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Current status of low-density lipoprotein cholesterol for primary prevention of coronary artery disease in late-stage elderly persons with type 2 diabetes mellitus: A retrospective, single-center study

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ABSTRACT

Aims/Introduction: The importance of low-density lipoprotein cholesterol (LDL-C) in the primary prevention of cardiovascular disease has recently been reported in the population aged ≥75 years with hypercholesterolemia. Therefore, the current status of LDL-C management for primary prevention of coronary artery disease in patients aged ≥75 years with type 2 diabetes mellitus was investigated.

Materials and Methods: A total of 124 patients aged ≥75 years who had type 2 diabetes mellitus, but no coronary artery disease, were investigated. The patients' background characteristics, LDL-C, glycemic status, ankle-brachial index and cardio-ankle vascular index were compared between patients taking and not taking LDL-C-lowering agents, such as hydroxymethylglutaryl-CoA reductase inhibitors (statins) and ezetimibe. The details of the antihyperlipidemic and antidiabetic agents used in the present study were also examined.

Results: LDL-C was significantly lower in patients taking LDL-C-lowering agents (LDLCLT [+]) than in patients not taking them (LDLCLT[–]), although LDL-C was maintained <120 mg/dL in both groups (93.0 mg/dL vs 102.1 mg/dL). Approximately half of the cases in the LDLCLT(+) group received moderate-intensity statins, with pitavastatin being the most prescribed statin. Glycated hemoglobin was significantly lower in the LDLCLT(+) group than in the LDLCLT(–) group (6.9% vs 7.3%). Sodium-glucose transporter 2 inhibitors were more frequently used in the LDLCLT(+) group than in the LDLCLT(–) group. The ankle-brachial index/cardio-ankle vascular index did not differ between the groups.

Conclusion: Low-density lipoprotein cholesterol was properly managed for primary prevention of coronary artery disease in patients aged ≥75 years with type 2 diabetes mellitus regardless of the presence or absence of LDL-C-lowering agents.

INTRODUCTION

The effects of low-density lipoprotein cholesterol (LDL-C) lowering by hydroxymethylglutaryl-CoA reductase inhibitors (statins) on the primary and secondary prevention of cardiovascular disease (CVD) have been established in individuals aged <75 years[1–4]. The secondary prevention of CVD with statins has also been reported in late-stage elderly persons aged ≥75 years[1,5]. However, little is known about the efficacy of plasma lipid-lowering therapies for the primary prevention of CVD in individuals aged ≥75 years; therefore, the treatment of hypercholesterolemia has been left to the discretion of the attending physician.

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Recently, the Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75) showed that LDL-C-lowering therapy with ezetimibe prevented cardiovascular events in patients aged ≥75 years with elevated LDL-C levels[6], implying the importance of LDL-C management for the primary prevention of CVD, even in individuals aged ≥75 years. The patients enrolled in EWTOPIA 75, of whom 25.4% had type 2 diabetes mellitus, were at high risk of CVD. The frequency of CVD is higher in patients with type 2 diabetes mellitus than in those without type 2 diabetes mellitus, and the risk of CVD increases incrementally with age in type 2 diabetes mellitus[7]. Whereas the importance of LDL-C-lowering for primary prevention of CVD was shown in the aforementioned study[6], the current status of LDL-C management for patients aged ≥75 years with type 2 diabetes mellitus in clinical practice is still unclear. Therefore, the current status of LDL-C in the primary prevention of coronary artery disease (CAD) was retrospectively investigated in patients aged ≥75 years with type 2 diabetes mellitus visiting an outpatient department specializing in diabetes.

MATERIALS AND METHODS

Patients aged ≥75 years with type 2 diabetes mellitus who had been in our outpatient department specializing in diabetes at Tsukuba University Hospital Mito Clinical Education and Training Center, Mito Kyodo General Hospital, Mito Japan, for >1 year and visited the department within the previous 4 months, from August to November 2019, were extracted using the electronic medical record database. As the patients regularly visited our department within 4 months, the extraction period was sufficient to cover all of the outpatients in our department. The patients were excluded if they had a history of ischemic heart disease, brain stroke within half a year, liver dysfunction with aspartate aminotransferase (AST) ≥100 U/L and/or alanine aminotransferase (ALT) ≥100 U/L, liver cirrhosis, severe renal dysfunction with creatinine ≥3.0 mg/dL or familial hypercholesterolemia.

