. The SBP achievement and its significant effects on risk reduction was consistent with the findings in our study. Lowering the SBP which was originally higher than 138 mmHg (SD=2.86) had the potential benefits of risk reduction. However, if SBP in both groups were lower than the optimal point, no excess benefit associated with intensive BP control was demonstrated by RCTs.

Figure 15: Smooth Surface of SBP and DBP with Risk of Mortality from Multivariate Analysis



The optimal SBP of 138 mmHg (SD=2.86) (**Figure 15**) with minimal risk of mortality in this study was consistent with the optimal SBP interval (135-145 mmHg) in the UK study (3). The SBP higher than 145 mmHg did not show significant association with higher risk of death, however, SBP<115 mmHg was found related to risk increasing markedly in the UK study. In our study, quadratic relationship was detected and too high/low SBP were both associated with risk growth significantly. The relationship of DBP and risk of death was almost linear. The risk decreased with higher DBP, which was different with the optimal range of 82.5–87.5 mmHg in UK study. However, except the DBP of lower than 72.5mmHg, all other DBP intervals had no significant influence on mortality.

2. BP and risk of vascular complications

The lower SBP linearly associated with lower risk of microvascular complication was estimated from the multivariate analysis model. (**Figure 16**) While another retrospective study aimed for evaluating non-linear effects found an optimal SBP of 128 mmHg (95% confidence interval = 107–139 mmHg) was associated with best outcome of diabetic nephropathy (91). For minimizing the risk of macrovascular complication, optimal SBP was found at 131 mmHg (SD=6.64) by the regression model. (**Figure 17**) SBP lower than 125 mmHg may increase the risk of macrovascular complication in our study. Considered both risks of mortality and macrovascular complication, 135-138 mmHg might be the best SBP value for general population with T2DM. Non-linear relationship between BP and vascular disease were found from a population with symptomatic vascular disease. BP of 143/82 mmHg was estimated with lowest risk of vascular events (92). However, the population used in this study was not patients with T2DM.

Figure 16: Smooth Surface of SBP and SBP with Risk of Microvascular Complication from Multivariate Analysis

