【 ORIGINAL ARTICLE 】

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

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Abstract:
Objective We previously reported that, among asymptomatic patients with type 2 diabetes mellitus (T2DM) without a history of cardiovascular disease (CVD), up to 19% of the patients with myocardial ischemia were detected by annual cardiovascular screening tests (ACVSTs). Thus, the present study assessed the long-term clinical outcomes of ACVSTs in those patients.
Methods Six hundred and fifty-seven outpatients with T2DM who received ACVSTs at least once or not at all from April 2014 to March 2018 were defined as the S and NS groups, respectively. The data were compared between these two groups.
Results This study revealed that, among outpatients with T2DM in our hospital over those four years, with the increasing frequency of receiving ACVSTs, 1) the frequency of the internal use of statins, anti-platelets, and renin-angiotensin system inhibitors, which are well-known as medications for preventing CVD, significantly increased; 2) low-density lipoprotein-cholesterol and triglyceride levels significantly improved; 3) levels of highly sensitive C-protein, a strong predictors of CVD, were significantly suppressed; 4) the progression of renal dysfunction was significantly suppressed; 5) the cumulative of four-point major adverse cardiovascular events and admissions due to heart failure significantly decreased; and 6) the cumulative of all-cause mortality was significantly suppressed.
Conclusions Given the above, it may be important to continue ACVSTs in outpatients with T2DM without a history of CVD for several years.

Key words: all-cause mortality, heart failure, coronary artery disease, cardiovascular events, cardiovascular screening test, diabetes mellitus

Introduction

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

Recently, the Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 recommended screening tests be performed for CVD, and preferably once a year in patients with T2DM (5, 6). We previously reported that, among asymptomatic patients with T2DM without a history of CVD, up to 19% were found to have silent myocardial ischemia by annual cardiovascular screening tests (ACVSTs), and a long disease duration of T2DM and coexisting family history of CVD were independent risk factors in those patients (6). However, the long-term clinical out-
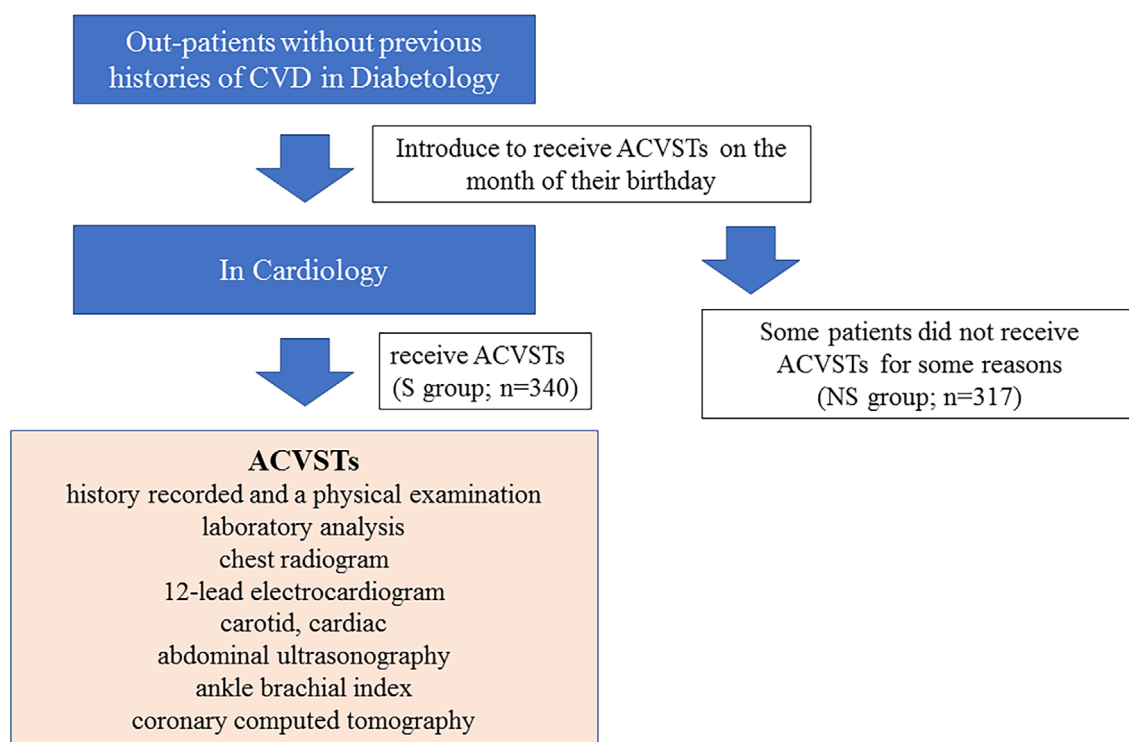
Figure 1. The detailed flow-chart of the annual cardiovascular screening test (ACVST) in our hospital. CVD: cardiovascular disease