Type 2 diabetes mellitus and dyslipidemia were treated in accordance with the guidelines from the Japan Diabetes Society and the Japan Geriatric Society or the Japan Atherosclerosis Society, respectively[8–10]. The glycemic target was determined according to three categories classified based on activities of daily living disabilities, cognitive function or multimorbidity, along with the use of antidiabetic agents that confer a risk of severe hypoglycemia[8]. As lipid-lowering therapy for primary prevention of CAD has not yet been established in individuals aged ≥75 years, the physician in charge applied the guideline for patients aged <75 years to the patients in the present study. As all patients had type 2 diabetes mellitus, LDL-C was controlled with a goal <120 mg/dL[9,10].

Age, sex, body mass index, systolic blood pressure and diastolic blood pressure, glycated hemoglobin (HbA1c), plasma lipids (total cholesterol [TC], LDL-C, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, triglycerides), AST, ALT, γ-glutamyl transpeptidase, creatinine phosphokinase, serum creatinine (Cr), estimated glomerular filtration rate, urinary albumin and comorbidities (chronic kidney disease, non-cardioembolic stroke, hypertension, cognitive dysfunction and malignant tumor under treatment) were evaluated. LDL-C was calculated by the Friedewald equation. Furthermore, the controlling nutritional status (CONUT) score was calculated based on the TC, plasma albumin and lymphocyte count[11]. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 or the presence of albuminuria, defined as an albumin-to-Cr ratio >30 mg/g or a protein-to-Cr ratio >0.15 g/gCr in two of three spot urine specimens. Cognitive dysfunction was diagnosed based on the medical records or scores on the dementia assessment sheet for community-based integrated care system 8-items[12]. The ankle-brachial index (ABI) and the cardio-ankle vascular index (CAVI) were measured in some, but not all, patients to screen for atherosclerosis.

Plasma lipids including LDL-C were compared between the patients requiring LDL-C-lowering agents (statins and ezetimibe; LDLCLT[+] group) or not (LDLCLT[−] group). The LDLCLT(−) group included patients receiving diet therapy alone, eicosapentaenoic acid (EPA) or fibrates. The patients taking both statins and EPA or both ezetimibe and EPA were included in the LDLCLT(+) group. The types and doses of statins were also investigated, and LDL-C levels were compared according to the intensity of the statins classified based on the guideline from The American College of Cardiology and American Heart Association[13]. Because 5 mg of simvastatin, 5 mg of pravastatin, 5 mg of atorvastatin and 2.5 mg of rosuvastatin, which were used regularly in Japan, were not mentioned in the guideline[13], these statins were defined as low-intensity. Therefore, whereas low-intensity statins included 5 mg of simvastatin; 5, 10 and 20 mg of pravastatin; 5 mg of atorvastatin; and 2.5 mg of rosuvastatin, moderate-intensity statins were 10 mg of atorvastatin, 5 mg of rosuvastatin, and 1 and 2 mg of pitavastatin in the present study. Achievement of LDL-C <120 mg/dL, the goal for primary prevention of CAD recommended by the Japan Atherosclerosis Society[9,10], was compared between the LDLCLT(−) and LDLCLT(+) groups, and between patients taking moderate-intensity statins and patients taking low-intensity statins. Glycemic control and the use of antidiabetic agents were also compared between the LDLCLT(−) and LDLCLT(+) groups. The Ethics Committees of Mito Medical Center, Tsukuba University Hospital and Mito Kyodo General Hospital approved the study (approval number 19–26), and it was carried out in compliance with the tenets of the Declaration of Helsinki.

Continuous variables with normal distributions are presented as means (standard deviation), and non-normally distributed variables are expressed as medians (interquartile range). The *t*-test was used for continuous variables with a normal distribution, and the Mann–Whitney *U*-test was used for continuous variables with a non-normal distribution to compare the differences between two groups. The χ^2-test or Fisher's exact test

were used for categorical variables. Analysis of variance and the χ^2-test were used for continuous variables and for categorical variables, respectively, in four-group comparisons. Spearman's rank correlation coefficient was used to evaluate linear correlations. Significance was defined as $P < 0.05$. Statistical analyses were carried out using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 155 patients aged ≥75 years with type 2 diabetes mellitus were identified. After applying the exclusion criteria, 124 patients were enrolled in the study (57 men, 67 women, age 80.5 years [interquartile range 78.0–84.0 years]; Table 1). The groups did not differ significantly in sex, age, durations of type 2 diabetes mellitus or dyslipidemia, body mass index, estimated glomerular filtration rate, chronic kidney disease, non-cardioembolic disease, hypertension, cognitive impairment, or history of smoking. Systolic blood pressure was higher in the LDLCLT(−) group than in the LDLCLT(+) group, but it did not differ significantly between them. The enzymes; that is, AST, ALT, γ-glutamyl transpeptidase, creatinine phosphokinase and Cr, remained normal, irrespective of whether the patients received LDL-C-lowering therapy, and did not differ between the LDLCLT(−) and LDLCLT(+) groups. The urinary albumin level was quantified. The cases in whom proteinuria instead of albuminuria was measured at the analysis were excluded. Urinary albumin was significantly higher in the LDLCLT(−) group than in the LDLCLT(+) group.