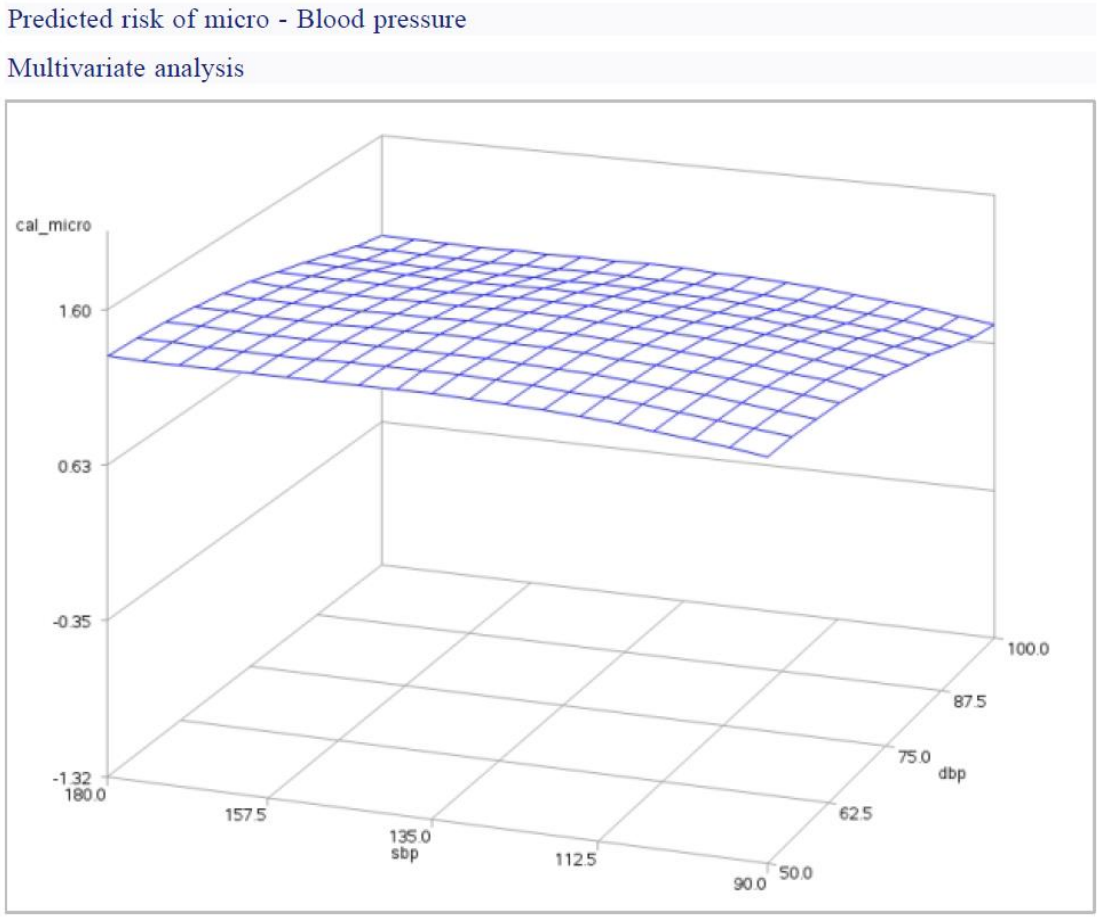
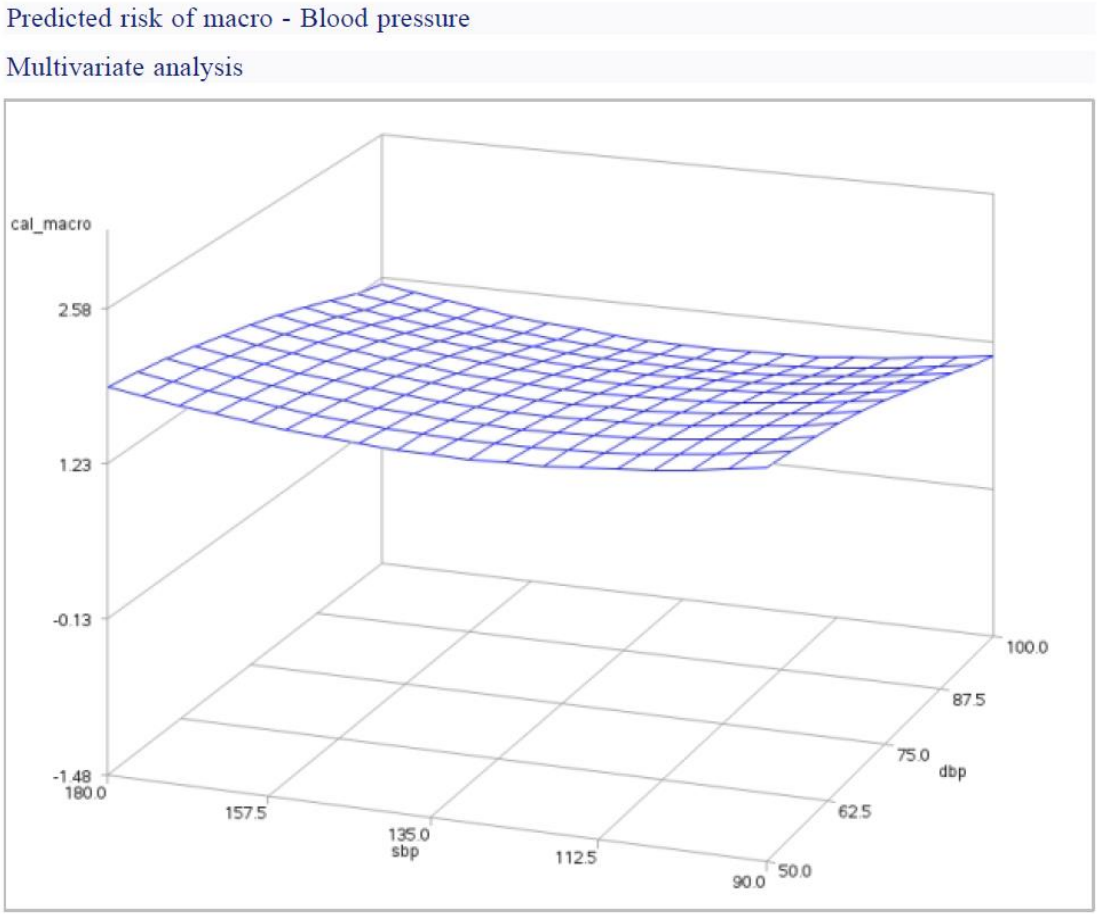


Figure 17: Smooth Surface of SBP and SBP with Risk of Macrovascular Complication from Multivariate Analysis



3. BP in subgroup analysis

The optimal SBP with lowest risk of mortality for younger patients was lower, 131 mmHg for patients aged <60 years old and 147 mmHg for patients older than 60 years old. While, to achieve lower risk of macrovascular complication, the optimal SBP was 121 mmHg and 124 mmHg for patients <50 years old and 50-60 years old respectively. For patients elder than 60 years old, SBP at 134-137 mmHg was associated with lowest risk.

