Articles

Title

Seasonal variations in the achievement of guideline targets for HbA1c, blood pressure, and cholesterol among type 2 diabetic patients: A nationwide population-based study (ABC study) (JDDM49)

List full names

Masaya Sakamoto[1], Daisuke Matsutani[1], Soichiro Minato[1], Yuki Tsujimoto[1], Yosuke Kayama[2], Norihiko Takeda[3], Seiichi Ichikawa[4], Ryuzo Horiuchi[5], Kazunori Utsunomiya[1], Masako Nishikawa[6]

[1] Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo, 105-8461, Japan

[2] Department of Cardiology, The Jikei University School of Medicine, Tokyo, Japan, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo, 105-8461, Japan

[3] Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8654, Japan

[4] Department of Cardiology, Tsuruoka Kyoritsu Hospital, Yamagata, Japan, 9-34, Fumizonomachi, Tsuruoka-shi, Yamagata, 997-0816, Japan

[5] Department of Pathology, Tsuruoka Kyoritsu Hospital, Yamagata, Japan, 9-34, Fumizonomachi, Tsuruoka-shi, Yamagata, 997-0816, Japan

[6] Clinical Research Support Center, The Jikei University School of Medicine, Tokyo, Japan, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo, 105-8461, Japan

Address correspondence to:

Corresponding author: Masaya Sakamoto, MD, PhD

Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan

Address: 3-25-8 Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan

E-mail: m-sakamoto@umin.ac.jp

Telephone number: +81-3-3433-1111

Fax number: +81-3-3578-9753

Institutional addresses

Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine,

3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo, 105-8461, Japan

Email addresses for all authors

Masaya Sakamoto E-mail: m-sakamoto@umin.ac.jp

Daisuke Matsutani E-mail: daisuke19870116@yahoo.co.jp

Soichiro Minato E-mail: minato425@gmail.com

Yuki Tsujimoto E-mail: youmekoki@gmail.com

Yosuke Kayama E-mail: kayama@jikei.ac.jp

Norihiko Takeda E-mail: ntakeda-tky@umin.ac.jp

Seiichi Ichikawa E-mail: s.ichikawa@shonai-mcoop.jp

Ryuzo Horiuchi E-mail: horiuchi@shonai-mcoop.jp

Kazunori Utsunomiya E-mail: kazu-utsunomiya@jikei.ac.jp

Masako Nishikawa E-mail: mnishikawa@jikei.ac.jp

Indicate the corresponding author

The corresponding author is Masaya Sakamoto.

Masaya Sakamoto, Daisuke Matsutani, and Masako Nishikawa contributed equally to this study.

Summary

OBJECTIVE

Precise monthly achievement rates for reaching guideline targets for HbA1c, blood pressure (BP), and lipid levels remain unknown. We evaluated achievement rates on a monthly basis in persons with type 2 diabetes mellitus (T2DM) and explored related factors.

RESEARCH DESIGN AND METHODS

This retrospective study initially analyzed data on 104,601 persons with T2DM throughout Japan. Patients whose HbA1c, BP, and low-density lipoprotein (LDL)-cholesterol were measured ≥12 times during a 24-month period were included. We evaluated monthly achievement rates. Achieved targets were defined as HbA1c <7%, BP <130/80 mmHg, and

LDL-cholesterol <100 mg/dL. Achievement of all targets was expressed as the "all ABC achievement".

RESULTS

Analyzed were 4,678 patients. The achievement rates of all ABC, HbA1c, BP, and LDL-cholesterol were lowest in winter, with those for systolic BP (SBP) being particularly low (all ABC, summer 15.6%, winter 9.6%; HbA1c, 53.1%, 48.9%; SBP, 56.6%, 40.9%; LDL-cholesterol, 50.8%, 47.2%). In winter, age ≥65 years (odds ratio 0.47 [95% CI 0.34-0.63]) was independently related to decreased achievement rates for SBP, and BMI ≥25 kg/m^2 (BMI 25-30 kg/m^2, 0.45 [0.29-0.70]; BMI ≥30 kg/m^2, 0.35 [0.22-0.57]) and diabetes duration ≥10 years (0.53 [0.37-0.76]) were independently related to lower achievement rates for HbA1c. Insulin use and sulfonylurea use were independently associated with the decreased all ABC achievement rates in both summer and winter.

CONCLUSIONS

The all ABC achievement rate for guideline targets changed on a monthly basis. Seasonal variations in the all ABC achievement rate should be considered when managing T2DM in ordinary clinical practices.

Trial registration

UMIN Clinical Trials Registry UMIN000034231

INTRODUCTION

The goal of treatment of type 2 diabetes mellitus (T2DM) is to reduce the incidence of cardiovascular (CV) events and improve the prognosis. In T2DM, comprehensively controlling blood glucose levels, blood pressure (BP), and lipid levels was reported to lead to decreased CV events and an improved prognosis (1). Conversely, some large-scale clinical trials reported different results for CV outcome and mortality in the achievement of the same HbA1c target (2-4). A similar phenomenon was reported for BP (5; 6) and lipid levels (7; 8); therefore, target values are difficult to establish and should be revised as necessary. Currently, various academic societies have established target values as guidelines for blood glucose levels (9), BP (10), and lipid levels (11). Some recent statements have defined target values

as ranges. In 2018, the American College of Physicians recommended in an evidence-based guidance statement that T2DM should be treated to achieve HbA1c between 7% and 8% rather than 6.5% to 7% as previously recommended (12).

The reason for the different results for CV outcome and mortality in those having achieved the same target values might be that values were measured at different time points and frequencies in many large-scale clinical trials. Differences may also be due to seasonal variations (13-15), with worse values during the winter and more favorable values during the summer. To improve the prognosis of patients with T2DM, values should be evaluated at time points that would account for seasonal variations. It is important to intensify treatment when control worsens and to prevent adverse events such as hypoglycemia (16) and low BP (17) when the control is satisfactory. However, the achievement rates necessary to formulate effective specific treatment strategies remain unknown.

In the present study, we evaluated for the first time rates of achieving guideline targets for HbA1c, BP, and low-density lipoprotein (LDL)-cholesterol on a monthly basis in patients with T2DM and explored factors affecting the achievement rates.

RESEARCH DESIGN AND METHODS

Patients

Thirty-eight medical clinics or general/university-affiliated hospitals specializing in diabetes care volunteered to participate in this study. These clinics were located in different areas in Japan (latitude variations of hospitals [Degrees North], 26°12′44″ ~ 43°11′46″). They all used the same software, which was specifically developed for the Japan Diabetes Clinical Data Management (JDDM) Study Group (CoDiC, Novo Nordisk Pharm Ltd., Tokyo, Japan) to incorporate patient records from January 2013 to December 2014. Details of the JDDM and CoDiC were described previously (18).