comes of ACVSTs for patients with T2DM remain unclear and controversial (7).

The present study therefore assessed the four-year clinical outcomes of ACVSTs in patients with T2DM without histories of CVD.

Materials and Methods

Study population and laboratory analyses

This study was approved by the institutional review committee and ethics review board of our hospital, the Ethics Review Board of Munakata Suikokai General Hospital. Before we started performing ACVSTs in March of 2014, there were 657 outpatients in the diabetology department of our hospital, not including the outpatients in the cardiology department, who had T2DM and no history of CVD, including cerebral infarctions, carotid artery stenosis, CAD, hemodialysis, renal artery stenosis, arteriosclerosis obliterans, and aortic aneurysms [434 men and 223 women with a mean age of 66±11 years old and body mass index (BMI) of 24.9 ±4.5 kg/m^2; Fig. 1)]. The diabetologists recommended ACVSTs be performed in diabetology outpatients during their birthday month each year.

All patients had their history recorded, and underwent a physical examination, laboratory analysis; chest radiogram; 12-lead electrocardiogram; carotid, cardiac, and abdominal ultrasonography; ankle brachial index evaluation; and coronary computed tomography (8), as previously reported (6) (Fig. 1).

The outpatients with T2DM who received ACVSTs at least once or not at all from April 2014 to March 2018 were defined as the S and NS groups, respectively. In the S group, ACVSTs were performed after informed consent was obtained at our hospital. The data in 2014 and 2018 were collected from the medical records and compared between the S and NS groups. For patients who moved to another hospital, we requested the 2018 data from the family doctor's office. Furthermore, the number of patients who received ACVSTs; internal use of medicine, including metformin, 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 four-point major adverse cardiovascular events (MACEs) (9) including cardiovascular death, non-fetal myocardial, and cerebral infarctions, and admissions due to ACS were also evaluated. In the S group, the highly sensitive C-reactive protein (hs-CRP) level was measured during each ACVST.

Statistical analyses

The numerical results are expressed in the text as the mean ± standard deviation. The statistical analyses were performed using a Fisher's exact test and Student's *t*-test or a two-way analysis of variance (ANOVA) for the comparison of the two groups. The trend in the proportions and correla-

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				
Metformin	273 (42%)	144 (42%)	129 (41%)	0.667
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

tion between the frequency of receiving the ACVST, 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, four-point MACEs, and years were determined by a Cochran-Armitage analysis. All analyses were performed with the SAS version 9.2 software program (SAS Institute, Cary, USA). p<0.05 was considered to indicate statistical significance.

Results

Patient characteristics and laboratory analyses in 2014 (Table 1)

There were 340 and 317 outpatients in the S and NS groups, respectively. Of the 340 patients in the S group, 305 received ACVSTs more than twice. The average reception number of ACVSTs was 3.98 times per patient. There were no significant differences in the number of men, systolic and diastolic blood pressures, prevalence of the co-existence of hypertension, dyslipidemia, ex- or current smokers, a family history of CVD, HbA1c, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, triglyceride, and serum creatinine levels, or the prevalence of the internal use of baseline therapies for T2DM (e.g. metformin, SGLT-2 in-

hibitors, and GLP-1 receptor agonists) or CVD (e.g., statins, anti-platelets, and RAS inhibitors). The age (68±11 vs. 64± 11 years old; p<0.001) was significantly older in the S group than in the NS group.

ACVSTs, arteriosclerosis, and myocardial ischemia

Of the 340 outpatients who received ACVSTs, 62 (18%) 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. All patients with coronary arteriosclerosis without myocardial ischemia similarly received OMTs.