For minimizing the risk of macrovascular complication, the optimal SBP values are significantly different between whites and blacks. It was much higher in whites (139 mmHg, SD=6) than blacks (123 mmHg, SD=5). Also, the patients with normal weight had the potential to lower the SBP under 120 mmHg for risk reduction. While the overweight patients' optimal SBP was 124 mmHg and the best SBP target for obesity

patients was much higher (148 mmHg). But the racial and BMI differences were not found for mortality.

This finding implied that SBP target should be differentiated to patients with different races. Using the SBP target of <140 mmHg may be not suitable for obesity patients. Younger black patients with normal weight can be recommended to control their SBP at around 120 mmHg. However, patients who are elder, whites and/or with obesity should have less intensive SBP control plan. Target of <140 mmHg is not universal, even not safety for every patients with T2DM. In several specific subgroups, optimal DBP value was found in the fitted curve, however, the value was quite close to the maximum value of the range.

Method discussion

1. Sample size

Based on the estimation, there were about 500,000 veterans who had diagnosis of diabetes per year and the prevalence was about 19.6% in 2000 [42]. Therefore, we expect a large sample of patients with T2DM in the National Veterans Health System.

2. LOESS regression model for univariate analysis

In this study, LOESS was chosen to show the potential non-linear relationship between each lab measurement and a specific clinical outcome.

Local regression (general model of LOESS) is a nonparametric method for fitting a smooth curve between two variables, or fitting a smooth surface between an outcome and up to four predictor variables. It fits at point x is weighted toward the data nearest to x and combines multiple regression models in a k-nearest-neighbour-based meta-model. This nonparametric regression focuses on the fitted curve. The linearity assumptions of conventional regression methods have been relaxed.

LOESS (Local Polynomial Regression) combines much of the simplicity of linear least squares regression with the flexibility of nonlinear regression. It does this by fitting simple models to localized subsets of the data to build up a function that describes the deterministic part of the variation in the data, point by point. In fact, one of the chief attractions of this method is that the data analyst is not required to specify

a global function of any form to fit a model to the data, only to fit segments of the data.

In the LOESS method, weighted least squares is used to fit linear or quadratic functions of the predictors at the centres of neighbourhoods. The radius of each neighbourhood is chosen so that the neighbourhood contains a specified percentage of the data points. The fraction of the data, called the smoothing parameter, in each local neighbourhood controls the smoothness of the estimated surface. Data points in a given local neighbourhood are weighted by a smooth decreasing function of their distance from the centre of the neighbourhood. "Smoothing parameter" determines how much of the data is used to fit each local polynomial. The smoothing parameter, α, is a number between $(\lambda + 1) / n$ and 1, with λ denoting the degree of the local polynomial.

If chosen smoothing parameter is too small then there will be insufficient data near specific data point for an accurate fit, resulting in a large variance. If the smoothing parameter is too large then the regression will be over-smoothed, resulting in a loss of information. With the width increasing, the curve tends to be a line.

The trade-off between bias and variance also depends on the degree of the polynomial selected. A higher degree will provide a better approximation of the population mean, so less bias, but there are more factors to consider in the model, resulting in greater variance. The default degree is 2 (quadratic). Higher degrees don't improve the fit much. The lower degree (i.e. 1, linear) has more bias but pulls back variance at the boundaries.

The default degree ($\lambda = 2$) was used and smoothing parameter was set as 0.1 for univariate analysis of A1C and clinical outcomes; 0.5 as smoothing parameter for LDL-C, SBP and DBP in this study. Within each weighted least square estimation, quadratic relationship has enough flexibility to fit the potential curve between lab measurement and clinical outcome. For finding appropriate smoothing parameter, the strategy of minimizing the AIC was applied by fitting models with a group of smoothing parameters. Using the relationship between A1C and death as an example, 0.1 to 0.5 by every 0.1 were separately used for fitting the LOESS regression models as the first step. The bias corrected AICs were generated from each model and the model with 0.1 as smoothing parameter had smallest AIC. At the same time, the

LOESS fit curves were shown and found the smoothing parameter larger than 0.1 produced excessive smoothing. Then 0.01 to 0.1 by every 0.02 were used as smoothing parameters to fit LOESS models for outputting the AICs and fitted curves. The smaller parameter used, the more fluctuations were shown in the scatterplot, but the AIC did not improve with the variance increasing. So, 0.1 was chosen as smoothing parameter for fitting the LOESS model of A1C and mortality.

There is no golden standard for selecting smoothing parameter. A good one lies somewhere between the two extremes of too smoothing as a linear relationship and overfitting with too many sharp fluctuations. The minimized AIC can provide a useful guide for decision making.

3. Generalized linear model (GLM) with splines and repeated measures for multivariate analysis

GLM has a wide class of regression models where the effect of the independent variables on the mean of the dependent variable is modelled throughout the link function. It has the flexibility to define appropriate link function and distribution to fit different data types. Also, it can takes care of the repeated measured data structure by GEE technique and specifying correlation type and correlation structure.