The inclusion criteria were patients whose HbA1c, BP, and LDL-cholesterol were measured ≥12 times during the two-year period; who were age ≥20 years and <75 years; and who had T2DM diagnosed based on criteria in the 'Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus' (19). Exclusion criteria were irregular clinic visits; visit intervals of >2 months; type 1 diabetes mellitus; hemodialysis for end-stage renal failure; and no information on anti-diabetic drugs, anti-hypertensive agents, lipid-lowering agents, antiplatelet drug use, current smoking status, alcohol drinking status, family history of diabetes, or diabetes duration.

Of the 104,601 registered patients in 38 medical clinics, 4,678 were included in the analysis after excluding 82,092 patients with diabetes whose HbA1c, body weight, or BP were not measured ≥12 times during the two years, who had irregular clinic visits, or who had visit-intervals >2 months. Also excluded were 4,152 patients under <20 years old or ≥75 years old, 1,275 patients with type 1 diabetes or end-stage renal failure on hemodialysis, and 12,404 patients whose LDL-cholesterol was not measured ≥12 times within 2 years, or with no available information on anti-diabetic drugs, anti-hypertensive agents, lipid-lowering agents, antiplatelet drug use, current smoking status, alcohol drinking status, family history of diabetes, or diabetes duration (Supplemental Figure 1).

The ethics committee of the JDDM, which also included outside members such as lawyers and ethics experts, approved the present study. The JDDM operates as an aggregate organization under the supervision of the central analytical facility and an ethics committee. All patients provided informed consent at each participating institute in accordance with the Guidelines for Epidemiological Studies of the Ministry of Health, Labor and Welfare of Japan.

Measurements

HbA1c, expressed in National Glycohemoglobin Standardization Program units, was measured by high-performance liquid chromatography. Plasma glucose was measured by a glucose-oxidase method. BP was measured at each local medical institution according to the recommendations of the Japanese Ministry of Health, Labor, and Welfare. Plasma total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides (TG) were assessed with standard enzymatic spectrophotometric techniques. Plasma LDL-cholesterol was calculated by the Friedewald equation or beta-quantification methods (20). eGFR was calculated with the MDRD-formula. Clinical data (duration of diabetes; body mass index [BMI]; smoking status [never, current]; alcohol drinking status [never, current]; use of anti-diabetic drugs, anti-hypertensive agents, and lipid-lowering agents; family history of diabetes) were obtained from medical records and a questionnaire.

Definitions

T2DM was defined according to fasting plasma glucose (FPG) ≥200 mg/dL or provision of pharmacological treatment. In patients with FPG between ≥126 mg/dL and <200 mg/dL, measurement of FPG was repeated at another time. If the second FPG value was also ≥126 mg/dL, a diagnosis of T2DM was confirmed. Those with FPG <126 mg/dL underwent a

standard oral glucose tolerance test (75-g glucose 2 h), and if FPG was ≥126 and/or 2-h plasma glucose was ≥200 mg/dL, patients were considered to have T2DM. Hypertension was defined as systolic BP (SBP) ≥140 mmHg, diastolic BP (DBP) ≥90 mmHg, and/or the current use of antihypertensive agents based on criteria of the American Heart Association and the American College of Cardiology (21; 22). Dyslipidemia was defined as abnormal values for ≥1 among HDL-cholesterol <40 mg/dL, LDL-cholesterol ≥120 mg/dL, TG ≥150 mg/dL, and/or the current use of lipid-lowering agents based on criteria in the Japan Atherosclerosis Society Guidelines (23).

Summer was defined as June, July, and August and winter as December, January, and February. The mean values for HbA1c, SBP, DBP, and LDL-cholesterol measured in the summer (two years) and winter (two years) were calculated for each patient by the same methods.

Achievements of targets were defined as HbA1c <7% (9), SBP <130 mmHg, and DBP <80 mmHg (10) according to the American Diabetes Association (ADA), and LDL-cholesterol <100 mg/dL according to the American Association for Clinical Endocrinologists (11). Achievement rates for both HbA1c <8% and HbA1c <7% were analyzed. In this study, the proportion of achievement of all guideline targets for HbA1c,

SBP, DBP, and LDL-cholesterol was expressed as the "all ABC achievement rate". "A" stands for HbA1c, "B" for BP, and "C" for LDL-cholesterol. We named this study the ABC study.

Study outcome

The primary objective was to evaluate the all ABC achievement rate for each month (Fig. 1A). Secondary objectives included evaluation of the achievement rates for HbA1c, SBP, DBP, and LDL-cholesterol for each month (Fig. 1B); the all ABC achievement rates in summer and winter (Fig. 1C); and the achievement rates for HbA1c, SBP, DBP, and LDL-cholesterol, respectively, in summer and winter (Fig. 1D). The factors affecting the all ABC achievement rate in summer and winter as well as those affecting the achievement rates for HbA1c, SBP, DBP, and LDL-cholesterol individually in summer and winter were also studied (Table 2). Objectives also included the following evaluations for the summer and winter: the proportion of patients in the BP target groups (SBP <130 mmHg and DBP <80 mmHg or SBP ≥130 or DBP ≥80) for each HbA1c target group (HbA1c <7% or ≥7%) (Supplemental Figure 2A), the proportion of patients in the LDL-cholesterol target groups (LDL-cholesterol <100 mg/dL or ≥100 mg/dL) for each HbA1c target group (Supplemental

Figure 2B), and the proportion of patients in the BP target groups for each LDL-cholesterol target group (Supplemental Figure 2C) .

Statistical Methods

Patients' characteristics and results are presented as means ± SD or median with the interquartile range as appropriate according to data distribution. Multiple logistic regression analysis was used to determine the independent associations between achievement of All ABC, HbA1c, SBP, DBP, and LDL-cholesterol targets, respectively, in summer and winter and the variables of gender, age, diabetes duration, family history of diabetes, BMI, eGFR, history of hypertension, anti-hypertensive agent use, history of dyslipidemia, lipid-lowering agent use, antiplatelet drug use, insulin use, sulfonylurea (SU) use, metformin use, dipeptidyl peptidase-4 (DPP-4) inhibitor use, glucagon-like peptide (GLP)-1 receptor agonists use, glinide use, α-glucosidase inhibitor use, thiazolidinediones use, current smoking status, and current alcohol drinking status (Table 2). Age, diabetes duration, BMI, and eGFR were included as quadrichotomous variables. For the BMI, which was included as a covariate, the average BMI for summer and winter, respectively, was used for multiple logistic regression analysis. Separate models were constructed using the following dependent variables: in

summer and winter, achievement of (1) all ABC, (2) HbA1c <7%, (3) SBP <130 mmHg, (4) DBP <80 mmHg, and (5) LDL-cholesterol <100 mg/dL. The results were expressed as an odds ratio (OR) with 95% confidence interval (CI). A *p* value <0.001 was considered significant. Data analyses were performed using the Statistical Package for the Social Sciences 22.0 software (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics of study participants

A total of 4,678 patients were analyzed. Table 1 shows the characteristics of the study participants. Mean age of participants was 61.3 ± 9.4 years (mean ± SD), and mean HbA1c was 57.2 ± 13.5 mmol/mol (mean % HbA1c 7.4 ± 1.2%). The prevalence of study participants ever diagnosed with hypertension or dyslipidemia was 65.3% or 83.7%, respectively.