Triglycerides, HDL-C and non-HDL-C levels were similar between the LDLCLT(+) and LDLCLT(−) groups, and they were well controlled in both groups. LDL-C was significantly lower in the LDLCLT(+) group than in the LDLCLT(−) group (93.0 mg/dL vs 102.1 mg/dL, $P < 0.05$), but both groups had LDL-C <120 mg/dL, the recommended value for primary prevention of CAD by the Japan Atherosclerosis Society. HbA1c was significantly lower in the LDLCLT(+) group than in the LDLCLT(−) group (6.9% vs 7.3%, $P = 0.04$; Table 1).

As shown in Table 2, almost half of the patients ($n = 65$) were not taking any antihyperlipidemic agents, in whom only diet intervention was given. The numbers of patients taking statins, ezetimibe, fibrates and EPA were 52, 3, 3 and 3, respectively. Concomitant use of lipid-lowering agents was low; whereas two patients taking 5 mg of simvastatin or 10 mg of ezetimibe were also taking 1,800 mg of EPA, none of the patients took fibrates with statins or ezetimibe (Table 2). Moderate-intensity statins accounted for half of the patients taking statins, with pitavastatin being the most prescribed.

The LDL-C level and achievement rate of LDL-C <120 mg/dL based on the types of LDL-C lower agents are shown in Table 3. In the LDLCLT(+) group, 55 of the patients were taking LDL-C-lowering agents (statins or ezetimibe) alone or in combination with EPA, and in the LDLCLT(−) group, 65 were on diet therapy alone, one on EPA and three on fibrates (Table 2). A patient taking both simvastatin and EPA, and a patient taking both ezetimibe and EPA were included in the low-intensity statin and ezetimibe groups, respectively (Table 3). The mean LDL-C was <120 mg/dL regardless of treatment. LDL-C was well controlled at 102.1 ± 24.1 mg/dL, despite the absence of LDL-C-lowering agents in the LDLCLT(−) group. As expected, the patients taking moderate-intensity statins had LDL-C of 89.5 ± 22.9 mg/dL, with the lowest value among the four groups, albeit not significantly. The rate of achievement of LDL-C <120 mg/dL was 78.3, 84.6, 92.3 and 66.7% in the LDLCLT(−), low-intensity statin, moderate-intensity statin and ezetimibe groups, respectively, with no significant difference among the four groups. Overall, 82.3% of the patients achieved an LDL-C goal <120 mg/dL. These data showed that LDL-C could be properly managed for primary prevention of CAD in patients aged ≥75 years with type 2 diabetes mellitus regardless of the type of LDL-C-lowering therapy. AST, ALT, γ-glutamyl transpeptidase, creatinine phosphokinase and Cr remained normal regardless of statin intensity, and did not differ significantly between patients taking low-intensity statins and those taking moderate-intensity statins (Table 4).

The CONUT score was calculated based on the TC, plasma albumin and lymphocyte count (Table 5). The patients without lymphocyte counts measured at the time of analysis were excluded. A score of 0–1 is considered normal, and scores of 2–4, 5–8 and 9–12 indicate mild, moderate and severe malnutrition, respectively. Based on the CONUT score, normal nutritional status, and mild, moderate and severe malnutrition were seen in 55.4, 40.5, 4.1 and 0%, respectively, of the patients in the present study. Focusing on the LDLCLT(−) group, where TC was not decreased by LDL-C-lowering agents, 56.8% of the patients showed normal nutritional status, followed by 38.6 and 4.5% of the patients having mild and moderate malnutrition, respectively. Nutritional status was similar between the LDLCLT(−) and LDLCLT(+) groups.

The antidiabetic agents used in the present study are listed in Table 6. Whereas 11.3% of the patients required diet therapy alone, 88.7% of the patients took antidiabetic agents. Dipeptidyl peptidase-4 inhibitors were the most prescribed oral antidiabetic agents, followed by alpha-glucosidase inhibitors. Interestingly, sodium-glucose cotransporter 2 (SGLT2) inhibitors were prescribed only in the LDLCLT(+) group ($P = 0.006$). In contrast, the use of other oral antidiabetic agents did not differ significantly between the two groups. Although almost half of the patients required injection therapy, the use of a glucagon-like peptide-1 receptor agonist or insulin was comparable between the two groups (Table 6). With respect to antihypertensive agents (Table 7), calcium antagonists were prescribed most, followed by angiotensin II receptor blockers. The use of each class of antihypertensive agent was similar between the LDLCLT(−) and LDLCLT(+) groups.