In this study, GLM was used with logit link function and binomial distribution for response variable, which is basically For risk prediction of binary clinical outcomes, logistic regression is not only a classic model, but also has several advantages. Firstly, it is more robust which has no requirements of normal distribution for independent variables. Second, logistic regression does not assume a linear relationship between outcomes and predictors, and has the potential to handle nonlinear effects. Furthermore, normally distributed error terms are not assumed. Most importantly, as one of GLM family, it is compatible with repeated measures and self-defined splines.

To fulfil the study question, precisely fitting the potential non-linear relationship between lab measurements and clinical outcomes was the emphasis of analysis. The absolute magnitude of predicted risk was not significant because risk prediction was not study objective. However, the smooth curve which was represented the changing of predicted risk followed with the changing of 4 groups of lab measurements (A1C, LDL-C, SBP and DBP) was crucial. First of all, it can visually show the existence of optimal point of lab values with lowest risk of complications or death and the

tendency of deviating from the optimal point. Also, the predicted risk from regression model can be used for navigating the exact lab values associated with optimal clinical outcomes.

4. Splines

Splines were used in GLM for estimating the potential non-linear relationship. A spline function is typically used to relax the linearity assumption of predictors in GLM. The basic function was created based on potential optimal points which were shown associated with lowest risk of outcomes in smooth curve from local regression (univariate analysis). For example, the A1C at around 6.5 was shown with relatively lower risk of all clinical outcomes (death, microvascular and macrovascular complications). Lower or higher than 6.5 were both associated with elevated risk. It implied the optimal lab value of A1C may locate around 6.5; and quadratic splines potentially has enough flexibility to fit the curves of two segments. So 7 of A1C was set as the cut point (interior knot) for creating the spline functions. (**Figure 9-11**)

Model fitting started from spline function with 1 knot and 2^{nd} degree (polynomial). Higher degree of splines was the second choice when the model fitting was bad. Applying spline function has the flexibility of increasing the number of knots and degree for better model fitting.

5. Repeated measures in GLM

The longitudinal data structure with repeated measures is an important feature of the data set. The clinical outcomes (microvascular and macrovascular complications), except death, can be recurrent and were examined in every 6-month cycle. Furthermore, the lab measurements and diabetes-related medications were all changed by cycle.

Repeated measures in GLM is commonly used when measuring the effect of a predictor at different time points, which takes the response variable measured as correlated, non-independent data. It can be used to test the main effects within and between the subjects, interaction effects between factors, covariate effects and effects of interactions between covariates and between subject factors.

Correlation was set as autoregressive (corr=AR) and TYPE=EXCH option was specified an exchangeable working correlation structure for the regression models.

The variances in autoregressive structure are homogenous, and correlations decline exponentially with time. This means the variability in a measurement is constant at different equidistant cycles, and consecutive lab measurements in two adjacent cycles are more highly correlated than non-consecutive measurements. The data structure suits for the feature of autoregressive structure.

6. Comparison of survival model, local regression and general additive model

There are couple options for semi-parametric and nonparametric regressions but they cannot fit with the analysis requirements due to specific features and limitations. Survival model, Cox proportional hazards regression, which is widely used for time related outcomes was removed from alternative methods list. In this study, absolute predicted risk was needed for assessing the optimal points, composite of lab measurements. So the methods estimate relative risk cannot satisfy the objective of this study.

Local regression can be used for surface fitting with up to four predictors. It is feasible to estimate the association between the clinical outcome and 4 lab values (A1C, LDL-C, DBP and DBP). The plot can indicate a nonparametric surface and provide the optimal points of clinical outcome. However, local regression cannot take care of repeated measured data structure and cannot set outcome with logit function either.

Generalized additive model (GAM) is another alternative of fitting the potential non-linear relationship between lab measurements and risk of clinical outcomes. A GAM (93) is a generalized linear model with a linear predictor involving a sum of smooth functions of covariates. However, not like the generalized linear regression model assume a linear form for the covariate effects, the GAM releases the link function limitation in a more nonparametric fashion. It estimates the scatterplot smoother by local scoring algorithm and generalize the usual Fisher scoring procedure for computing maximum likelihood estimates. The smooth function has the flexibility to allow a smooth estimate for all of the covariate, or fit some of covariates linearly.

Limitations

The study has several limitations. As a retrospective study, unobserved or unmeasured heterogeneity may exist. Although VA EHR has standard data model and high completeness, the unobserved effects still potentially place influences on the model fitting. Some qualitative measurement, like health cognition, may be both relate to long-term clinical outcomes and diabetes management. But it is not available in EHR and may bias the relationship between lab measurements and the risk of clinical outcomes. In this study, patients' demographic characteristics, comorbidities at baseline, medications aimed to manage A1C, LDL-C and BP at follow-up were all controlled in regression models to minimize the heterogeneity between patients. Furthermore, there is a lack of information about diabetes duration in our data. To minimize this problem, the patients with history of microvascular and macrovascular complication at baseline period were excluded for releasing the bias due to the different severity of T2DM caused by DM duration.

