

Impact of Cardiovascular Screening Tests in Patients with Type 2 Diabetes Mellitus without Previous Histories of Cardiovascular Disease: 5-year Clinical Outcomes.

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Abstract

Background

We previously reported that, among the asymptomatic patients with type 2 diabetes mellitus (T2DM) without history of cardiovascular disease (CVD), up to 19% of the patients with myocardial ischemia were detected by cardiovascular screening tests (CVSTs). We concluded that the CVSTs in patients with T2DM may be one of the most effective strategies to find CVD in those patients. Thus, the aim of the study was to assess the long-term clinical outcomes of CVSTs in patients with T2DM without previous histories of CVD.

Methods

Six hundred fifty-seven out-patients with T2DM who received CVSTs at least more than one time or not at all from April in 2014 to March in 2019 were defined as the S group or NS group, respectively. The data in 2104 and 2018 were collected from the medical records, and compared between the S and NS groups.

Results

This study revealed that, in the out-patients with T2DM in our hospital over those 5 years; 1) the frequency of receiving CVSTs was significantly increasing, 2) in accordance with that increase, the frequency of the internal use for CVD of statins, anti-platelets, and renin-angiotensin system inhibitors, which are well-known as medications for preventing CVD, was significantly increasing, 3) however, there was only a small increase in the internal use of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptors, which are well-known to suppress cardiovascular events in patients with T2DM, 4) LDL-cholesterol and triglycerides significantly improved more in the S group than the NS group, 5) highly sensitive C-protein, which is one of the strongest predictors of CVD, was significantly suppressed by CVSTs, 6) the progression of renal dysfunction was significantly more suppressed in the S group than the NS group, 7) in an inverse proportion to the CVST increase, the frequency of acute coronary syndrome, cerebral infarctions, 4-point major adverse cardiovascular events, and admissions due to heart failure were significantly decreasing, and 8) finally, the frequency of all-cause mortality was significantly suppressed during those 5 years.

Conclusions

Thus, it may be important to continue CVSTs in out-patients with T2DM without a previous history of CVD for several years.

Background

The number of patients with type 2 diabetes mellitus (T2DM) continues to increase all over the world[1]. Moreover, cardiovascular (CV) disease (CVD), especially coronary artery disease (CAD), is well-known to be the leading cause of complications and death in the patients with T2DM[2–4]. In 2013, the Evidence-

based Practice Guideline for the Treatment for Diabetes in Japan 2013[5] recommended CV screening tests (CVST), and it is desirable that those examinations should be performed in patients with T2DM once a year[5]. Further, we previously reported that, among the asymptomatic patients with T2DM without a history of CVD, up to 19% of the patients with silent myocardial ischemia were detected by CVSTs, and a long disease duration of T2DM and a co-existence of a family history of CVD were independent risk factors in those patients[6]. Finally, we concluded that the CVST for patients with T2DM may be one of the most effective and useful strategies to find CVD in those patients[6]. Thus, the aim of the study was to assess the long-term clinical outcomes of CVSTs in patients with T2DM without previous histories of CVD.

Methods

Study Population and Laboratory Analysis: This study was approved by the institutional review committee and ethics review board of our hospital. Before we started the CVST in March of 2014, there were 657 out-patients (434 males and 223 females with a mean age of 66 ± 11 years and body mass index (BMI) of 24.9 ± 4.5 kg/m²) with T2DM and no previous history of CVD, including cerebral infarctions, carotid artery stenosis, CAD, hemodialysis, renal artery stenosis, arteriosclerosis obliterans, and aortic aneurysms, that visited the Munakata Suikokai General Hospital. Those out-patients with T2DM who received CVSTs at least more than one time or not at all from April in 2014 to March in 2019 were defined as the S group and NS group, respectively. In the S group, the CVSTs were performed after informed consent was obtained at our hospital. The data including the recorded histories, physical examinations, laboratory analyses, and baseline therapies, in 2014 and 2018 were collected from the medical records and compared between the S and NS groups. For the patients who moved to another hospital, an order for the data in 2018 from the family doctor's office was performed. Further, the number of patients who received the CVSTs, internal use of medicine including sodium-glucose cotransporter (SGLT)-2 inhibitors, glucagon-like peptide (GLP)-1 receptor agonists, statins, anti-platelets, and renin-angiotensin system (RAS) inhibitors, all-cause mortality, and cerebro- and cardio-vascular events including acute coronary syndrome (ACS), cerebral infarction, and admissions due to heart failure, were also evaluated from 2014 through 2018. The 4-point major adverse cardiovascular events (MACE)[7] including cardiovascular death, non-fatal myocardial and cerebral infarctions, and admissions due to ACS were also evaluated. In the S group, the highly sensitive C-reactive protein (hs-CRP) was measured during each CVST.