The ABI and CAVI were measured in 72 patients (Table 8). The ABI did not differ between the LDLCLT(+) and LDLCLT(−) groups. No significant correlation was noted between ABI values and LDL-C measured simultaneously ($r = -0.049$,

Table 1 | Patients' baseline characteristics

	Total (n = 124)	LDLCLT(–) (n = 69)	LDLCLT(+) (n = 55)	P-value
Sex (male/female), n (%)	57 (46.0)/67 (54.0)	31 (44.9)/38 (55.1)	26 (47.3)/29 (52.7)	0.80†
Age (years)	80.5 (78.0, 84.0)	81.2 (78.0, 83.5)	81.3 (77.0, 85.0)	1.00‡
Duration of T2DM (years)	19.0 (10.0, 29.0)	19.0 (10.0, 31.0)	18.0 (9.0, 28.0)	0.54‡
Duration of dyslipidemia (years)	6.5 (1.0, 14.0)	7.0 (3.0, 15.0)	5.0 (0.0, 11.0)	0.18‡
BMI (kg/m²)	23.1 ± 3.6	23.1 ± 3.5	23.1 ± 3.7	0.97§
Systolic blood pressure (mmHg)	135.4 ± 17.1	137.6 ± 16.1	132.7 ± 18.1	0.12§
Diastolic blood pressure (mmHg)	70.3 ± 10.9	70.5 ± 10.9	70.0 ± 10.9	0.80§
HbA1c (%)	7.0 (6.4, 7.7)	7.3 (6.5, 8.0)	6.9 (6.4, 7.6)	0.04‡
TC (mg/dL)	179.2 ± 30.7	182.0 ± 32.2	175.7 ± 28.6	0.26§
LDL-C (mg/dL)	98.1 ± 24.9	102.1 ± 24.1	93.0 ± 25.1	0.04§
Non-HDL-C (mg/dL)	124.7 ± 27.9	128.0 ± 28.7	120.6 ± 26.7	0.14§
TG (mg/dL)	115.5 (74.3, 160.8)	117.0 (73.0, 154.5)	115.0 (75.0, 175.0)	1.00‡
HDL-C (mg/dL)	53.0 (42.0, 64.0)	52.0 (42.0, 60.5)	54.0 (42.0, 66.0)	0.37‡
AST (U/L)	22.5 (19.0, 29.0)	22.0 (18.5, 28.0)	23.0 (20.0, 30.0)	0.27‡
ALT (U/L)	19.0 (16.0, 28.0)	17.0 (12.8, 25.3)	20.0 (15.0, 26.0)	0.20‡
γGTP (U/L)	20.0 (16.0, 28.0)	20.0 (16.9, 29.0)	19.5 (15.3, 27.3)	0.73‡
CK (U/L)	91.0 (58.0, 124.5)	87.0 (58.0, 128.0)	91.0 (58.5, 123.3)	1.00‡
Cr (mg/dL)	0.85 (0.69, 1.04)	0.88 (0.71, 1.05)	0.85 (0.68, 1.03)	0.68‡
eGFR (mL/min/1.73 m²)	56.2 ± 17.5	55.7 ± 17.6	57.0 ± 17.5	0.70§
Urinary albumin (mg/g Cr)	125.1 ± 257.2 (n = 94)	169.2 ± 315.2 (n = 53)	68.1 ± 136.8 (n = 41)	0.04§
Chronic kidney disease (%)	71 (57.3)	42 (60.9)	29 (52.7)	0.36†
Non-cardioembolic stroke (%)	10 (8.1)	6 (8.7)	4 (7.3)	1.00¶
Hypertension (%)	80 (64.5)	49 (71.0)	31 (56.4)	0.09†
Cognitive impairment (%)	14 (11.3)	10 (14.5)	4 (7.3)	0.21†
Malignancy undertreatment (%)	8 (6.5)	6 (8.7)	2 (3.6)	0.30¶
History of smoking, n (%) Yes/No	44 (35.5)/65 (52.4) (n = 109)	26 (37.7)/33 (47.8) (n = 59)	18 (32.6)/32 (58.2) (n = 50)	0.39†

Data are expressed as the mean ± standard deviation or medians (interquartile range), as appropriate. Categorical variables are expressed as number (percentage). †χ^2-test. ‡Mann–Whitney U-test §t-test. ¶Fisher's exact test. γGTP, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK, creatinine phosphokinase; Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLCLT, LDL-C-lowering therapy; TC, total cholesterol; TG, triglycerides.