Cause of death in patients with T2DM from 2014 to 2018 (Table 2)

From 2014 to 2018, 39 patients died of pneumonia (31%), cancer (21%), CV events (e.g. acute coronary syndrome and heart failure; 21%), cerebrovascular apoplexy (CVA; 10%), sepsis (10%), and others (8%). Of the 39 patients who died, there were 16 and 23 in the S and NS groups, respectively. There were no significant differences in the mortality due to pneumonia, cancer, CV events, CVA, or sepsis between the two groups. Furthermore, the mortality due to cardio- and cerebro-vascular events, including CV events and CVA, in the S group tended to be lower than that

Table 2.   Cause of Death from 2014 to 2018.

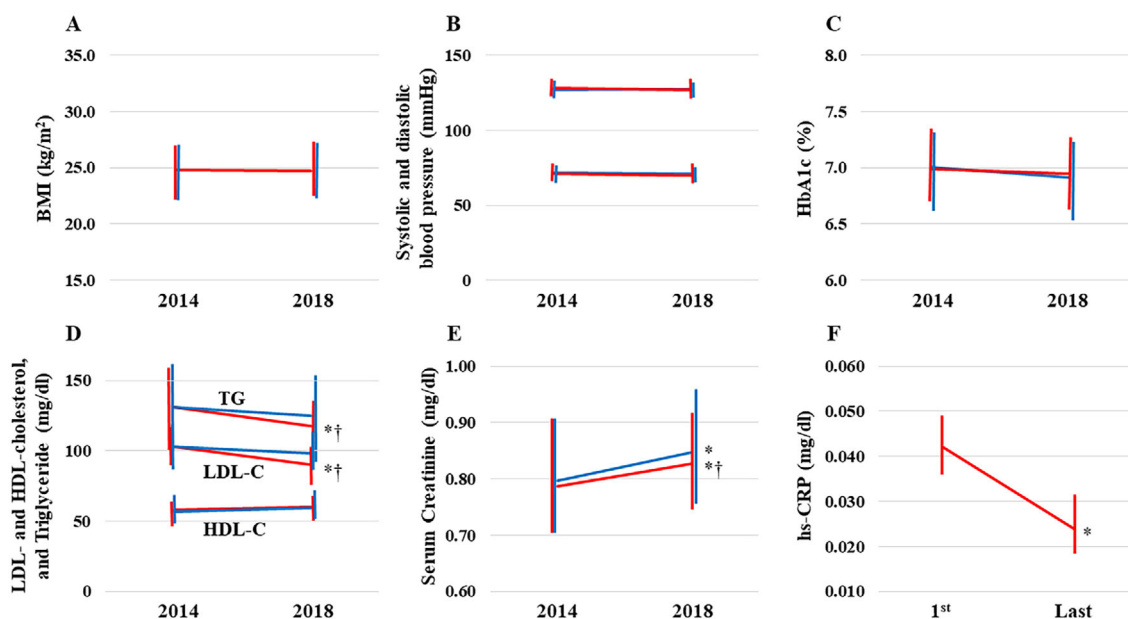| Cause of Death	Number of patients	S group	NS group	p value (S vs. NS)
all	39	16	23	0.167
Pneumonia	12 (31%)	6	6	0.903
Cancer	8 (21%)	5	3	0.541
Cardiovascular events	8 (21%)	2	6	0.128
Cerebrovascular apoplexy	4 (10%)	1	3	0.284
Sepsis	4 (10%)	2	2	0.944
Others	3 (8%)	0	3	0.072

Figure 2.   The values of the 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 among outpatients with type 2 diabetes mellitus. The levels of highly sensitive C-reactive protein (hs-CRP) (F) during the first and last cardiovascular screening test in the S group of outpatients with type 2 diabetes mellitus (n=305). *p<0.05 compared to the values in 2014. †p<0.05 compared to the values in the NS group in 2018.

in the NS group, although not to a significant degree (3 vs. 9 patients; p=0.061).