As specialty of VA population, more than 90% patients are male in our sample, the results may be found hard to generalize 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. So, we share the limitations of accuracy in risk prediction model. Spline was applied to release the pre-assumption of relationship. The numbers of knots and degree can be flexibly defined to better fit the 'true' relationship. However, the method can make the fitted smooth curve closer to 'truth', however, error cannot be eliminated.

Conclusions

Optimal treatment goals were identified for diabetes management in the US veterans with T2DM. Non-linear relationships between blood glucose, blood pressure and lipid levels and patients' long-term clinical outcomes were described and displayed by surface plots. Individualized optimal values were estimated for diabetes management based on patients' demographics.

Considering the risk of mortality, 6.0% <A1C< 6.5% without hypoglycemia may be the optimal DM management target for patients who can tolerate the treatment and without complications, while the A1C level should be higher (6.5% <A1C< 7.0%) for lowering the risks of microvascular, macrovascular complications. In general population, 6.5% may be the optimal value for blood glucose management after taking into account all kinds of major clinical outcomes. Lower bond of A1C should be recommended. Even the patients can tolerate with A1C <6.0%, physician may think about releasing the strength of medication therapy for consideration of potential elevated risk of microvascular and macrovascular complications. Elder age may not be an independent factor to influence the decision making of A1C target. But patients with different races should be carefully provided customized A1C management target for minimizing the risk of vascular complications.

Explicit goal of LDL-C is meaningful for DM lipid management and preventing DM related complications. In general population with T2DM, LDL-C of about 110 mg/dL was associated best long-term clinical outcomes. Lower and higher than the goal were both shown elevated risk. And the optimal LDL-C varied between racial groups for all clinical outcome studies.

SBP is more sensitive with age. Higher optimal SBP values were found for elder patients for better outcomes of mortality and macrovascular complication. Also, patients with obesity may be recommended less stringent SBP goal for lowest risk of macrovascular complication. Racial difference of optimal SBP was found in the model for macrovascular complication too. No obvious non-linear or U-shape relationship between DBP and clinical outcome was found in this study. Higher level DBP is better for almost all patients.

Above all, optimum clinical blood glucose, blood pressure and blood lipid targets with both upper and lower limits for creating a 'security zone' should be evaluated and suggested as part of diabetes management. Multi-faceted 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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Appendix A: Outcome Definitions

Diseases	ICD-9-CM Diagnosis Codes	Description	ICD-10-CM Diagnosis Codes	Description
Microvascular complications				
Retinopathy				
	250.5x	Diabetes with ophthalmic manifestations	E08.3%	Diabetes mellitus due to underlying condition with ophthalmic complications
Diabetic ophthalmologic disease	362.0x	Diabetic retinopathy	E10.3%	Type 1 diabetes mellitus with ophthalmic complications
			E11.3%	Type 2 diabetes mellitus with ophthalmic complications
			E13.3%	Other specified diabetes mellitus with ophthalmic complications
Background retinopathy	362.1x	Other background retinopathy and retinal vascular changes	H35.0%	Background retinopathy and retinal vascular changes
Other non-diabetic proliferative retinopathy	362.1x	Other background retinopathy and retinal vascular changes	H35.2%	Other non-diabetic proliferative retinopathy
			H35.4%	Peripheral retinal degeneration
			H35.7%	Separation of retinal layers
			H35.8%	Other specified retinal disorders
Retinal edema	362.83	Retinal edema	H35.81%	Retinal edema
CSME	362.53	Cystoid macular degeneration	H35.35%	Cystoid macular degeneration
Other retinal disorders	362.81	Retinal hemorrhage	H35.9%	Unspecified retinal disorder
	362.82	Retinal exudates and deposits		
Proliferative diabetic retinopathy	362.02	Proliferative diabetic retinopathy	H35.2%	Other non-diabetic proliferative retinopathy
			E08.35%, E10.35%, E11.35%, E13.35%	proliferative diabetic retinopathy in diabetes mellitus

