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High-Density Lipoprotein Cholesterol Efflux Capacity as a Novel Prognostic Surrogate for Coronary Artery Disease

Itaru Hisauchi[1], Tetsuya Ishikawa[1], Makoto Ayaori[2], Harumi Uto-Kondo[2, 3], Yuri Koshikawa[1], Tomoaki Ukaji[1], Hidehiko Nakamura[1], Yukiko Mizutani[1], Isao Taguchi[1], Takatomo Nakajima[4], Makoto Mutoh[4] and Katsunori Ikewaki[2]

[1]Department of Cardiology, Dokkyo Medical University, Saitama Medical Center, Koshigaya, Saitama, Japan
[2]Division of Anti-aging and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Tokorozawa, Saitama, Japan
[3]Department of Bioscience in Daily Life, Nihon University, Fujisawa, Kanagawa, Japan
[4]Division of Cardiology, Saitama Cardiovascular Respiratory Center, Kumagaya, Saitama, Japan

Aim: We examined the impact of baseline high-density lipoprotein cholesterol efflux capacity (CEC) on major cardiac adverse events (MACE) in patients with coronary artery disease (CAD) during a long-term secondary prevention.

Method: CEC was measured using a cell-based efflux system in (3)[H]-cholesterol-labeled J774 macrophages in apolipoprotein B-depleted plasma between January 2011 and January 2013. Patients with CAD were divided into 2 groups as a boundary CEC value of 1: 0.19 ≤ CEC <1 (impaired CEC group, mean CEC of 0.76 ± 0.16, n=136), and 1 ≤ CEC ≤ 2.08 (enhanced CEC group, 1.20 ± 0.19, n=44). MACE, comprised the incidence of cardiac death, non-fatal myocardial infarction, and any revascularizations (RV) without restenosis approximately 1 year after vascularization, was retrospectively investigated at September 2019. Impact of enhanced CEC on MACE among 22 variables was examined by applying a Cox proportional hazard model.

Result: The frequency of MACE in impaired CEC group (16.9%, mean observational interval of 2111 ± 888 days) was significantly higher than that in enhanced CEC group (2.3%, 2,252 ± 685, p=0.013), largely driven by the significantly higher RV incidence (14.0 % versus 2.3 %, p=0.032). Enhancement of CEC was the significant predictor of MACE (hazard ratio: 0.11; 95% CI: 0.013-0.879; p=0.038).

Conclusion: A baseline CEC level of more than 1 in patients with CAD brought favorable long-term clinical outcomes, suggesting that CEC is a useful prognostic and therapeutic surrogate for secondary prevention of CAD.

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Key words: Coronary artery disease, High-density lipoprotein cholesterol efflux capacity, Major adverse cardiac event, Coronary revascularization

Introduction

In addition to low-density lipoprotein cholesterol (LDL-C), it has been essential to clarify both the prognostic surrogate and the therapeutic target for secondary prevention in patients with coronary artery disease (CAD); this is because relative risks of secondary cardiac events remained despite the lowering therapy of LDL-C[1]. Among the pleiotropic atheroprotective effects of high-density lipoprotein cholesterol (HDL-C), cholesterol efflux from macrophage (cholesterol efflux capacity, CEC) was consistently demonstrated as a negative predictor of CAD, independent of HDL-C and LDL-C levels[2, 3]. In addition, the CEC in asymptomatic healthy subjects predicts the incidence of atherosclerotic cardiovascular events

Address for correspondence: Tetsuya Ishikawa, Department of Cardiology, Dokkyo Medical University, Saitama Medical Center, Koshigaya, Saitama, Japan
E-mail: tetsuya50ishikawa@gmail.com

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(ASCVD) corresponding to the baseline CEC level besides the baseline LDL-C level[4]. However, the prognostic impact of the baseline CEC on patients with CAD during long-term secondary prevention therapy is not fully understood.

Therefore, we sought to clarify the impact of CEC on cardiac events during secondary prevention in patients with CAD in the present drug-eluting stent era. In order to examine the relationship between the baseline CEC levels and the incidences of major adverse cardiac events (MACE), we retrospectively investigated the frequency of MACE by dividing 180 patients with CAD enrolled in our previous study[3] into 2 groups with the border baseline CEC value of 1.0, the normal function of CEC. The baselines and the frequencies of clinical outcomes were compared between the two groups, i.e. impaired CEC group (CEC less than 1) versus enhanced CEC group (CEC more than 1). In addition, the impact of enhancement of CEC on MACE among 22 variables was examined by using a Cox proportional hazard model.