P = 0.68, Figure 1). In contrast, age had a weak, but significant, negative correlation with the ABI (r = –0.253, P = 0.03). There were no associations between the ABI and other risk factors for CVD; that is, systolic blood pressure, diastolic blood pressure, HbA1c, triglycerides and HDL-C. The CAVI was also similar between the LDLCLT(+) and LDLCLT(–) groups (Table 8), and had no significant correlations with those risk factors, including LDL-C or age.

DISCUSSION

In the present study, the current status of LDL-C for primary prevention of CAD was assessed in patients aged ≥75 years with type 2 diabetes mellitus in clinical practice. LDL-C was lower in patients taking statins than in those not taking statins. However, LDL-C was controlled at <120 mg/dL irrespective of the presence or absence of LDL-C-lowering agents. Overall, 82.3% of the patients achieved the LDL-C goal <120 mg/dL. HbA1c was significantly decreased, and SGLT2 inhibitors were more often prescribed in patients taking LDL-C-lowering agents than in those not taking these agents. The groups did not differ with respect to the ABI and CAVI.

Although the evidence of lipid-lowering therapy for the primary prevention of CAD was limited in individuals aged ≥75 years with elevated LDL-C levels[13,14], it is entirely possible that this age group is the most likely to benefit, because the risk of CVD increases with age. Recently, EWTOPIA 75 showed the importance of LDL-C-lowering for the primary prevention of CAD in individuals aged ≥75 years with elevated LDL-C in whom 25.4% had type 2 diabetes mellitus[6]. Ezetimibe significantly decreased LDL-C by 25.9% from the baseline value during 5 years of follow up, which led to a reduction of the primary outcomes by 34% compared with usual care. Therefore, the present study was carried out to assess the current status of LDL-C and the achievement of the recommended LDL-C goal in clinical practice, focusing especially on patients with type 2 diabetes mellitus.

Table 2 | Antihyperlipidemic therapies

	n
Diet therapy	65
Pravastatin	
5 mg†	9
10 mg†	5
20 mg†	1
Atorvastatin	
5 mg†	5
10 mg‡	3
Rosuvastatin	
2.5 mg†	5
5 mg‡	2
Pitavastatin	
1 mg‡	17
2 mg‡	4
Ezetimibe	
10 mg	2
Bezafibrate	
200 mg	1
400 mg	1
Pemafibrate	
0.2 mg	1
EPA	
1,800 mg	1
Combination	
Simvastatin 5 mg†, EPA 1,800 mg	1
Ezetimibe 10 mg, EPA 1,800 mg	1

†Low-intensity statins. ‡Moderate-intensity statins. EPA, eicosapentaenoic acid.

The Japan Atherosclerosis Society has recommended controlling LDL-C to <120 mg/dL in patients with type 2 diabetes mellitus for the primary prevention of atherosclerotic cardiovascular diseases[9]. In the present study, LDL-C was significantly lower in patients taking LDL-C-lowering agents than in those not taking LDL-C-lowering agents (93.0 mg/dL vs 102.1 mg/dL; Table 1). However, LDL-C was controlled at <120 mg/dL irrespective of the presence or absence of LDL-C-lowering agents (Tables 1 and 3). Indeed, 55.6% of the patients were not taking LDL-C-lowering agents, in whom 78.3% of the patients achieved the LDL-C goal <120 mg/dL. The LDL-C goal was achieved in 84.6 and 92.3% of the patients taking low-intensity statins and moderate-intensity statins, respectively. Overall, 82.3% of the patients in the study achieved the LDL-C goal of <120 mg/dL. The findings from the present study are consistent with a previous study examining LDL-C achievement based on the electronic hospital-based health insurance claims database in Japan, in which the percentage of an LDL-C <130 mg/dL in lieu of <120 mg/dL was 80% in patients aged 65.8 years with diabetes, but without coronary artery disease[15]. In that study, 35% of the patients were taking statins, which was slightly lower than in the present study, in which 42% of the patients were taking statins. Laboratory tests showed normal levels of the enzymes associated with liver, skeletal muscle and kidney injuries regardless of statin intensity, implying their safety for elderly patients treated with statins in the present study (Table 4).