Achievement rates of All ABC, HbA1c, BP, and LDL-cholesterol in all seasons

The achievement rates for all ABC (Fig. 1A), HbA1c, BP, and LDL-cholesterol varied seasonally (Fig. 1B). The achievement rate for HbA1c <8% was the highest, followed by that for DBP <80 mmHg (Fig. 1B). Equivalent achievement rates for HbA1c <7%, SBP <130

mmHg, and LDL-cholesterol <100 mg/dL were found (Fig. 1B). The achievement rates for all ABC (Fig. 1C), HbA1c, SBP, DBP, and LDL-cholesterol (Fig. 1D) in the summer were higher than in the winter. Differences between the achievement rates in summer and winter were the largest for SBP (Fig. 1D).

Factors involved in the decrease in achievement rates for all ABC, HbA1c, BP, or LDL-cholesterol were revealed by the multiple logistic regression analysis (Table 2). In winter, BMI ≥25 kg/m^2 and diabetes duration ≥10 years were independently related to lower achievement rates for HbA1c. Age ≥65 years was independently related to the decreased achievement rate for SBP in winter. No obvious factor was related to the decreased achievement rate for LDL-cholesterol in winter. Proportion of patients who achieved HbA1c, BP, or LDL-cholesterol targets within each HbA1c target group, BP target group, or LDL-cholesterol target group in summer and winter are shown in Supplemental Figure 2.

CONCLUSIONS

This is the first clinical study to assess the monthly achievement rates for guideline targets for HbA1c, BP, and LDL-cholesterol and the all ABC achievement rate in those with T2DM. We

retrospectively assessed data on patients with T2DM whose HbA1c, BP, and LDL-cholesterol were measured ≥12 times during a two-year period.

The results showed that the achievement rates for guideline targets for HbA1c, BP, and LDL-cholesterol and the all ABC achievement rate varied seasonally (Fig. 1A, 1B). The analysis of achievement rates by season (summer and winter) indicated that the all ABC achievement rate was highest in the summer (Jun, Jul, Aug) and lowest in the winter (Dec, Jan, Feb) (Fig. 1C). As to guideline targets for HbA1c, BP, and LDL-cholesterol, the achievement rate for SBP was particularly low in the winter (Fig. 1D).

Our results further support existing data showing that there are seasonal variations in blood glucose, BP, and lipid levels (13). However, the limitation of previous studies was that these parameters were measured only once or twice a year. These parameters have been reported to be controlled by various factors, including physical activity (24; 25), eating behaviors (25), insulin resistance (26), and body composition (27). Since a previous study reported that resting sympathetic nerve activity varies seasonally with peak levels evident in winter, the seasonal variation in sympathetic activity may contribute to the all ABC achievement rate (28). Temperature was also reported to be the most influential factor in seasonal variations in these parameters (13; 24). Although this study did not compare

achievement rates between the southern and northern areas of Japan, the pattern of seasonal variations in achievement rates can be expected to differ depending on the climate pattern. In fact, in a country with minimal monthly temperature variations, HbA1c variations were reported to be small throughout the year (29). Regarding BP, since it was reported that SBP increases by 5.7 mmHg every time the temperature decreases by 10°C regardless of latitude (30), the seasonal variation in the achievement rate may be smaller in areas with small temperature differences between summer and winter, such as southern areas in Japan. On the other hand, during the winter holidays, in particular the New Year holidays, people are customarily physically inactive because of snow and temperature drops, and they traditionally indulge in salty meals, such as soup. Body weight tends to increase over holidays (31), which may be a factor in the yearly increased levels of HbA1c, BP, and lipids among persons with T2DM. In fact, HbA1c and cholesterol levels were reported to be increased during winter holiday periods (32). Another study reported that adult outpatients in a tropical country have a circannual pattern of HbA1c values reflecting holiday celebrations in the preceding 3 months (33). These reports may explain why it is more difficult for diabetic patients to meet targets in winter.

This study explored and evaluated factors affecting the rates for the achievement of guideline targets for HbA1c, BP, and LDL-cholesterol on a monthly basis. In the winter, advanced age was found to be an independent factor for the lower SBP achievement rate. Since the SBP achievement rate was particularly low in winter, these results may be an important factor in lowering the all ABC achievement rate in winter. Among patients of advanced age, atherosclerosis might have prevented meeting BP goals in winter. Atherosclerosis impairs vasodilatability and cardiovascular autonomic function (34), and the effectiveness of functions for regulating BP decreases. Therefore, BP increases may be due to the exacerbation of various factors affecting BP in the winter, further decreasing the rate of achieving BP targets. BMI $\geq$25 kg/m^2 and diabetes duration $\geq$10 years were independently associated with the decreased achievement rates for HbA1c in winter. Obese T2DM patients and/or those with diabetes of a long duration may experience large changes in physical activity and food intake in winter.

The analysis according to anti-diabetic drug use revealed that insulin use and SU use were independently associated with decreased all ABC achievement rates in both summer and winter. Insulin and SU are administered to patients whose hyperglycemia is relatively difficult to treat. In fact, Table 2 shows that these drugs were independently associated with

decreased HbA1c achievement rates. Interestingly, insulin use was independently associated with a lower achievement rate for SBP. Thus, physicians should pay more attention to the all ABC achievement rates throughout the year in patients using these drugs.

A recent investigation of prognosis of T2DM showed that in patients with T2DM, the percentage of preventable CV events was approximately one third even if the patient succeeded in smoking cessation in addition to appropriate control of blood glucose, BP, and lipid levels (35). Causes may be long-term glycemic variability (36; 37), long-term BP variability (38; 39), and long-term lipid level variability (40), which are residual risk factors for CV events, were not evaluated.

The design and methods of this study had several strengths. First, it included data only on patients with T2DM whose HbA1c, BP, and LDL-cholesterol were measured ≥12 times during a two-year period. Second, patients with T2DM (n = 4,678) from throughout Japan (latitude variation of hospitals [Degrees North] 26°12′44″-43°11′46″) were analyzed. This study also has some limitations. First was its retrospective design, which carries the risk of selection bias. Second, the number of study patients was small and participants were a subgroup from a prior study. Third, medication adherence was not considered during the two-year period. Fourth, the effects of temperature, physical activity, food intake including

salt intake, and cultural factors on the achievement rates were not examined. In addition, although the range of the latitudes of the locations of the study hospitals were disclosed, individual hospital data were not disclosed so that we could not examine the effects of latitude differences on achievement rates. Fifth, participants included patients with T2DM who were under treatment for co-morbidities such as arterial hypertension and dyslipidemia. Sixth, the basis of diabetic treatment of Japanese patients differs from that for Caucasians, such as metformin use and DPP-4 inhibitors use.