The comparison of data from 2014 and 2018 in the S and NS groups (Fig. 2)

Because there were 324 and 294 alive outpatients with T2 DM in 2018 in the S and NS groups, respectively, a comparison was performed between the data from 2014 and 2018 for these groups. The red and blue lines indicate the parameters in the S and NS groups, respectively. Between 2014 and 2018, there were no significant differences for the S vs. NS groups 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. 2A), systolic (128±11 vs. 128±11 mmHg; p=0.968, and 128±11 vs. 128±10 mmHg; p=0.764, respectively) or diastolic (72±10 vs. 72±10 mmHg; p=0.977 and 73±10 vs. 72±10 mmHg; p=0.195, respectively) blood pressures (Fig. 2B), and HbA1c (7.02±0.85% vs. 6.9±0.73%; p=

0.075 and 7.05±0.84% vs. 6.98±0.77%; p=0.314, respectively) (Fig. 2C) 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. 2D) levels. In contrast, 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 (Fig. 2D) 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 the S vs. 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 (Fig. 2E). 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 (Fig. 2D) and serum creatinine levels (0.82±0.20 vs. 0.85±0.19 mg/dL; p=0.032) (Fig. 2E) were significantly lower in the S vs. NS group in 2018.
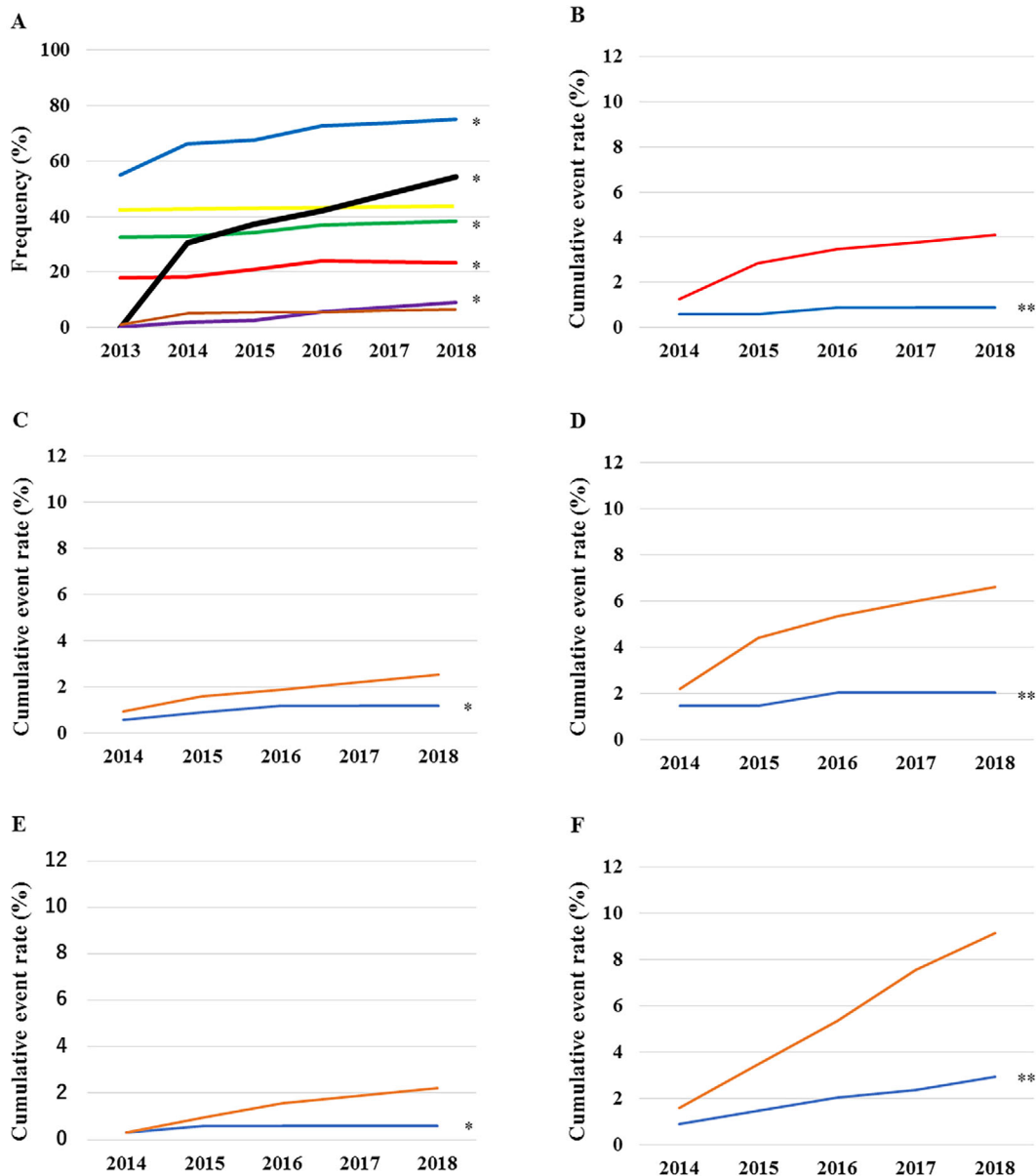
Figure 3. The frequencies of receiving of annual cardiovascular screening tests (bold black line); internal use of statins (blue line), anti-platelets (red line), and RAS inhibitors (green line) for cardio-vascular disease; and internal use of sodium-glucose cotransporter (SGLT)-2 inhibitors (purple line) and glucagon-like peptide (GLP)-1 receptor agonists for type 2 diabetes mellitus are demonstrated in A. The cumulative event rates of acute coronary syndrome (B), cerebral infarctions (C), four-point major adverse cardiovascular events (D), admission due to heart failure (E), and all-cause mortality (F) in the S group (blue lines) and NS group (red lines) among outpatients with type 2 diabetes mellitus are demonstrated in B-F. **$p<0.01$ and *$p<0.05$ compared to the S group.