Statistical Analysis. The numerical results are expressed in the text as the mean \pm standard deviation. The statistical analyses were performed using a Fisher's exact test and Student t test or two-way Analysis of Variance (ANOVA) for the comparison of the 2 groups. The trend in the proportions and correlation between the frequency of receiving the CVST, internal use of SGLT-2 inhibitors, GLP-1 receptor agonists, statins, anti-platelets, and RAS inhibitors, all-cause mortality, cerebro- and cardio-vascular events, admissions due to heart failure, 4-point MACEs, and the years were determined by a Cochran-Armitage analysis. All analyses were performed with SAS version 9.2 software (SAS Institute, Cary, NC). A $p < 0.05$ was considered to indicate statistical significance.

Results

Patient Characteristics and Laboratory Analysis in 2014 (Table 1). There were 340 and 317 out-patients in the S and NS groups, respectively. There were no statistical differences among the males (63% vs. 69%; $p = 0.114$), BMI (24.8 ± 4.4 vs. 24.9 ± 4.6 kg/m²; $p = 0.856$), systolic (128 ± 11 vs. 128 ± 11 mmHg; $p = 0.716$) and diastolic (72 ± 10 vs. 73 ± 10 mmHg; $p = 0.130$) blood pressures, prevalence of the co-existence of hypertension (58% vs. 58%; $p = 0.854$), dyslipidemia (64% vs. 65%; $p = 0.752$), ex- or current smokers (47% vs. 52%; $p = 0.772$), a family history of CVD (26% vs. 25%; $p = 0.772$), HbA1c ($7.01 \pm 0.84\%$ vs. $7.02 \pm 0.83\%$; $p = 0.950$), LDL- (103 ± 25 vs. 102 ± 25 mg/dl; $p = 0.463$) and HDL- (58 ± 16 vs. 59 ± 17 mg/dl; $p = 0.700$) cholesterol, triglyceride (131 ± 66 vs. 131 ± 68 mg/dl; $p = 0.986$), and serum creatinine (0.79 ± 0.20 vs. 0.80 ± 0.19 mg/dl; $p = 0.726$) levels, and the prevalence of the internal use of baseline therapies for T2DM including SGLT-2 inhibitors (2% vs. 2%; $p = 0.897$) and GLP-1 receptor agonists (5% vs. 5%; $p = 0.834$) and for CVD including statins (54% vs. 56%; $p = 0.501$), anti-platelets (19% vs. 17%; $p = 0.544$), and RAS inhibitors (30% vs. 34%; $p = 0.281$). The age (68 ± 11 vs. 64 ± 11 ; $p < 0.001$) was significantly older in the S group than NS group.

Table 1
Patient Characteristics in 2014.

	All (n = 657)	S group (n = 340)	NS group (n = 317)	p value (S vs. NS)
Male	434 (66%)	215 (63%)	219 (69%)	0.114
Age (years)	66 ± 11	68 ± 11	64 ± 11	< 0.001
Body mass index (kg/m ²)	24.9 ± 4.5	24.8 ± 4.4	24.9 ± 4.6	0.856
Systolic blood pressure (mmHg)	128 ± 11	128 ± 11	128 ± 11	0.716
Diastolic blood pressure (mmHg)	72 ± 10	72 ± 10	73 ± 10	0.130
Co-existence				
Hypertension	381 (58%)	196 (58%)	185 (58%)	0.854
Dyslipidemia	425 (65%)	218 (64%)	207 (65%)	0.752
Ex- or current smoking	327 (50%)	161 (47%)	166 (52%)	0.772
Family history of CVD	165 (25%)	87 (26%)	78 (25%)	0.772
Laboratory Analysis				
HbA1c (%)	7.01 ± 0.83	7.01 ± 0.84	7.02 ± 0.83	0.950
LDL-cholesterol (mg/dl)	102 ± 25	103 ± 25	102 ± 25	0.463
HDL-cholesterol (mg/dl)	59 ± 17	58 ± 16	59 ± 17	0.700
Triglyceride (mg/dl)	131 ± 67	131 ± 66	131 ± 68	0.986
Serum creatinine (mg/dl)	0.79 ± 0.19	0.79 ± 0.20	0.80 ± 0.19	0.726
Baseline Therapies				
SGLT-2 inhibitor	13 (2%)	7 (2%)	6 (2%)	0.897
GLP-1 receptor agonist	34 (5%)	17 (5%)	17 (5%)	0.834
Statins	360 (55%)	182 (54%)	178 (56%)	0.501
Anti-platelets	116 (18%)	63 (19%)	53 (17%)	0.544
Renin-angiotensin system inhibitors	210 (32%)	102 (30%)	108 (34%)	0.281
S group = the group received cardiovascular screening tests, NS group = the group did not receive cardiovascular screening tests, CVD = cardiovascular disease, SGLT = sodium- glucose cotransporter, GLP = glucagon-like peptide,				