In summary, this study showed that in patients with T2DM, the achievement rates for blood glucose, BP, and lipid target levels varied seasonally and that the achievement rates for these parameters were lowest in winter. The individual background of each patient would also affect achievement rates. It is important to take seasonal variations in the all ABC achievement rate into consideration in managing patients in ordinary clinical practice. Furthermore, it could be expected that intensifying treatment for each value in the winter might lead to the prevention of CV events. A large-scale clinical trial needs to be conducted to verify which intervention to reduce seasonal variations would lead to the greatest decrease in CV events in the near future.

Acknowledgements

Masaya Sakamoto is the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

None

Duality of Interest

The authors of this manuscript have the following competing interests: M.S. has participated in speaker's bureaus/advisory panels for Sanofi, Daiichi-Sankyo, Astellas, and Tanabe-Mitsubishi. N.T. has received a research grant and support from Daiichi-Sankyo and Otsuka Pharmaceutical and has participated in speaker's bureaus organized by Daiichi-Sankyo and MSD. K.U. has received research support from Terumo, Kowa, Taisho, Kyowa Kirin, Boehringer Ingelheim, Ono, Novo Nordisk, Sumitomo Dainippon, and Tanabe-Mitsubishi and has participated in speaker's bureau/advisory panels for Boehringer

Ingelheim, Tanabe-Mitsubishi, and Eli Lilly. The other authors have no conflict of interest to declare.

Author Contributions

M.S. contributed to the study design, data acquisition, data analysis, and wrote the manuscript. D.M. and M.N. contributed to the study design, data analysis and wrote the manuscript. S.M., Y.T., Y.K., N.T., S. I., R.H., and K. U. reviewed the manuscript and edited it for intellectual content. All authors gave final approval for this version to be published. The funder had no role in study design, analysis, interpretation of data, writing of the manuscript, and the decision to submit the manuscript for publication.

References

1. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. The New England journal of medicine 2003;348:383-393
2. Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. The New England journal of medicine 2008;358:2545-2559
3. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive

blood glucose control and vascular outcomes in patients with type 2 diabetes. The New England journal of medicine 2008;358:2560-2572
4. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet (London, England) 1998;352:837-853
5. Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F: Effects of intensive blood-pressure control in type 2 diabetes mellitus. The New England journal of medicine 2010;362:1575-1585
6. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. The New England journal of medicine 2015;373:2103-2116
7. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R: Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (London, England) 2010;376:1670-1681
8. Shepherd J: Resource management in prevention of coronary heart disease: optimising prescription of lipid-lowering drugs. Lancet (London, England) 2002;359:2271-2273
9. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes care 2018;41:S55-s64
10. 9. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2018. Diabetes care 2018;41:S86-s104
11. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2017;23:1-87

12. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA: Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Annals of internal medicine 2018;168:569-576
13. Liang WW: Seasonal changes in preprandial glucose, A1C, and blood pressure in diabetic patients. Diabetes care 2007;30:2501-2502
14. Marti-Soler H, Gubelmann C, Aeschbacher S, Alves L, Bobak M, Bongard V, Clays E, de Gaetano G, Di Castelnuovo A, Elosua R, Ferrieres J, Guessous I, Igland J, Jorgensen T, Nikitin Y, O'Doherty MG, Palmieri L, Ramos R, Simons J, Sulo G, Vanuzzo D, Vila J, Barros H, Borglykke A, Conen D, De Bacquer D, Donfrancesco C, Gaspoz JM, Giampaoli S, Giles GG, Iacoviello L, Kee F, Kubinova R, Malyutina S, Marrugat J, Prescott E, Ruidavets JB, Scragg R, Simons LA, Tamosiunas A, Tell GS, Vollenweider P, Marques-Vidal P: Seasonality of cardiovascular risk factors: an analysis including over 230 000 participants in 15 countries. Heart (British Cardiac Society) 2014;100:1517-1523
15. Bardini G, Dicembrini I, Rotella CM, Giannini S: Lipids seasonal variability in type 2 diabetes. Metabolism 2012;61:1674-1677
16. Desouza CV, Bolli GB, Fonseca V: Hypoglycemia, diabetes, and cardiovascular events. Diabetes care 2010;33:1389-1394
17. Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, Pepine CJ: Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. Jama 2010;304:61-68
18. Oishi M, Yamazaki K, Okuguchi F, Sugimoto H, Kanatsuka A, Kashiwagi A: Changes in oral antidiabetic prescriptions and improved glycemic control during the years 2002-2011 in Japan (JDDM32). Journal of diabetes investigation 2014;5:581-587
19. The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes M, Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M, Ueki K: Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. Journal of diabetes investigation 2010;1:212-228
20. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical chemistry 1972;18:499-502
21. Go AS, Bauman MA, Coleman King SM, Fonarow GC, Lawrence W, Williams KA, Sanchez E: An effective approach to high blood pressure control: a science advisory from the

American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention. Hypertension 2014;63:878-885
22. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Jr., Svetkey LP, Taler SJ, Townsend RR, Wright JT, Jr., Narva AS, Ortiz E: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama 2014;311:507-520
23. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K: Diagnostic criteria for dyslipidemia. Journal of atherosclerosis and thrombosis 2013;20:655-660
24. Ockene IS, Chiriboga DE, Stanek EJ, 3rd, Harmatz MG, Nicolosi R, Saperia G, Well AD, Freedson P, Merriam PA, Reed G, Ma Y, Matthews CE, Hebert JR: Seasonal variation in serum cholesterol levels: treatment implications and possible mechanisms. Archives of internal medicine 2004;164:863-870
25. Ryu OH, Lee S, Yoo HJ, Choi MG: Seasonal variations in glycemic control of type 2 diabetes in Korean women. Journal of endocrinological investigation 2014;37:575-581
26. Berglund L, Berne C, Svärdsudd K, Garmo H, Melhus H, Zethelius B: Seasonal variations of insulin sensitivity from a euglycemic insulin clamp in elderly men. Upsala Journal of Medical Sciences 2012;117:35-40
27. Sohmiya M, Kanazawa I, Kato Y: Seasonal changes in body composition and blood HbA1c levels without weight change in male patients with type 2 diabetes treated with insulin. Diabetes care 2004;27:1238-1239
28. Cui J, Muller MD, Blaha C, Kunselman AR, Sinoway LI: Seasonal variation in muscle sympathetic nerve activity. Physiological reports 2015;3
29. Higgins T, Saw S, Sikaris K, Wiley CL, Cembrowski GC, Lyon AW, Khajuria A, Tran D: Seasonal variation in hemoglobin A1c: is it the same in both hemispheres? Journal of diabetes science and technology 2009;3:668-671
30. Lewington S, Li L, Sherliker P, Guo Y, Millwood I, Bian Z, Whitlock G, Yang L, Collins R, Chen J, Wu X, Wang S, Hu Y, Jiang L, Yang L, Lacey B, Peto R, Chen Z: Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. Journal of hypertension 2012;30:1383-1391
31. Diaz-Zavala RG, Castro-Cantu MF, Valencia ME, Alvarez-Hernandez G, Haby MM, Esparza-Romero J: Effect of the Holiday Season on Weight Gain: A Narrative Review. Journal of obesity 2017;2017:2085136