Retinal detachment	361.xx	Retinal detachments and defects	H33.0% H33.2%	Retinal detachments and breaks Serous retinal detachment
Blindness	369.xx	Blindness and low vision	H54.0% H54.1% H54.4% H54.8%	Blindness, both eyes Blindness, one eye, low vision other eye Blindness, one eye Legal blindness, as defined in USA
Vitreous hemorrhage	379.23	Vitreous hemorrhage	H43.1%	Vitreous hemorrhage
Nephropathy				
Diabetic nephropathy	250.4x	Diabetes with renal manifestations	E08.2% E10.2% E11.2% E13.2%	Diabetes mellitus due to underlying condition with kidney complications Type 1 diabetes mellitus with kidney complications Type 2 diabetes mellitus with kidney complications Other specified diabetes mellitus with kidney complications
Acute glomerulonephritis	580.xx	Acute glomerulonephritis	N00.%	Acute nephritic syndrome
Nephrotic syndrome	581.xx	Nephrotic syndrome	N04.%	Nephrotic syndrome
Hypertension, nephrosis	581.81	Nephrotic syndrome in diseases classified elsewhere	I12.% I13.%	Hypertensive chronic kidney disease Hypertensive heart and chronic kidney disease
Chronic glomerulonephritis	582.xx	Chronic glomerulonephritis	N03.%	Chronic nephritic syndrome
Unspecified Nephritis/nephropathy	583.xx	Nephritis and nephropathy, not specified as acute or chronic	N05.%	Unspecified nephritic syndrome
Chronic kidney disease (CKD)	585.xx	Chronic kidney disease (CKD)	N18.%	Chronic kidney disease (CKD)
Renal failure	586.xx	Unspecified renal failure	N19.%	Unspecified kidney failure

Renal insufficiency	593.9x	Unspecified disorder of kidney and ureter	N28.9%	Disorder of kidney and ureter, unspecified
			N18.9%	Chronic kidney disease, unspecified
Neuropathy				
Diabetic neuropathy	250.6x	Diabetes with neurological manifestations	E08.4%	Diabetes mellitus due to underlying condition with neurological complications
	356.9x	Unspecified, Hereditary and idiopathic peripheral neuropathy	E10.4%	Type 1 diabetes mellitus with neurological complications
			E11.4%	Type 2 diabetes mellitus with neurological complications
			E13.4%	Other specified diabetes mellitus with neurological complications
Amyotrophy (nondiabetic)	358.1x	Myasthenic syndromes in diseases classified elsewhere	G12.21%	Amyotrophic lateral sclerosis
			G54.5%	Neuralgic amyotrophy
Cranial nerve palsy (including opthalmic)	951.0x, 951.1x, 951.3x	Injury to oculomotor nerve; Injury to trochlear nerve; Injury to abducens nerve	G51.0%, G52.%, H49.0%, H49.1%, H49.2%	Bell's palsy; Disorders of other cranial nerves; Third [oculomotor] nerve palsy; Fourth [trochlear] nerve palsy; Sixth [abducent] nerve palsy
Mononeuropathy	354.xx	Mononeuritis of upper limb and mononeuritis multiplex	G56.%	Mononeuropathies of upper limb
	355.xx	Mononeuritis of lower limb and unspecified site	G57.%	Mononeuropathies of lower limb
			G58.%	Other mononeuropathies
			G59.%	Mononeuropathy in diseases classified elsewhere

Charcot’s arthropathy	713.5x	Arthropathy associated with neurological disorders	E08.610, E09.610, E10.610, E11.610, E13.610	Charcot's joint in diabetes mellitus (E08, E10-E13 with .610)
			M14.6%	Charcot's joint - Excludes Charcot's joint in diabetes mellitus (E08-E13 with .610)
Polyneuropathy	357.2x	Polyneuropathy in diabetes	E08.42, E09.42, E10.42, E11.42, E13.42	polyneuropathy in diabetes mellitus (E08-E13 with .42)
			G61.%	Inflammatory polyneuropathy
			G62.%	Other and unspecified polyneuropathies
			G63.%	Polyneuropathy in diseases classified elsewhere
			G60.3%	Idiopathic progressive neuropathy
Neurogenic bladder	596.54	Neurogenic bladder NOS	N31.9%	Neuromuscular dysfunction of bladder, unspecified
Autonomic neuropathy	337.0x	Idiopathic peripheral autonomic neuropathy	G90.0%	Idiopathic peripheral autonomic neuropathy
	337.1x	Peripheral autonomic neuropathy in disorders classified elsewhere	G90.8%	Other disorders of autonomic nervous system
			G90.9%	Disorder of the autonomic nervous system, unspecified
Gastroparesis (including diabetic)	536.3x	Gastroparesis	K31.84%	Gastroparesis
	564.5	Functional diarrhea	E08.43%, E10.43%, E11.43%, E13.43%	diabetic autonomic (poly)neuropathy in diabetes mellitus
Orthostatic hypotension	458.0x	Orthostatic hypotension	I95.1%	Orthostatic hypotension
			I95.2%	Hypotension due to drugs
			G90.3%	Multi-system degeneration of the autonomic nervous system