CVSTs and Myocardial Ischemia: Out of 340 out-patients who received CVSTs, there were 62 patients (18%) who had myocardial ischemia (data not shown). All 62 patients received treatment for their CAD with coronary revascularization and/or optimal medical therapies (OMTs) using statins, anti-platelets, RAS inhibitors, etc.

Cause of Death in Patients with T2DM from 2014 to 2018 (Table 2/):

Table 2
Cause of Death from 2014 to 2018.

Cause of Death	Number of patients	S group	NS group	p value (S vs. NS)
all	39	16	23	0.167
Pneumonia	12 (31%)	6	6	0.903
Cancer	8 (21%)	5	3	0.541
Cardiovascular events	8 (21%)	2	6	0.128
Cerebrovascular apoplexy	4 (10%)	1	3	0.284
Sepsis	4 (10%)	2	2	0.944
Others	3 (8%)	0	3	0.072

From 2014 to 2018, 39 patients died from pneumonia (31%), cancers (21%), CV events including acute coronary syndrome and heart failure (21%), cerebrovascular apoplexy (CVA) (10%), sepsis (10%), and others (8%). Out of the 39 patients that died, there were 16 and 23 patients in the S and NS groups, respectively. There were no significant differences regarding mortality due to pneumonia ($p = 0.903$), cancers ($p = 0.541$), CV events ($p = 0.128$), CVAs ($p = 0.284$), and sepsis ($p = 0.944$) between the 2 groups. Furthermore, the mortality due to cardio- and cerebro-vascular events including CV events and CVAs in the S group tended to be lower, but was not significant compared to that of the NS group (3 vs. 9 patients; $p = 0.061$).

Comparison Between the Data in 2014 and 2018 for the S and NS groups (Fig. 1A-E): Because there were 324 and 294 alive out-patients with T2DM in 2018 in the S and NS groups, respectively, a comparison was performed between the data from 2014 and 2018 for the S and NS group patients. The red and blue lines indicate the parameters in the S and NS groups, respectively. In both the S and NS groups, there was no statistical difference in the BMI (24.9 ± 4.4 vs. 24.8 ± 4.3 kg/m²; $p = 0.910$, and 24.9 ± 4.7 vs. 24.7 ± 4.2 kg/m²; $p = 0.575$, respectively) (Fig. 1A), systolic (128 ± 11 vs. 128 ± 11 mmHg; $p = 0.968$, and 128 ± 11 vs. 128 ± 10 mmHg; $p = 0.764$, respectively) and diastolic (72 ± 10 vs. 72 ± 10 mmHg; $p = 0.977$ and 73 ± 10 vs. 72 ± 10 mmHg; $p = 0.195$, respectively) blood pressures (Fig. 1B), and HbA1c (7.02 ± 0.85 vs. $6.91 \pm 0.73\%$; $p = 0.075$ and 7.05 ± 0.84 vs. $6.98 \pm 0.77\%$; $p = 0.314$, respectively) (Fig. 1C) and HDL-cholesterol (59 ± 16 vs. 60 ± 16 mg/dl; $p = 0.238$ and 59 ± 18 vs. 61 ± 18 mg/dl; $p = 0.300$, respectively) (Fig. 1D) levels, between 2014 and 2018 in the 2 groups. On the other hand, in the S group, the LDL-cholesterol