32. Chen HS, Jap TS, Chen RL, Lin HD: A prospective study of glycemic control during holiday time in type 2 diabetic patients. Diabetes care 2004;27:326-330
33. Hawkins RC: Circannual variation in glycohemoglobin in Singapore. Clinica chimica acta; international journal of clinical chemistry 2010;411:18-21
34. Gianaros PJ, Jennings JR, Olafsson GB, Steptoe A, Sutton-Tyrrell K, Muldoon MF, Manuck SB: Greater Intima–Media Thickness in the Carotid Bulb Is Associated With Reduced Baroreflex Sensitivity. American journal of hypertension 2002;15:486-491
35. Vazquez-Benitez G, Desai JR, Xu S, Goodrich GK, Schroeder EB, Nichols GA, Segal J, Butler MG, Karter AJ, Steiner JF, Newton KM, Morales LS, Pathak RD, Thomas A, Reynolds K, Kirchner HL, Waitzfelder B, Elston Lafata J, Adibhatla R, Xu Z, O'Connor PJ: Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes care 2015;38:905-912
36. Forbes A, Murrells T, Mulnier H, Sinclair AJ: Mean HbA1c, HbA1c variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. The lancet Diabetes & endocrinology 2018;6:476-486
37. Hirakawa Y, Arima H, Zoungas S, Ninomiya T, Cooper M, Hamet P, Mancia G, Poulter N, Harrap S, Woodward M, Chalmers J: Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. Diabetes care 2014;37:2359-2365
38. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, Sever PS, Poulter NR: Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet (London, England) 2010;375:895-905
39. Hata J, Arima H, Rothwell PM, Woodward M, Zoungas S, Anderson C, Patel A, Neal B, Glasziou P, Hamet P, Mancia G, Poulter N, Williams B, Macmahon S, Chalmers J: Effects of visit-to-visit variability in systolic blood pressure on macrovascular and microvascular complications in patients with type 2 diabetes mellitus: the ADVANCE trial. Circulation 2013;128:1325-1334
40. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH: Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. J Am Coll Cardiol 2015;65:1539-1548

Table 1. Baseline characteristics of the study population

Data	
No. of patients	4,678
Male/female	2,948/1,730
Age (years)	61.3 ± 9.4
Latitude variation of hospitals (Degrees North)	26°12′44″-43°11′46″
Diabetes duration (years)	12.6 ± 8.6
Hypertension, n (%)	3,055 (65.3)
Dyslipidemia, n (%)	3,914 (83.7)
Glycemic control	
Casual blood glucose (mg/dL)	161.4 ± 63.6
HbA1c (mmol/mol)	57.2 ± 13.5
HbA1c (%)	7.4 ± 1.2
No. HbA1c measurements in 2 years (times/2 years)	19.0 ± 3.7
BP (mmHg)	
Systolic	133.8 ± 16.0
Diastolic	77.3 ± 11.5
No. SBP measurements in 2 years (times/2 years)	19.0 ± 3.7
No. DBP measurements in 2 years (times/2 years)	19.0 ± 3.7
Lipid profile (mg/dL)	
Triglycerides	122 (85-180)
LDL-cholesterol	107.0 ± 29.7
HDL-cholesterol	54.8 ± 14.5
No. LDL-cholesterol measurements in 2 years (times/2 years)	17.8 ± 4.0
BMI (kg/m^2)	
Baseline	25.5 ± 4.3
Summer mean	25.3 ± 4.4
Winter mean	25.4 ± 4.3
eGFR ($ml/min/1.73m^2$)	74.4 ± 20.1
First visit, n (%)	
January	3,701 (79.1)
February	715 (15.3)
March	85 (1.8)
Others	177 (3.8)
Anti-diabetic drugs	
Insulin, n (%)	1,127 (24.1)
Sulfonylureas, n (%)	1,916 (41.0)
Metformin, n (%)	2,206 (47.2)
DPP-4 inhibitors, n (%)	2,161 (46.2)
GLP-1 receptor agonists, n (%)	143 (3.1)
Glinides, n (%)	180 (3.8)
α-glucosidase inhibitors, n (%)	762 (16.3)
Thiazolidines, n (%)	593 (12.7)
Anti-hypertensive agents, n (%)	2,314 (49.5)
Anti-hypertensive agent use for hypertension, (%)	75.8
Lipid-lowering agents, n (%)	2,468 (52.8)
Lipid-lowering agent use for dyslipidemia, (%)	63.1
Antiplatelet drugs, n (%)	433 (9.3)
Current smokers, n (%)	609 (13.0)
Current alcohol drinking, n (%)	966 (20.6)

Values are mean ± SD, or median (25th-75th percentiles) or no. (%). BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index; eGFR, estimated glomerular filtration rate; DPP, dipeptidyl Peptidase-4; GLP, glucagon-like peptide

Table 2. Multiple logistic regression analysis for achievement of All ABC, HbA1c, blood pressure, and LDL-cholesterol guideline targets in summer and winter