It has been reported that LDL-C gradually decreases in older people[16], which might be a major contributing factor to the LDL-C levels in the present study. The decrease of LDL-C is explained by the changes in hepatic cholesterol homeostasis with aging[17]. The underlying malnutrition should also be considered when assessing LDL-C in older persons. Because older people with malnutrition are likely to develop hypocholesterolemia, the number of patients with LDL-C <70 mg/dL was investigated[18]. Four of 69 patients (5.8%) in the LDLCLT(−) group, whose LDL-C was not affected by LDL-C-lowering agents, had LDL-C <70 mg/dL. Nutritional status was further assessed using the CONUT score[11,18]. In the LDLCLT(−) group, 56.8% of the patients had a normal nutritional status, followed by 38.6% of the patients having mild malnutrition (Table 5). Although 4.5% of the patients developed moderate malnutrition, none of the patients had severe malnutrition. Therefore, the majority of the patients in the present study appeared to have been in a state of health that did not impair activities of daily living[19]. The prevalence of each nutritional status was similar between the LDLCLT(−) and LDLCLT(+) groups. However, it is notable that the CONUT score might have been underestimated in the LDLCLT(+) group owing to the LDL-C-lowering agents that reduced TC, although there was no significant difference in TC between the two groups.

Commonly prescribed agents; that is, antidiabetic and antihypertensive agents in the present study, affect LDL-C levels[20]. Of the antidiabetic agents, sulfonylureas, insulin, glinides, α-glucosidase inhibitors and dipeptidyl peptidase-4 inhibitors have a neutral effect on LDL-C levels[20–23], although the effect might differ between the compounds even in the same class[20]. Whereas metformin and glucagon-like peptide-1 receptor agonists decrease LDL-C levels[24,25], pioglitazone and SGLT2 inhibitors increase LDL-C with shifts from atherogenic small dense LDL particles to less atherogenic large buoyant LDL particles[23,26,27]. Metformin and glucagon-like peptide-1 receptor agonists were used similarly between the LDLCLT(−) and LDLCLT(+) groups, in 24.2% of the patients in the present study. SGLT2 inhibitors were prescribed only in the LDLCLT (+) group. Therefore, it is possible that these agents had some effects on LDL-C in the present study. With respect to antihypertensive agents, whereas calcium antagonists, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and β-blockers without intrinsic sympathetic activity are neutral with respect to LDL-C levels, thiazide diuretics increase LDL-C levels[20,28,29]. In the present study, 46.8% of the patients were taking calcium antagonists, followed by 39.5% taking angiotensin II receptor blockers. Less than 10% of the patients were taking angiotensin-converting enzyme inhibitors, diuretics, β-blockers without intrinsic sympathetic activity or other agents (Table 7). Because just four of the nine patients taking diuretics

Table 3 | Low-density lipoprotein cholesterol management status

	LDLCLT(–)	LDLCLT(+)			*P*-value
	No LDL-C-lowering agents (*n* = 69)	Low-intensity statins (*n* = 26)	Moderate-intensity statins (*n* = 26)	Ezetimibe (*n* = 3)	
LDL-C (mg/dL)	102.1 ± 24.1	94.1 ± 27.6	89.5 ± 22.9	113.7 ± 12.6	0.08†
Achievement of LDL-C <120 mg/dL, *n* (%)	54 (78.3)	22 (84.6)	24 (92.3)	2 (66.7)	0.37‡

Data are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (percentage). †One-way analysis of variance. ‡χ^2-test. LDL-C, low-density lipoprotein cholesterol; LDLCLT, LDL-C-lowering therapy.

Table 4 | Laboratory test results of patients on statins

	Low-intensity statins (*n* = 26)	Moderate-intensity statins (*n* = 26)	*P*-value
AST (U/L)	24.5 (20.0, 30.3)	23.5 (19.8, 31.0)	0.75†
ALT (U/L)	20.5 (14.0, 26.5)	20.5 (16.5, 26.8)	0.64†
γGTP (U/L)	18.5 (14.0, 25.0)	23.0 (16.5, 44.5)	0.22†
CK (U/L)	90.5 (59.0, 146.0)	82.0 (59.0, 97.0)	0.28†
Cr (mg/dL)	0.92 (0.71, 1.08)	0.81 (0.64, 0.99)	0.10†

Data are expressed as medians (interquartile range). †Mann–Whitney *U*-test. γGTP, γ-glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; CK, creatinine phosphokinase.

Table 5 | Nutritional status

CONUT score	Total (*n* = 74)	LDLCLT(–) (*n* = 44)	LDLCLT(+) (*n* = 30)	*P*-value
n (%)				
Normal	41 (55.4)	25 (56.8)	16 (53.3)	0.90†
Mild malnutrition	30 (40.5)	17 (38.6)	13 (43.3)	
Moderate malnutrition	3 (4.1)	2 (4.5)	1 (3.3)	
Severe malnutrition	0 (0)	0 (0)	0 (0)	

Data are expressed as numbers (percentage). †χ^2-test. CONUT, controlling nutritional status.