(103 ± 25 vs. 88 ± 25 mg/dl; $p < 0.001$) and triglyceride (131 ± 67 vs. 117 ± 67 mg/dl; $p = 0.010$) levels (Figure D) were significantly lower in 2018 than in 2014, but not in the NS group (102 ± 25 vs. 97 ± 30 mg/dl; $p = 0.059$ and 130 ± 69 vs. 125 ± 62 mg/dl; $p = 0.336$, respectively). In both the S and NS groups, the serum creatinine levels were significantly higher (0.78 ± 0.20 vs. 0.82 ± 0.20 mg/dl; $p = 0.010$, and 0.79 ± 0.19 vs. 0.85 ± 0.19 mg/dl; $p < 0.001$, respectively) in 2018 than in 2014 (Figure E). Furthermore, the LDL-cholesterol (88 ± 25 vs. 97 ± 30 mg/dl; $p = 0.001$) and triglyceride (117 ± 27 vs. 125 ± 62 mg/dl; $p = 0.003$) levels (Figure D) and serum creatinine levels (0.82 ± 0.20 vs. 0.85 ± 0.19 mg/dl; $p = 0.032$) (Figure E) were significantly lower in the S group than NS group in 2018. Because there were 305 patients who received repeated CVSTs, the hs-CRP levels during the 1st and last CVSTs were compared (Fig. 1F). The level during the last CVST was significantly lower than that during the 1st CVST (0.042 ± 0.013 vs. 0.024 ± 0.014 mg/dl; $p < 0.001$).

The Frequency of Receiving CVSTs and All-cause Mortality (Fig. 2AB): During those 5 years, the frequency of receiving a CVST (bold black line; $p < 0.001$) in the out-patients with T2DM had significantly increased (Fig. 2A). In accordance with that increase, the frequency of the internal use of statins (blue line; $p < 0.001$), anti-platelets (red line; $p < 0.001$), and RAS inhibitors (green line; $p < 0.001$) for CVD in those patients also significantly increased (Fig. 2A). The frequency of the internal use of SGLT-2 inhibitors (purple line; $p = 0.030$) for T2DM in those patients also significantly, but slightly increased (Fig. 2A), but not of the GLP-1 receptor agonists (brown line; $p = 0.104$). Further, in an inverse proportion to those increases, the frequency of ACS (green line; $p = 0.006$), cerebral infarctions (purple line; $p = 0.006$), 4-point MACEs (red line; $p < 0.001$), or admissions due to heart failure (blue line; $p = 0.011$), in those patients significantly decreased (Fig. 2B). Finally, the frequency of all-cause mortality (bold black line; $p = 0.006$) was significantly suppressed during those 5 years (Fig. 2B).

Discussion

This study revealed that, in the out-patients with T2DM in our hospital over those 5 years, 1) the age of the out-patients who did not receive a CVST was younger than that of those that did receive a CVST (Table 1), 2) the frequency of receiving a CVST significantly increased (bold black line in Fig. 2A), 3) in accordance with that increase, the frequency of the internal use of statins, anti-platelets, and RAS inhibitors for CVD significantly increased (blue, red, and green lines in Fig. 2A, respectively), 4) however, there was only a small increase in the internal use of SGLT-2 inhibitors and GLP-1 receptor agonists for T2DM (Fig. 2A), 5) dyslipidemia including the LDL-cholesterol and triglyceride significantly improved more in the out-patients who received a CVST than in those who did not (Fig. 1D), 6) the hs-CRP, which is one of the strongest predictors[8] of CVD was significantly suppressed by the CVSTs (Fig. 1F), 7) the progression of renal dysfunction was significantly more suppressed in the out-patients who received CVSTs than in those who did not (Fig. 1E), 8) in an inverse proportion to the CVST increase, the frequency of ACS, cerebral infarctions, 4-point MACEs, and admissions due to heart failure significantly decreased (green, purple, red, and blue lines in Fig. 2B, respectively), and 9) finally, the frequency of all-cause mortality (bold black line in Fig. 2B) was significantly suppressed during those 5 years. Thus, the

underlying potential mechanism(s) of the suppression of CV events in this study was considered, as described below.