Macrovascular complications				
Cerebrovascular				
Stroke - hemorrhage	430.xx	Subarachnoid hemorrhage	I60.%	Nontraumatic subarachnoid hemorrhage
	431.xx	Intracerebral hemorrhage	I61.%	Nontraumatic intracerebral hemorrhage
	432.xx	Other and unspecified intracranial hemorrhage	I62.%	Other and unspecified nontraumatic intracranial hemorrhage
Stroke - ischemic	433.xx	Occlusion and stenosis of precerebral arteries	I65.%	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	434.xx	Occlusion of cerebral arteries	I63.%	Cerebral infarction
TIA	435.xx	Transient cerebral ischemia	G45.%	Transient cerebral ischemic attacks and related syndromes
Other cerebrovascular disease	436.xx	Acute, but ill-defined, cerebrovascular disease (excluded stroke)	I67.%	Other cerebrovascular diseases
	437.xx	Other and ill-defined cerebrovascular disease	I68.%	Cerebrovascular disorders in diseases classified elsewhere
	438.xx	Late effects of cerebrovascular disease	I69.%	Sequelae of cerebrovascular disease
			G46.%	Vascular syndromes of brain in cerebrovascular diseases
Cardiovascular				
Myocardial infarction (acute)	410.xx	Acute myocardial infarction	I21.%	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
			I22.%	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction

			I23.%	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)
Other acute IHD	411.xx	Other acute and subacute forms of ischemic heart disease	I24.%	Other acute ischemic heart diseases
Old myocardial infarction	412.xx	Old myocardial infarction	I25.2%	Old myocardial infarction
Angina pectoris	413.xx	Angina pectoris	I20.%	Angina pectoris
Other chronic IHD	414.xx	Other forms of chronic ischemic heart disease	I25.%	Chronic ischemic heart disease
Atherosclerosis	440.xx	Atherosclerosis	I70.%	Atherosclerosis
Aortic aneurysm/dissection	441.xx	Aortic aneurysm and dissection	I71.%	Aortic aneurysm and dissection
Other aneurysm	442.xx	Other aneurysm	I72.%	Other aneurysm
Arterial embolism and thrombosis	444.xx	Arterial embolism and thrombosis	I74.%	Arterial embolism and thrombosis
Atheroembolism	445.xx	Atheroembolism	I75.%	Atheroembolism
Ventricular fibrillation	427.4x	Ventricular fibrillation and flutter	I49.0%	Ventricular fibrillation and flutter
Atrial fibrillation	427.3x	Atrial fibrillation and flutter	I48.%	Atrial fibrillation and flutter
Heart failure	428.xx	Heart failure	I50.%	Heart failure
Cardiovascular disease, unspecified	429.2x	Cardiovascular disease, unspecified	I69.9%	Sequelae of unspecified cerebrovascular diseases
Peripheral vascular disease				
Diabetic PVD	249.7x	Secondary diabetes mellitus with peripheral circulatory disorders		
	250.7x	Diabetes with peripheral circulatory disorders	E08.5%, E10.5%, E11.5%. E13.5%	Diabetes mellitus with circulatory complications

Other PVD	443.xx	Other peripheral vascular disease	I73.%	Other peripheral vascular diseases
Other disorders of arteries and arterioles	447.xx	Other disorders of arteries and arterioles	I77.%	Other disorders of arteries and arterioles
Gangrene/Ulcer				
Gangrene in diabetes mellitus	250.7x	Diabetes with peripheral circulatory disorders (gangrene)	E08.52%	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
	249.7x	Secondary diabetes mellitus with peripheral circulatory disorders (diabetic gangrene)	E10.52%	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
			E11.52%	Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
			E13.52%	Other specified diabetes mellitus with diabetic peripheral angiopathy with gangrene
Foot ulcer	250.8x	Diabetes with other specified manifestations (any associated ulceration)	E08.621	Diabetes mellitus due to underlying condition with foot ulcer
	249.8x	Secondary diabetes mellitus with other specified manifestations (any associated ulceration)	E10.621	Type 1 diabetes mellitus with foot ulcer
			E11.621	Type 2 diabetes mellitus with foot ulcer
			E13.621	Other specified diabetes mellitus with foot ulcer
Ulcer of lower limbs	707.1x	Ulcer of lower limbs, except pressure ulcer	L89.5%	Pressure ulcer of ankle
			L89.6%	essure ulcer of heel
			L97.%	Non-pressure chronic ulcer of lower limb, not elsewhere classified

Gas gangrene	040.xx		A48.0%	Other bacterial diseases, not elsewhere classified, Gas gangrene
Foot wound	892.1x	Open wound of foot except toe(s) alone, complicated	S91.%	Open wound of ankle, foot and toes
Gangrene (not diabetic)	785.4x	Gangrene	I96.%	Gangrene, not elsewhere classified (excluded gangrene in diabetes mellitus)

CSME: cystoid macular edema/degeneration; NOS, not otherwise specified; TIA, transient ischemic attack; IHD, ischemic heart disease; ASCVD, atherosclerotic cardiovascular disease; PVD, peripheral vascular disease; LE, lower extremity.