	Odds ratio (95% CI)									
	All ABC		HbA1c < 7%		SBP < 130 mmHg		DBP < 80 mmHg		LDL-C < 100 mg/dL	
	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter	Summer	Winter
Female sex	0.73 (0.61-0.88)*	1.10 (0.88-1.38)	0.77 (0.67-0.89)*	0.87 (0.75-1.00)	0.94 (0.82-1.07)	1.16 (1.01-1.34)	2.61 (2.21-3.09)*	3.04 (2.61-3.55)*	0.61 (0.53-0.69)*	0.72 (0.63-0.83)*
Age										
< 45 years (reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
46-55 years	0.86 (0.53-1.38)	0.84 (0.47-1.52)	0.86 (0.63-1.18)	1.03 (0.75-1.41)	1.03 (0.76-1.39)	0.76 (0.56-1.03)	0.86 (0.63-1.17)	0.98 (0.72-1.34)	1.12 (0.82-1.51)	1.04 (0.77-1.42)
56-65 years	1.17 (0.76-1.82)	0.99 (0.57-1.70)	1.11 (0.82-1.49)	1.33 (0.98-1.80)	1.01 (0.76-1.35)	0.65 (0.48-0.87)	1.79 (1.33-2.40)*	2.14 (1.59-2.89)*	1.29 (0.97-1.73)	1.30 (0.97-1.75)
≥ 65 years	1.31 (0.84-2.06)	1.21 (0.69-2.11)	1.41 (1.04-1.92)	1.76 (1.28-2.41)*	0.79 (0.59-1.07)	0.47 (0.34-0.63)*	3.52 (2.55-4.84)*	3.78 (2.76-5.18)*	1.52 (1.13-2.06)	1.45 (1.07-1.97)
Diabetes duration										
< 1 years (reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1-5 years	0.68 (0.43-1.06)	0.84 (0.45-1.54)	1.15 (0.80-1.67)	0.79 (0.55-1.15)	0.99 (0.69-1.40)	0.69 (0.48-0.99)	1.02 (0.70-1.48)	0.80 (0.56-1.16)	1.06 (0.74-1.52)	1.13 (0.78-1.63)
5-10 years	0.58 (0.37-0.90)	0.74 (0.40-1.36)	0.85 (0.59-1.23)	0.62 (0.43-0.89)	0.92 (0.65-1.31)	0.63 (0.44-0.90)	0.93 (0.64-1.35)	0.62 (0.43-0.90)	1.11 (0.78-1.59)	1.18 (0.82-1.70)
≥ 10 years	0.63 (0.41-0.97)	0.94 (0.52-1.70)	0.66 (0.47-0.94)	0.53 (0.37-0.76)*	0.96 (0.69-1.35)	0.77 (0.55-1.10)	1.31 (0.91-1.88)	1.02 (0.71-1.45)	1.12 (0.79-1.58)	1.23 (0.86-1.75)
Family history of diabetes	0.92 (0.75-1.13)	1.19 (0.93-1.51)	0.89 (0.76-1.04)	0.94 (0.80-1.10)	1.23 (1.06-1.44)	1.12 (0.96-1.30)	1.40 (1.17-1.69)*	1.34 (1.13-1.59)*	0.77 (0.66-0.90)*	0.86 (0.74-1.01)
BMI										
< 18.5 (kg/m^2) (reference)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
18.5-25 (kg/m^2)	0.76 (0.48-1.18)	0.81 (0.45-1.44)	1.09 (0.73-1.61)	0.71 (0.46-1.10)	0.59 (0.39-0.90)	0.79 (0.52-1.20)	0.86 (0.50-1.47)	1.10 (0.67-1.82)	0.67 (0.46-0.99)	0.71 (0.47-1.08)
25-30 (kg/m^2)	0.48 (0.30-0.77)	0.52 (0.28-0.95)	0.65 (0.43-0.97)	0.45 (0.29-0.70)*	0.45 (0.29-0.69)*	0.61 (0.40-0.94)	0.60 (0.35-1.04)	0.83 (0.50-1.37)	0.62 (0.42-0.92)	0.69 (0.45-1.05)
≥ 30 (kg/m^2)	0.39 (0.23-0.66)*	0.43 (0.22-0.86)	0.50 (0.32-0.77)	0.35 (0.22-0.57)*	0.31 (0.20-0.49)*	0.43 (0.27-0.68)*	0.42 (0.24-0.75)*	0.64 (0.38-1.09)	0.60 (0.39-0.91)	0.68 (0.43-1.06)
eGFR										
< 30 mL/min/1.73m^2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
30-60 mL/min/1.73m^2	1.04 (0.49-2.21)	0.64 (0.27-1.48)	0.82 (0.47-1.42)	0.91 (0.52-1.60)	1.24 (0.74-2.09)	1.04 (0.60-1.79)	0.36 (0.15-0.87)	0.37 (0.17-0.80)	1.36 (0.79-2.33)	1.27 (0.74-2.17)
60-90 mL/min/1.73m^2	0.91 (0.44-1.92)	0.68 (0.30-1.56)	0.76 (0.44-1.32)	0.81 (0.47-1.40)	1.08 (0.65-1.80)	1.05 (0.61-1.80)	0.24 (0.10-0.58)	0.24 (0.11-0.52)*	1.44 (0.84-2.45)	1.28 (0.75-2.17)
≥ 90 mL/min/1.73m^2	0.78 (0.36-1.69)	0.66 (0.28-1.58)	0.55 (0.31-0.97)	0.57 (0.33-1.01)	0.93 (0.55-1.58)	0.89 (0.51-1.55)	0.21 (0.09-0.51)*	0.26 (0.12-0.55)*	1.53 (0.88-2.65)	1.43 (0.83-2.47)