Methods

Population

The current study was an observational study that investigated the relationship between the baseline CEC levels and the clinical outcomes in 180 patients with CAD corresponding to our previous report[3]; there were two cases of in-hospital mortality among the CAD patients in our previous report[3]. Fasting blood sampling was performed at the time of elective CAG, elective percutaneous coronary intervention (PCI), or multi-slice coronary computed tomography (MSCT) between January 2011 and January 2013 at Saitama Cardiovascular Respiratory Center (SCRC). All the patients had continuous secondary prevention according to the guideline of the Japanese Circulation Society[5]. All patients were informed of the study objectives, and consent was obtained from all participants. The rationale of the present study was approved by the local ethics committee of SCRC on 14, February 2019 (accepted number: 2018040). Retrospective investigation of medical records from the SCRC, and telephone and letter interviews of the clinics and patients were conducted from March 2019 to September 2019.

Based on the baseline levels of CEC, patients were divided into two groups as the border value of 1, the normal range of CEC: $0.19 \leq \text{CEC} < 1.0$ (impaired CEC group, $n=136$), and $1.0 \leq \text{CEC} \leq 2.08$ (enhanced CEC group, $n=44$).

Measurement of Cholesterol Efflux Capacity of Macrophages

The CEC was determined according to the methods previously reported[2, 3]. In brief, J774 macrophages were purchased from RIKEN (Tsukuba, Japan), cultured in RPMI 1640 medium containing 10% fetal bovine serum, and kept under constant conditions of 5% carbon dioxide and a temperature of 37℃. J774 cells were plated in 24-well plates, grown to 80% confluence, and radiolabeled with 2 μCi/mL of ^{3}H-cholesterol. Apolipoprotein B-depleted serum was prepared by incubation with 13% polyethylene glycol 6000 solution (Wako Pure Chemicals). Subsequently, an efflux medium containing 2.8% apolipoprotein B-depleted serum was added and incubated for 4 h. All procedures were performed in the presence of the acyl-coenzyme A: cholesterol acyltransferase inhibitor Sandoz 58–035 (2 μg/mL; Sigma, St. Louis, MO, USA) and 8-bromoadenosine 3', 5'-cyclic monophosphate (0.3 mmol/L; Sigma). A liquid scintillation counter was used to quantify the efflux of radioactive cholesterol from the cells. The quantity of radioactive cholesterol incorporated into cellular lipids was calculated through hexane:isopropanol (v:v, 1:1) extraction in control wells not exposed to the serum. The percent efflux was calculated using the following formula: (cpm of ^{3}H-cholesterol in media containing 2.8% apolipoprotein B-depleted serum − cpm of ^{3}H-cholesterol in serum-free mediums)/(cpm of ^{3}H-cholesterol in cells extracted before the efflux step) × 100. All assays were performed in duplicate. The CECs of patients' sera were expressed as the values relative to those of the pooled sera.

Baseline Measurements

Baseline variables were collected from our previous report[3]. The patient variables included age, male sex, and the coronary risk factors such as hypertension, dyslipidemia, diabetes mellitus (diabetes), and family history of CAD. Patients with no history of smoking (nonsmoker) were included as the risk factor. Patients with hypertension were considered to be at risk if their blood pressure was ≥ 140 / 90 mm Hg or if they had a history of anti-hypertensive drug use. Patients with diabetes were considered to be at risk if their fasting glucose level was ≥ 126 mg/dL and their hemoglobin A1C (HbA1c) level was ≥ 6.5%, or if they had a history of hypoglycemic drug or insulin use. Patients with dyslipidemia were considered to be at risk if their LDL-C level was ≥ 140 mg/dL and their HDL-C level was ≤ 40 mg/dL, or if they were taking a lipid-lowering drug, including HMG-CoA reductase inhibitors (statins). Dyslipidemia-related variables, including serum total cholesterol, triglycerides, HDL-

C, LDL-C, and CEC were evaluated. Apolipoprotein (apo) A-I (apo-A1) and apo-B concentrations were measured by turbidimetric immunoassay. The administration of statins (statin administration) was not prospectively randomized, and patients who were prescribed statins at the time of blood sampling were evaluated as taking statins based on the physician's discretion. The cardiovascular baselines, serum hematocrit (Ht), creatinine (Cr), and brain natriuretic peptide (BNP) levels were evaluated. The percentage of left ventricular ejection fractions less than 40% (left ventricular dysfunction), prevalence of coronary artery bypass grafting (CABG), diseased left main coronary artery, and prevalence of peripheral artery disease (PAD) were also estimated, as were the mean numbers of diseased coronary vessels (number of diseased coronary vessel).