As there were 305 patients who received repeated ACVSTs, the hs-CRP levels during the first and last ACVSTs were compared (Fig. 2F). The level during the last ACVST was significantly lower than that during the first ACVST (0.042 ± 0.013 vs. 0.024 ± 0.014 mg/dL; $p<0.001$). Unfortunately, the hs-CRP level was not measured in patients who did not receive ACVSTs.

The frequency of receiving CVSTs and all-cause mortality (Fig. 3)

During those 4 years, the frequency of receiving an

ACVST (bold black line; $p<0.001$) in the outpatients with T 2DM significantly increased (Fig. 3A). 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. 3A). The frequency of the internal use of SGLT-2 inhibitors (purple line; $p=0.030$) for T2DM in those patients also significantly but only slightly increased (Fig. 3A), and no such increase was seen in the frequency of the internal use of metformin (yellow line; $p=0.667$) or GLP-1 receptor agonists (brown line;

p=0.104). Furthermore, inversely to those increases, the cumulative event rate of ACS (Fig. 3B); p=0.006), cerebral infarctions (Fig. 3C; p=0.016), 4-point MACEs (Fig. 3D); p<0.001), or admissions due to heart failure (Fig. 3E; p=0.011) in those patients was significantly lower in the S group than in the NS group. Finally, the cumulative event rate of all-cause mortality (F; p<0.001) was significantly lower in the S group than in the NS group during those 4 years.

Discussion

This study revealed that, among outpatients with T2DM in our hospital over a 4-year period, the cumulative event rate of ACS (Fig. 3B; p=0.006), cerebral infarctions (Fig. 3C; p=0.016), 4-point MACEs (Fig. 3D; p<0.001), or admissions due to heart failure (Fig. 3E; p=0.011) was significantly lower in the S group than in the NS group. ACVSTs were able to significantly suppress the all-cause mortality (F; p<0.001) over those 4 years.

Control 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 values for treatement. Statins (10, 11), anti-platelets (11), and RAS inhibitors (11, 12) are well-known medications not only for hypertension, dyslipidemia, and CAD but also for OMTs to prevent CVD (13) in patients with T2DM because of their clinical efficacy. However, the CV benefits of anti-platelets (11) in T2DM patients without histories of CVD remain controversial. The frequency of the internal use of those medications significantly increased during the four-year period evaluated (Fig. 3A). Furthermore, of the 340 outpatients with T2DM who received ACVSTs during those 4 years, myocardial ischemia was detected in 62 (18%), and all of those patients received treatment for CAD with coronary revascularization and/or OMTs using statins, anti-platelets, and/or RAS inhibitors. This may have helped suppress the CV events (Fig. 3B-F). In addition, RAS inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists may also help suppress admission due to heart failure.