Controls and Treatment of T2DM and the Risk Factors in Patients with T2DM: In this study, as described in our previous study[6] and Table 1, the values in 2014 for these common conditions including T2DM, hypertension, dyslipidemia, and obesity, may seem to be comparably acceptable for treatment. Statins [9, 10], anti-platelets[10], and RAS inhibitors[10, 11], are well-known as medications not only for hypertension, dyslipidemia, and CAD, but also for OMTs to prevent CVD[12] in patients with T2DM because of their clinical benefit. The increasing frequency of the internal use of those medications significantly increased during those 5 years (Fig. 2A). Moreover, out of 340 out-patients with T2DM who received CVSTs during those 5 years, myocardial ischemia was detected in 62 patients (18%), and those patients received treatment for CAD with coronary revascularization and/or OMTs using statins, anti-platelets, and/or RAS inhibitors. That may have contributed to suppressing the CV events (Fig. 2B). Further, RAS inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists may also contribute to suppressing the admission due to heart failure.

Suppression of the Progression of Renal dysfunction in Patients with T2DM: It has been reported that the progression of renal dysfunction in patients with T2DM is two times faster than that in those without T2DM[13], and the severity of the renal dysfunction is greater in those patients with T2DM, with an excessive risk of death from any cause and cardiovascular death that increases up to approximately 30-fold as high as the risk among patients without T2DM[14]. In this study, the progression of renal dysfunction in the S group was significantly more suppressed than that in the NS group (Fig. 1E). Because statins[15] and RAS inhibitors[16] are well-known to play a renal protective role in patients with T2DM, the increased use of statins and RAS inhibitors during those 5 years (Fig. 2A) may have played important roles in suppressing the progression of renal dysfunction leading to the suppression of CV events in patients with T2DM (Fig. 2B).

Anti-inflammatory Therapies in Patients with T2DM: The inflammatory markers, hs-CRP and LDL-cholesterol, are well-known to be one of the most important predictors of CV events[17]. A recent study reported that the suppression of the triglyceride level reduces the CV events in patients with T2DM[18]. In this study, the frequency of the internal use of statins[9, 17], anti-platelets[19], and RAS inhibitors[20, 21], which could play an important role in the suppression of the vascular inflammation contributing to the progression of atherosclerosis[22] had increased during those 5 years (Fig. 2A). Further, those 3 markers including the hs-CRP, LDL-cholesterol, and triglyceride levels, could be significantly suppressed in patients with T2DM who received CVSTs (Fig. 1DF). That may contribute to suppressing CV events (Fig. 2B).

New Drugs for T2DM to Suppress the CV events in Patients with T2DM: The SGLT-2 inhibitors[7, 23–25] and GLP-1 receptor agonists[24, 26, 27] are well-known to be new drugs for T2DM, which can suppress CV events in patients with T2DM. In this study, there was a small increase in the internal use of these drugs (Fig. 2A). Thus, although we could not completely deny that these drugs might have played an important role in the suppression of CV events during those 5 years (Fig. 2B), that effect probably was small.

Theme in the Future: The age of the out-patients who did not receive CVSTs was younger than that in those who did receive CVSTs (Table 1). We previously reported in a Japanese article that because young patients with T2DM in their prime are busy with work, they cannot make the time to undergo CVSTs[28]. Thus, creating systems that can support those young patients with T2DM to help them undergo CVSTs is needed in the future. It is recommended in the clinical guidelines of 2016 devised by the American Diabetes Association that lipid-lowering therapies using statins should be considered in all patients with T2DM of an age of > 40 years[10], if clinically indicated. Moreover, it is also recommended in the clinical guidelines of 2017 devised by the American Association of Clinical Endocrinologists and American Endocrine Society in the US that the cholesterol levels in patients with T2DM that were defined as an 'extremely high risk' group, which was the highest arteriosclerosis-related CV disease risk, should be kept at less than 55 mg/dl. In 2018, the frequency of the internal use of statins reached 75%, and the cholesterol levels in the out-patients with T2DM with and without CVSTs were 88 ± 25 and 97 ± 30 mg/dl, respectively. Thus, the induction of a more aggressive lipid-lowering therapy may be necessary to bring the frequency of statin use to nearly 100% and to reduce the LDL-cholesterol level to less than 55 mg/dl. Limitations of the Study: Our study was limited by a single-center trial and relatively small number of patients. Because of the short follow-up period, our study still could not demonstrate any long-term clinical benefits including an improvement in the prognosis or reduction in repeated revascularizations for patients with T2DM without a previous history of CVD. Whether our results can safely be extrapolated to multi-center trials with the inclusion of a larger number of patients and a longer follow-up period for those patients should be determined in further studies.