Hypertension	0.38 (0.28-0.51)*	0.15 (0.09-0.26)*	0.99 (0.81-1.20)	1.13 (0.93-1.38)	0.19 (0.15-0.23)*	0.11 (0.09-0.14)*	0.24 (0.20-0.30)*	0.20 (0.16-0.25)*	0.97 (0.80-1.17)	1.04 (0.86-1.26)
Anti-hypertensive agent use	2.16 (1.58-2.94)*	4.87 (2.78-8.53)*	1.28 (1.06-1.56)	1.06 (0.87-1.29)	1.91 (1.59-2.30)*	2.84 (2.26-3.56)*	1.81 (1.49-2.21)*	2.16 (1.77-2.62)*	1.32 (1.09-1.59)	1.15 (0.96-1.39)
Dyslipidemia	0.44 (0.34-0.58)*	0.35 (0.25-0.50)*	0.53 (0.43-0.65)*	0.58 (0.47-0.71)*	0.93 (0.77-1.13)	0.79 (0.65-0.96)	0.86 (0.68-1.08)	0.89 (0.72-1.09)	0.31 (0.26-0.38)*	0.30 (0.25-0.37)*
Lipid-lowering agent use	2.51 (2.00-3.16)*	3.05 (2.24-4.16)*	1.40 (1.20-1.63)*	1.41 (1.21-1.65)*	1.28 (1.11-1.49)	1.42 (1.21-1.66)*	0.92 (0.78-1.10)	0.90 (0.77-1.06)	3.65 (3.13-4.24)*	3.89 (3.34-4.54)*
Antiplatelet drugs	1.19 (0.91-1.56)	1.43 (1.04-1.98)	0.89 (0.71-1.12)	0.96 (0.77-1.21)	1.23 (0.99-1.52)	1.38 (1.11-1.71)	2.11 (1.56-2.86)*	1.92 (1.48-2.48)*	1.02 (0.82-1.26)	0.99 (0.80-1.23)
Anti-diabetic drugs										
Insulin use	0.41 (0.32-0.53)*	0.30 (0.22-0.42)*	0.18 (0.15-0.22)*	0.17 (0.14-0.21)*	0.61 (0.52-0.71)*	0.67 (0.56-0.79)*	1.06 (0.88-1.28)	1.17 (0.98-1.40)	1.02 (0.87-1.19)	1.01 (0.86-1.18)
Sulfonylurea use	0.60 (0.50-0.73)*	0.54 (0.42-0.69)*	0.35 (0.30-0.41)*	0.31 (0.26-0.36)*	0.84 (0.73-0.97)	0.83 (0.71-0.96)	1.06 (0.89-1.25)	1.09 (0.93-1.27)	0.91 (0.79-1.04)	0.84 (0.73-0.97)
Metformin use	0.96 (0.80-1.15)	0.88 (0.70-1.11)	0.92 (0.80-1.06)	0.93 (0.81-1.07)	0.89 (0.78-1.02)	0.83 (0.72-0.95)	1.00 (0.85-1.17)	0.88 (0.76-1.02)	1.40 (1.23-1.60)*	1.46 (1.28-1.67)*
DPP-4 inhibitor use	0.90 (0.75-1.07)	0.83 (0.66-1.03)	0.71 (0.62-0.82)*	0.77 (0.67-0.88)*	1.02 (0.89-1.16)	0.97 (0.85-1.11)	0.90 (0.77-1.05)	0.81 (0.69-0.93)	1.24 (1.09-1.42)	1.19 (1.04-1.36)
GLP-1 receptor agonists use	0.31 (0.14-0.69)	0.36 (0.14-0.90)	0.25 (0.16-0.38)*	0.26 (0.17-0.42)*	0.78 (0.53-1.13)	0.70 (0.47-1.04)	0.84 (0.56-1.27)	0.68 (0.46-1.01)	1.18 (0.81-1.71)	0.95 (0.65-1.38)
Glinide use	0.87 (0.56-1.35)	0.71 (0.41-1.25)	0.63 (0.45-0.89)	0.76 (0.54-1.08)	1.02 (0.73-1.43)	1.09 (0.78-1.54)	1.07 (0.72-1.60)	1.28 (0.88-1.86)	1.00 (0.72-1.39)	0.84 (0.60-1.17)
α-glucosidase inhibitor use	1.06 (0.85-1.33)	1.14 (0.86-1.51)	1.22 (1.02-1.46)	1.13 (0.95-1.36)	1.18 (0.99-1.40)	0.94 (0.79-1.12)	1.44 (1.17-1.78)*	1.36 (1.12-1.64)	1.07 (0.90-1.27)	1.01 (0.85-1.19)
Thiazolidinediones use	1.50 (1.18-1.91)*	1.15 (0.84-1.57)	1.07 (0.88-1.30)	1.13 (0.93-1.38)	1.28 (1.05-1.55)	0.90 (0.73-1.10)	1.36 (1.08-1.72)	1.37 (1.11-1.70)	1.55 (1.27-1.89)*	1.54 (1.27-1.87)*
Current smoker	1.05 (0.81-1.36)	1.20 (0.87-1.66)	0.80 (0.65-0.98)	0.94 (0.76-1.16)	1.28 (1.05-1.57)	1.00 (0.81-1.22)	1.46 (1.16-1.84)	1.34 (1.08-1.66)	1.08 (0.88-1.31)	1.01 (0.83-1.23)
Current alcohol drinking	1.12 (0.89-1.40)	0.99 (0.75-1.32)	1.31 (1.09-1.58)	1.26 (1.05-1.52)	1.11 (0.93-1.33)	1.20 (1.00-1.44)	0.74 (0.60-0.90)	0.89 (0.74-1.08)	1.19 (1.00-1.43)	1.20 (1.01-1.43)

*$p < 0.001$. LDL, low density lipoprotein; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; DPP, dipeptidyl peptidase-4; GLP, glucagon-like peptide

Figure titles and legends

Figure 1

Figure title: Achievement rates for All ABC, HbA1c, BP, and LDL-cholesterol throughout the year (A, B) and in summer and winter (C, D); **Figure legend**: **A**, All ABC (HbA1c [<7% or <8%], BP, and LDL-cholesterol) achievement rates monthly over a period of two years. **B**, Monthly achievement rates for HbA1c, BP, and LDL-cholesterol over a two-year period. **C**, All ABC achievement rates in summer and winter in a two-year period. **D**, Achievement rates for HbA1c [<7% or <8%], SBP, DBP, and LDL-cholesterol in summer and winter in a two-year period. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol

Supplemental Figure 1.

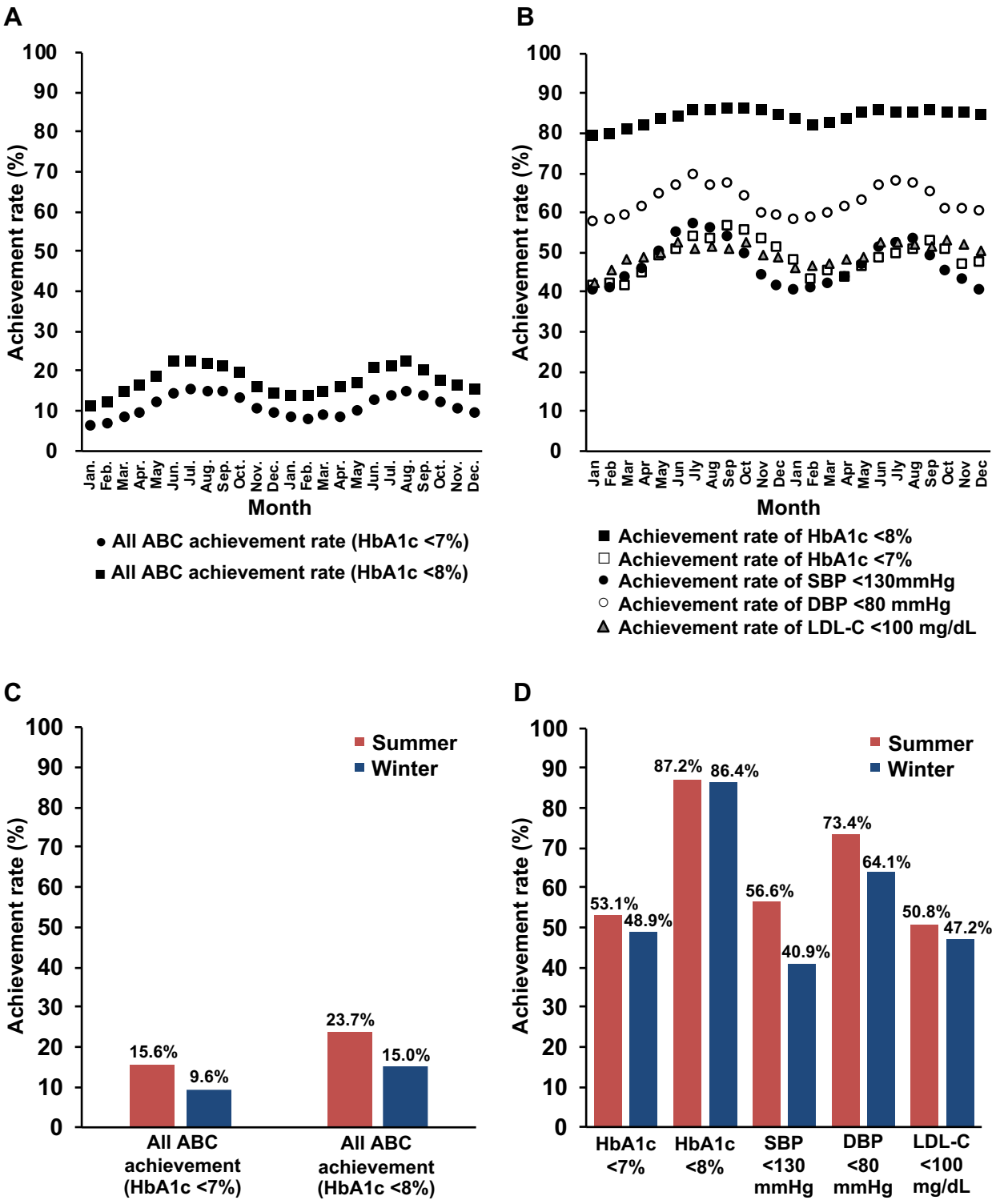
Figure title: Study population; **Figure legend**: none