Suppression of the progression of renal dysfunction in patients with T2DM

The progression of renal dysfunction in patients with T2DM is reportedly two times faster than in those without T2DM (14), 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 the risk among patients without T2DM (15). In the present study, the progression of renal dysfunction in the S group was significantly lower than that in the NS group (Fig. 2E). Because statins (16) and RAS inhibitors (17) are known to play a renal protective role in pa-

tients with T2DM, the increased use of statins and RAS inhibitors during those four years (Fig. 3A) may have played important roles in suppressing the progression of renal dysfunction, thereby leading to the suppression of CV events in patients with T2DM (Fig. 3B-F).

Anti-inflammatory therapies in patients with T2DM

The inflammatory markers hs-CRP and LDL-cholesterol are known to be important predictors of CV events (18). A recent study reported that the suppression of the triglyceride level reduced the CV events in patients with T2DM (19). In the present study, the frequency of the internal use of statins (10, 18), anti-platelets (20), and RAS inhibitors (21, 22), which can play an important role in suppressing vascular inflammation, thereby contributing to the progression of atherosclerosis (23), increased over the four-year study period (Fig. 3A). Furthermore, the three markers of hs-CRP, LDL-cholesterol, and triglyceride levels were significantly suppressed in patients with T2DM who received ACVSTs (Fig. 2D, F). This may have helped suppress CV events in these patients (Fig. 3B-F).

New T2DM drugs that also suppress CV events in patients with T2DM

SGLT-2 inhibitors (24-26) and GLP-1 receptor agonists (25, 27, 28) are new drugs for T2DM capable of suppressing CV events in patients with T2DM. Metformin (29) is a classical drug for T2DM that can reduce the risk of cardiovascular disease among patients with T2DM. In the present study, there was a small increase in the internal use of these drugs (Fig. 3A). Therefore, although we were unable to completely deny that these drugs played an important role in the suppression of CV events during those four years (Fig. 3B-F), that effect was probably small.

Future themes

The outpatients who did not receive ACVSTs were younger than those who did receive ACVSTs (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 ACVSTs (30). Thus, systems to support young patients with T2DM and help them undergo ACVSTs are needed in the future.

It is recommended in the 2016 clinical guidelines devised by the American Diabetes Association that lipid-lowering therapies using statins be considered in all patients with T2DM >40 years old (11), if clinically indicated. Furthermore, it is also recommended in the 2017 clinical guidelines devised by the American Association of Clinical Endocrinologists and American Endocrine Society that the cholesterol levels in patients with T2DM, who are considered an 'extremely high risk' group with the highest arteriosclerosis-related CV disease risk, be kept at <55 mg/dL. In 2018, the frequency of the internal use of statins reached 75%, and the cholesterol levels in the outpatients with T2DM with and without ACVSTs were 88±25 and 97±30 mg/dL, respec-

tively. Thus, the induction of a more aggressive lipid-lowering therapy may be necessary to bring the frequency of statin use to nearly 100% and reduce the LDL-cholesterol level to <55 mg/dL.

Mechanism underlying the suppression of cardiovascular events by ACVSTs

As described above, ACVSTs were able to detect myocardial ischemia and increase the usage of OMTs for arteriosclerosis and T2DM (Fig. 3A) as well as suppress the development of renal dysfunction (Fig. 2E) in patients with T2 DM, thereby contributing to the suppression of the cumulative event rates of ACS, cerebral infarctions, 4-point MACEs, or admission due to heart failure (Fig. 3B-E). Finally, the all-cause mortality was significantly suppressed by CVSTs performed once a year during those four years (Fig. 3F).

Limitations of the study

Our study was limited by its single-center setting, relatively small number of patients, and retrospective database analysis. Because of the short follow-up period, our study still failed to demonstrate any long-term clinical benefits, including an improvement in the prognosis or reduction in repeated revascularizations for patients with T2DM without a history of CVD. Whether or not 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.

Conclusion

Through the performance of ACVSTs, patients with T2 DM have the opportunity to visit a cardiologist every year and potentially build a relationship with mutual trust, thus helping deepen patients' understanding of their CVD conditions. Therefore, while performing ACVSTs in asymptomatic patients with T2DM (31) remains controversial (5, 7), it may be important to continue performing CVSTs once a year in patients with T2DM without a history of CVD for several years, which may help reduce the frequency of all-cause mortality. However, supporting data from prospective large clinical trials are needed before such recommendations can be made.

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