Conclusions

In performing CVSTs, the patients with T2DM can see the cardiologist every year and may be able to build a relationship with mutual trust contributing to deepening the patient's recognition of their CVD conditions. Thus, although it is still controversial that CVSTs are performed in asymptomatic patients with T2DM[29], it may be important to continue the CVSTs in those with T2DM without a previous history of CVD for several years. Supporting data from prospective large clinical trials, however, are needed before such recommendations can be made.

Abbreviations

ACS
acute coronary syndrome
BMI
body mass index
CAD
coronary artery disease
CVD
cardiovascular disease

CVST
cardiovascular screening test
GLP
glucagon-like peptide
hs-CRP
highly sensitive C-reactive protein
OMT
optimal medical therapy
RAS
renin-angiotensin system
SGLT
sodium-glucose cotransporter
T2DM
type 2 diabetes mellitus

Declarations

Ethics approval and consent to participate: This study was approved by the institutional review committee and ethics review board of our hospital. The cardiovascular screening tests were performed after informed consent was obtained at our hospital.

Consent for publication: All data analysis were performed after informed consent from the patients was obtained at our hospital.

Availability of data and materials: All data and materials are available.

Competing interests: None.

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Authors' contributions: Drs. Antoku Y, Takemoto M, Mito T, and Tanaka A, are cardiologists who were in charge of the patients and performed cardiovascular screening tests. Drs. Antoku Y, and Takemoto M wrote this paper. Drs. Mito T and Tsuchihashi T performed data analysis. Mr. Shiiyama R performed data collection. Drs. Otsuka-Morisaki H and Maeda are diabetologists who were in charge of the out-patients.