Table 6 | Antidiabetic therapies

	Total (*n* = 124)	LDLCLT(–) (*n* = 69)	LDLCLT(+) (*n* = 55)	*P*-value
Treatment, *n* (%)				
Diet therapy alone	14 (11.3)	8 (11.6)	6 (10.9)	0.91†
Oral antidiabetic agents				
Metformin	20 (16.1)	11 (15.9)	9 (16.4)	0.95†
Thiazolidinedione	0	0	0	—
Sulfonylureas	14 (11.3)	8 (11.6)	6 (10.9)	0.91†
Glinides	16 (12.9)	9 (13.0)	7 (12.7)	1.00†
DPP-4 inhibitors	70 (56.5)	40 (58.0)	30 (54.5)	0.70†
α-Glucosidase inhibitors	48 (38.7)	22 (31.9)	26 (47.3)	0.08†
SGLT2 inhibitors	6 (4.8)	0	6 (10.9)	0.01‡
Injection therapy				
GLP-1 receptor agonists	10 (8.1)	4 (5.8)	6 (10.9)	0.30‡
Insulin	58 (46.8)	30 (43.5)	28 (50.9)	0.41†

Data are expressed as numbers (percentage). †χ^2-test. ‡Fisher's exact test. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; LDLCLT, LDL-C-lowering therapy; SGLT2, sodium–glucose cotransporter 2.

Table 7 | Antihypertensive therapies

	Total (n = 124)	LDLCLT(–) (n = 69)	LDLCLT(+) (n = 55)	P-value
Treatment, n (%)				
Calcium blockers	58 (46.8)	34 (49.3)	24 (43.6)	0.53†
ARBs	49 (39.5)	32 (46.4)	17 (30.9)	0.08†
Diuretics	9 (7.3)	5 (7.2)	4 (7.3)	0.63‡
ACE inhibitors	7 (5.6)	2 (2.9)	5 (9.1)	0.24‡
α-Blockers	7 (5.6)	4 (5.8)	3 (5.5)	1.00‡
β-Blockers ISA (–)	4 (3.2)	2 (2.9)	2 (3.6)	1.00‡
αβ-Blockers	2 (1.6)	1 (1.4)	1 (1.8)	1.00‡

Data are expressed as numbers (percentage). †χ^2-test. ‡Fisher's exact test. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ISA, intrinsic sympathetic activity.

Table 8 | Ankle-brachial index and cardio-ankle vascular index values by group

	Total (n = 72)	LDLCLT(–) (n = 39)	LDLCLT(+) (n = 33)	P-value
ABI	0.99 (0.91, 1.07)	0.99 (0.90, 1.07)	1.01 (0.92, 1.07)	0.81†
CAVI	10.4 (9.6, 11.1)	10.4 (9.8, 11.3)	10.4 (9.5, 11.1)	0.80†

Data are expressed as medians (interquartile range). †Mann–Whitney U-test. ABI, ankle-brachial index; CAVI, cardio-ankle vascular index; LDLCLT, LDL-C-lowering therapy.

were on thiazide diuretics, it is conceivable that there was minimal effect of antihypertensive agents on LDL-C levels.

Pitavastatin was the most prescribed statin in the present study, taken by 40.4% of the patients on statins (Tables 2 and 3). After pitavastatin, pravastatin was prescribed in 28.8% of the patients taking statins. Statins have been shown to be associated with an increased risk of new-onset diabetes[30–32]. A meta-analysis of 13 statin trials with 91,140 participants showed that statin therapy was associated with a 9% increased risk of incident diabetes during a mean follow up of 4 years[30]. In contrast, a subanalysis of the West of Scotland Coronary Prevention Study showed that pravastatin reduced the rate of new-onset diabetes by 30%[33]. Statins have been further shown to adversely affect glycemic control in type 2 diabetes mellitus[34], but the effects on glucose homeostasis vary among the statins[35–38]. Pitavastatin has been shown to have a better effect on glycemic status than atorvastatin in type 2 diabetes mellitus[37,38]. Furthermore, pravastatin has a better effect on pancreatic β-cell function than atorvastatin in type 2 diabetes mellitus[36]. Therefore, it is presumed that pitavastatin and pravastatin, which have few adverse effects on glucose metabolism, were preferentially administered to the patients with type 2 diabetes mellitus in the present study.