Supplemental Figure 2.

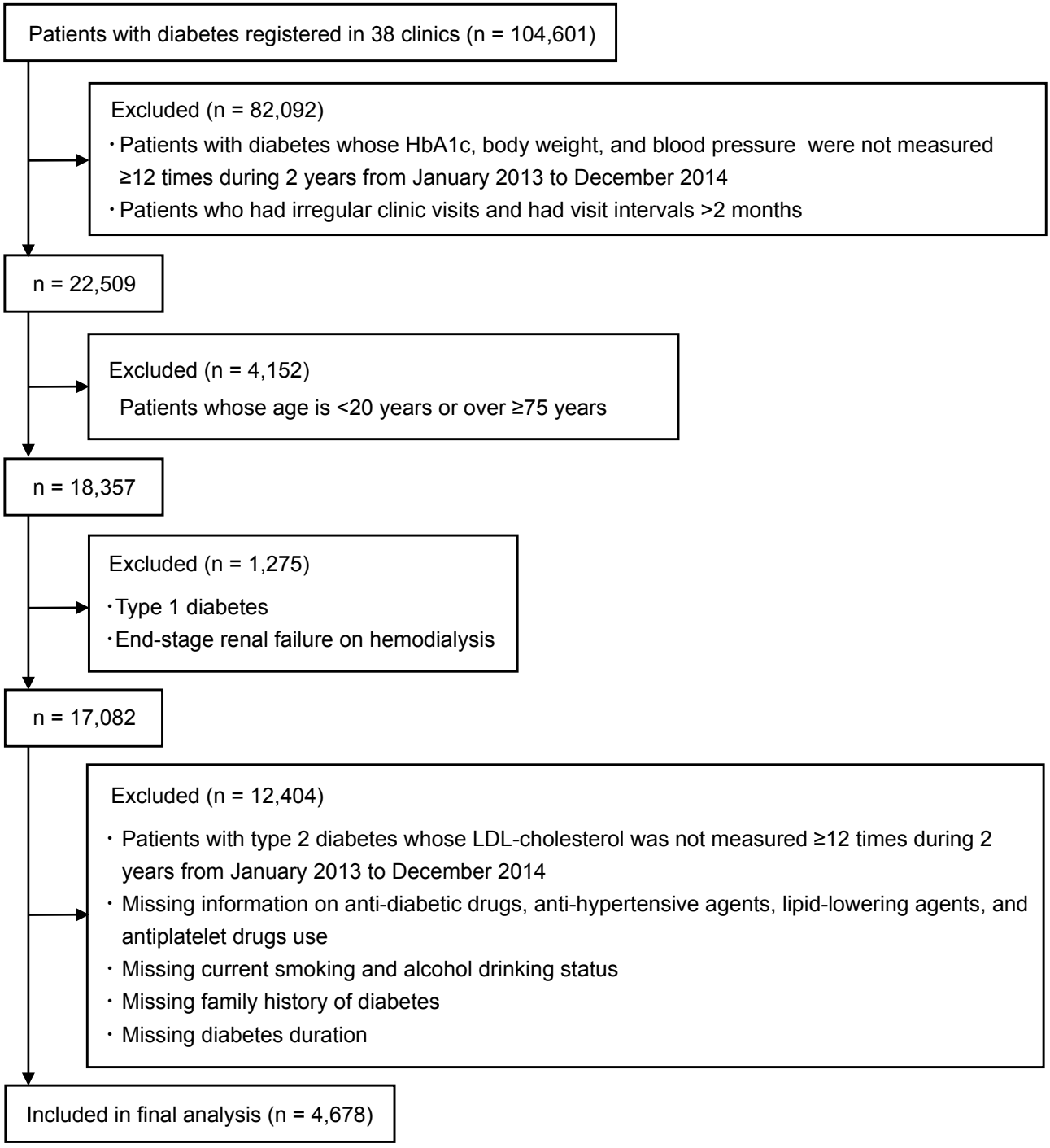
Figure title: none; **Figure legend**: **(A)** Proportion of patients with the indicated BP target groups (SBP <130 mmHg and DBP <80 mmHg or SBP ≥130 mmHg and DBP ≥80 mmHg)

within each HbA1c target group (HbA1c<7% or ≥7%) in summer and winter. **(B)** Proportion of patients with the indicated LDL-C target groups (LDL-C <100 mg/dL or ≥100 mg/dL) within each HbA1c target group in summer and winter. **(C)** Proportion of patients with the indicated BP target groups within each LDL-C target group in summer and winter. SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol

Figure 1


A
Achievement rate (%)
Month
Jan. Feb. Mar. Apr. May Jun. Jul. Aug. Sep. Oct. Nov. Dec. Jan. Feb. Mar. Apr. May Jun. Jul. Aug. Sep. Oct. Nov. Dec.
All ABC achievement rate (HbA1c <7%)
All ABC achievement rate (HbA1c <8%)
B
Achievement rate (%)
Month
Jan Feb Mar Apr May Jun Jly Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jly Aug Sep Oct Nov Dec
Achievement rate of HbA1c <8%
Achievement rate of HbA1c <7%
Achievement rate of SBP <130mmHg
Achievement rate of DBP <80 mmHg
Achievement rate of LDL-C <100 mg/dL
C
Achievement rate (%)
Summer
Winter
15.6%
9.6%
23.7%
15.0%
All ABC achievement (HbA1c <7%)
All ABC achievement (HbA1c <8%)
D
Achievement rate (%)
Summer
Winter
53.1%
48.9%
87.2%
86.4%
56.6%
40.9%
73.4%
64.1%
50.8%
47.2%
HbA1c <7%
HbA1c <8%
SBP <130 mmHg
DBP <80 mmHg
LDL-C <100 mg/dL

Supplemental Figure 1



Supplemental Figure 2