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Figures

Figure 1

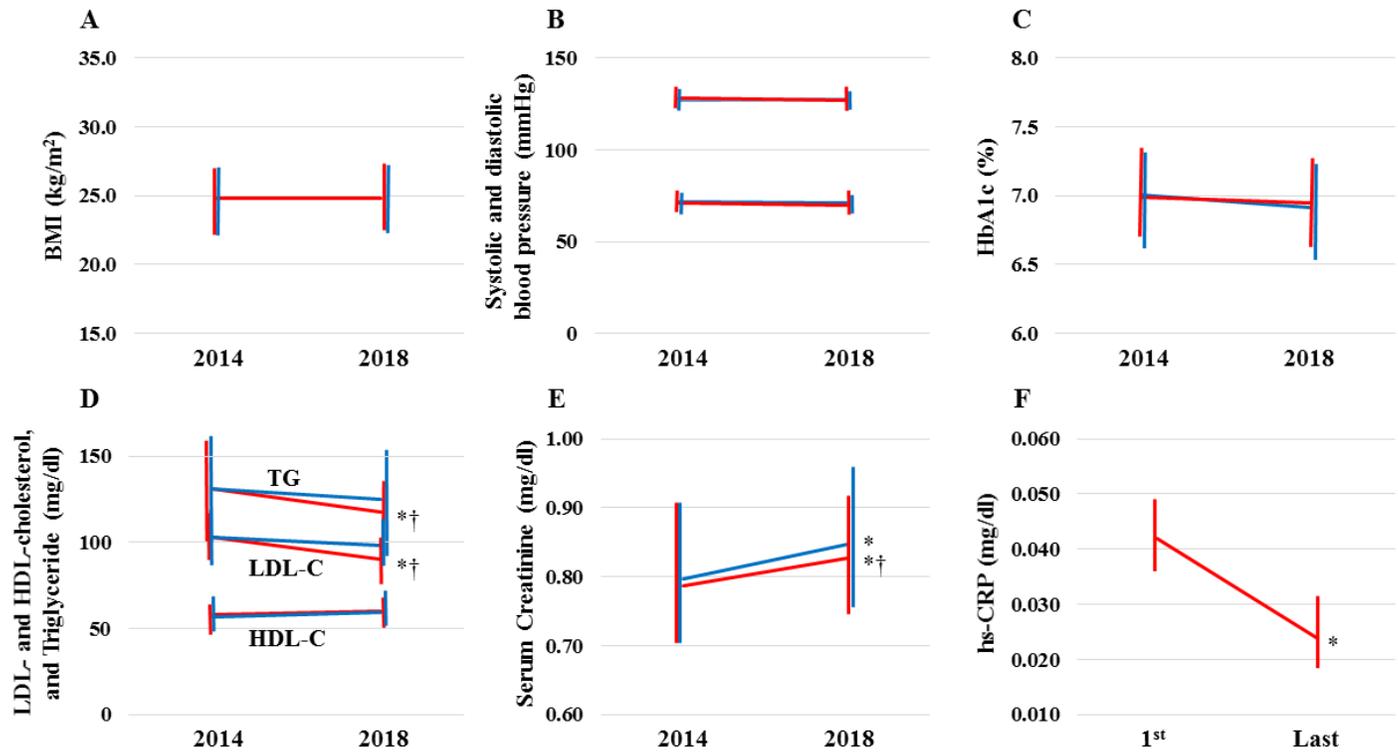


Figure 1

The values of body mass index (BMI) (A), systolic and diastolic blood pressures (B), HbA1c (C), LDL- and HDL-cholesterol and triglyceride (D), and serum creatinine (E), in the S (red lines) and NS (blue lines) groups in 2014 and 2018 in the out-patients with type 2 diabetes mellitus. The values of the highly sensitive C-reactive protein (hs-CRP) (F) during 1st and last cardiovascular screening test in the S group in the out-patients with type 2 diabetes mellitus. *p < 0.05 compared to the values in 2014. †p < 0.05 compared to the values in the NS group in 2018.

Figure 2

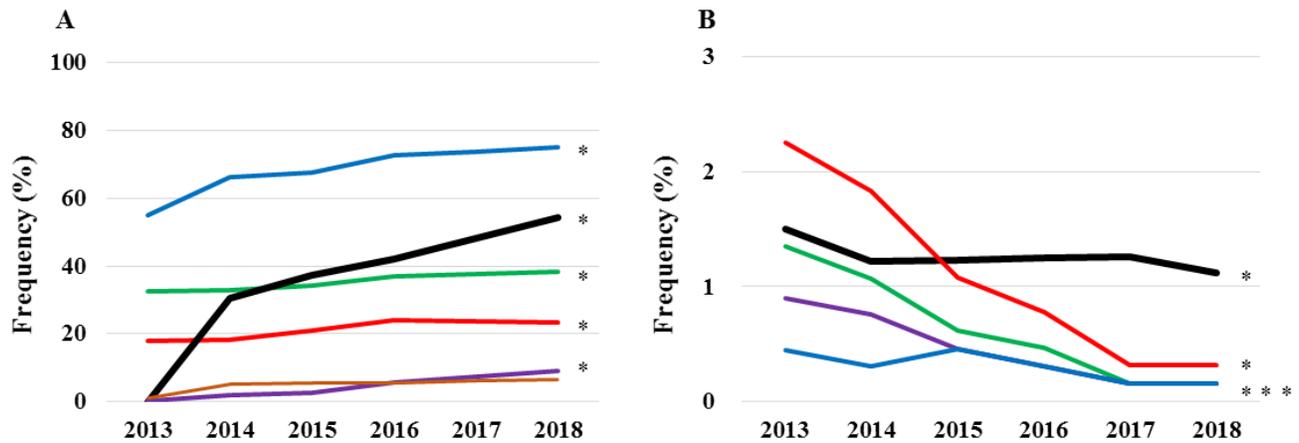


Figure 2

The frequency of receiving of cardiovascular screening tests (bold black line), internal use for cardiovascular disease of statins (blue line), anti-platelets (red line), and RAS inhibitors (green line), and the internal use for type 2 diabetes mellitus of sodium-glucose cotransporter (SGLT)-2 inhibitors (purple line) and glucagon-like peptide (GLP)-1 receptor agonists are demonstrated in Figure 2A. On the other hand, the frequency of acute coronary syndrome (green line), cerebral infarctions (purple line), 4-point major adverse cardiovascular events (red line), admissions due to heart failure (blue line), and all-cause mortality in the out-patients with type 2 diabetes mellitus are demonstrated in Figure 2B. *p < 0.05.