The number of older adults with diabetes has been increasing in proportion to the overall aging of the Japanese population. A study based on the Japanese medical administrative database for the period from January 2010 to December 2019 reported that the mean HbA1c was 6.82% in 3,946 patients with type 2 diabetes mellitus aged ≥65 years under continuous physician-supervised treatment[39]. Because the database

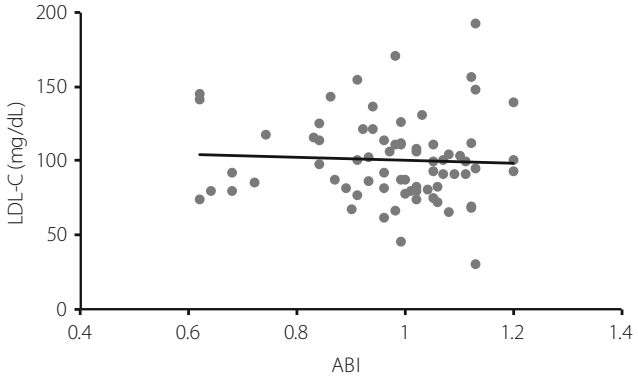

Figure 1 | Correlation between the ankle-brachial index (ABI) and the low-density lipoprotein cholesterol (LDL-C) level. No significant correlation is seen between the ABI and the LDL-C level measured simultaneously (r = –0.049, P = 0.68).

contained data collected from approximately 20% of all large hospitals across Japan, the study would represent the general glycemic status in Japanese elderly persons with diabetes. HbA1c in the present study was 7.0%, which was similar to, but slightly higher than in that study[39]. Interestingly, SGLT2 inhibitors were more prescribed in the patients receiving LDL-C-lowering therapy than in patients not receiving it. Because SGLT2 inhibitors have shown beneficial effects on kidney and cardiovascular outcomes in large clinical trials[40–42], it is presumed that SGLT2 inhibitors were used preferentially in patients receiving LDL-C-lowering therapy who are at high risk for CVD events.

Proteinuria has been shown to be a surrogate marker for CVD[43,44]. In a population-based cohort study, increasing graded levels of albuminuria were associated with an elevated risk of CVD in patients with type 2 diabetes mellitus[44]. In the present study, the patients in the LDLCLT(−) group had a higher urinary albumin level than those in the LDLCLT(+) group. Therefore, it should be emphasized that there are substantial risks of CVD even in late-stage elderly persons with type 2 diabetes mellitus whose LDL-C is controlled at <120 mg/dL without taking LDL-C-lowering agents. Better glycemic control, statins and SGLT2 inhibitors have been shown to reduce albuminuria[45–47], which might be associated with lower urinary albumin levels in the LDLCLT(+) group than in the LDLCLT(−) group. The beneficial impact of renin–angiotensin system blocking agents on albuminuria has also been reported[48], but the use of these agents was similar between the two groups.

An abnormal ABI has been shown to be independently associated with CVD events in type 2 diabetes mellitus[49–52]. The CAVI is also used in clinical practice as a surrogate marker of CVD[53]. Therefore, both examinations have been widely used to assess the risk of CVD in type 2 diabetes mellitus. In the present study, the ABI/CAVI did not differ significantly between patients with and without LDL-C-lowering therapy. Furthermore, no significant correlation between LDL-C and the ABI was noted in these patients. As previously reported[54], age had a negative correlation with the ABI. In contrast, other risk factors for CVD were not associated with the ABI. There were no significant correlations between the CAVI and risk factors, including LDL-C or age. It might also be that statins and SGLT2 inhibitors affected these examinations[55,56].

The present study had several limitations. First, this was a single-center, cross-sectional study. The lengths of treatment with LDL-C-lowering and antidiabetic agents, and changes of these agents in the past were not assessed. Second, the number of patients enrolled in the study, and who underwent nutritional assessment and ABI/CAVI measurement was small. Therefore, the findings in the present study require further evaluation with a large sample size from multiple centers.

In conclusion, the current status of LDL-C management for the primary prevention of CAD in patients aged ≥75 years with type 2 diabetes mellitus in clinical practice was presented. LDL-C was properly managed by any of the treatment methods in these patients, and primary prevention for CAD could be continued regardless of the presence or type of LDL-C-lowering agents by selecting appropriate treatments with careful attention to nutritional status and other CVD risk factors.

DISCLOSURE

The authors declare no conflict of interest.

Approval of research protocol: The Ethics Committees of Mito Medical Center, Tsukuba University Hospital and Mito Kyodo General Hospital (Approval no. 19–26, 31 October 2019).

Informed consent: Informed consent was obtained in the form of opt-out on the website.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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