Appendix B: Definitions of Comorbidities

Comorbidities	ICD-9
Mental illness (substance abuse, schizophrenia, depression, other mental disorders)	291.0-292.9, 295.0-295.9, 296.0-296.9, 300.4, 301.12, 303.0-305.9, 308.0, 309.0, 309.1, 309.28, 309.81, 311
Any cardiovascular disease	390-459
Hypertension	401-405
Coronary artery disease	410-414
Angina	411, 413
MI	410
Congestive heart failure (CHF)	398.91, 428
Peripheral vascular disease	443
Other cardiovascular diseases	390-459 (excluding 401-405,410-414, 428, 398.91, 394-397, 424, 443)
Tobacco	305.1, V15.82 , 649.0
Obesity	278.0
Hyperlipidemia	272.0-272.4
Renal disease	250.4, 590, 593, 791.0

Appendix C: Medication category

1. Anti-hyperglycemia
    1.1. Oral medication
        1.1.1. Alpha-Glucosidase Inhibitors: Acarbose, Miglitol
        1.1.2. Biguanides: Metformin
        1.1.3. DPP-4: Alogliptin, Linagliptin, Saxagliptin, Sitagliptin
        1.1.4. Glucagon-Like Peptides: Albiglutide, Dulaglutide, Exenatide, Liraglutide
        1.1.5. Meglitinides: Nateglinide, Repaglinide
        1.1.6. SGLT2 Inhibitors: Dapagliflozin, Canagliflozin, Empagliflozin
        1.1.7. Sulfonylureas: Glimepiride, Gliclazide, Glipizide, Glyburide, Chlorpropamide, Tolazamide, Tolbutamide
        1.1.8. Thiazolidinediones: Rosiglitazone, Pioglitazone
    1.2. Insulin
        1.2.1. Short-acting: Regular (R)
        1.2.2. Rapid-acting: Insulin aspart, Insulin glulisine, Insulin lispro
        1.2.3. Intermediate-acting: Insulin isophane
        1.2.4. Long-acting: Insulin detemir, Insulin glargine

2. Anti-Hypertension
    2.1. Diuretics:
        2.1.1. Diuretics: Chlorthalidone, Chlorothiazide, Furosemide, Hydrochlorothiazide, Indapamide, Metolazone
        2.1.2. Potassium-sparing diuretics: Amiloride hydrochloride, Spironolactone, Triamterene
        2.1.3. Loop diuretic: Bumetanide
    2.2. Beta-blocker: Acebutolol, Atenolol ,Betaxolol, Bisoprolol fumarate, Carteolol hydrochloride, Metoprolol tartrate, Metoprolol succinate, Nadolol, Penbutolol

sulfate, Penbutolol sulfate, Pindolol, Propranolol hydrochloride, Solotol hydrochloride, Timolol maleate

2.3. ACE inhibitors: Benazepril hydrochloride, Captopril, Enalapril maleate, Fosinopril sodium, Lisinopril, Moexipril, Perindopril, Quinapril hydrochloride, Ramipril, Trandolapril

2.4. Angiotensin II receptor blockers: Candesartan, Eprosartan mesylate, Irbesarten, Losartan potassium, Telmisartan, Valsartan

2.5. Calcium channel blockers: Amlodipine besylate, Bepridil, Diltiazem hydrochloride, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil hydrochloride

2.6. Alpha blockers: Doxazosin mesylate, Prazosin hydrochloride, Terazosin hydrochloride

2.7. Alpha-2 Receptor Agonist: Methyldopa

2.8. Central agonists: Alpha methyldopa, Clonidine hydrochloride, Guanabenz acetate, Guanfacine hydrochloride

2.9. Peripheral adrenergic inhibitors: Guanadrel, Guanethidine monosulfate, Reserpine

2.10. Blood vessel dilators (vasodilators): Hydralazine hydrocholoride, Minoxidil

3. Lipid Lowering Medication

3.1. Statins: Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin Calcium, Simvastatin

3.2. Niacin: Omega-3 Fatty Acid Ethyl Esters, Marine-Derived Omega-3 Polyunsaturated Fatty Acids

3.3. Bile-acid resins: Cholestyramine, Colestipol, Colesevelam Hcl

3.4. Fibric acid derivatives: Gemfibrozil, Fenofibrate, Clofibrate

3.5. Cholesterol absorption inhibitors