The Estimated Endpoint

The incidence of major adverse cardiac events (MACE) comprised the incidences of cardiac death, including sudden death, non-fatal myocardial infarction, and any target lesion revascularization (TLR) without restenosis, approximately 1 year after vascularization. The incidence of TLR was divided into late TLR, defined as TLR at the previous target lesion after 1-year secondary angiogram[6], and non-culprit TLR, defined as the TLR for de novo lesions without culprit revascularized lesions[7]. All of the late TLR was conducted against the failure of the first-generation drug-eluting stents (i.e. sirolimus-eluting stent placement, and paclitaxel-eluting stents) placed prior to February 2010.

In addition, the incidence of all-cause mortality was investigated as the other estimated outcome. The clinical observational interval was the interval from the date of blood sampling of CEC to the date of the final confirmation of the clinical course.

Statistical Analyses

The 23 baseline characteristic variables were expressed as percentages or mean values ± standard deviation. Baseline variables **(Table 1)** and clinical outcomes **(Table 2)** in impaired CEC group were individually compared with those in enhanced CEC group using unpaired *t*-tests for continuous values and the χ^2 test for categorical values. The cumulative MACE-free ratio of impaired CEC group was compared with that of enhanced CEC group by log-rank test **(Fig. 1)**. The predictors of MACE were examined by applying a Cox proportional hazard model among 22 variables. The CEC was enrolled as the categorical group, i.e. enhanced CEC group. Dyslipidemia was excluded from this statistics because of the duplication of the individual dyslipidemia-related variables. A p value <0.05 was considered statistically significant. The Stata version 14 software for Windows (StataCorp, College Station, TX, USA) was used for all statistical analyses.

Results

The baseline characteristics of the study subjects are shown in **Table 1**. None of the patient-related baselines and coronary risk factors in impaired CEC group was significantly different from those in enhanced CEC group. Among the dyslipidemia-related variables, the mean serum HDL-C, apo-A1, and CEC in impaired CEC group were significantly different from those in enhanced CEC group (HDL-C level: 48.2 ± 12.7 vs. 55.5 ± 15.9 mg/dL; $p=0.006$; apo-A1 level: 120 ± 25.1 vs. 129 ± 25.1 mg/dL; $p=0.039$; CEC: 0.76 ± 0.16 vs. 1.20 ± 0.19; $p<0.001$). None of other laboratory variables in impaired CEC group was significantly different from those in enhanced CEC group. Among the cardiovascular-related baselines, the number of diseased coronary vessel in impaired CEC group was significantly larger than that in enhanced CEC group (1.98 ± 0.80 vs. 1.68 ± 0.71; $p=0.018$).

The clinical outcomes are shown in **Table 2**. The frequencies of MACE, TLR, and non-culprit TLR in impaired CEC group were significantly higher than those in enhanced CEC group (16.9% vs. 2.3%; $p=0.013$, 14.0% vs. 2.3%; $p=0.032$, 9.6% vs. 0; $p=0.033$, respectively).

The cumulative MACE-free ratios are shown in **Fig. 1**. The cumulative MACE-free ratio of impaired CEC group was significantly lower than that in enhanced CEC group ($p=0.022$, log-rank test).

The predictors of MACE in the entire cohort are shown in **Table 3**. The PAD (hazard ratio [HR]: 32.3; 95% confidence interval [CI]: 4.60-226; $p<0.001$), and enhanced CEC (HR: 0.11; 95% CI: 0.013-0.879; $p=0.038$) were the significant predictors of MACE **(Table 3)**.

Discussion

The primary purpose of the present study was to examine the impact of the baseline CEC level of patients with CAD, particularly, the impact of the boarder CEC value of 1, on major adverse cardiac events (MACE) during long-term secondary prevention. As the backgrounds, in addition to the LDL-C level, it is essential to clarify the prognostic surrogate and/or the therapeutic target of secondary prevention in patients with CAD[1]. The diagnostic impact of

Table 1. Baseline variables in impaired CEC group and enhanced CEC group

(*n*)	Impaired CEC group 136	Enhanced CEC group 44	*p*-values
Patient baseline characteristics at CEC measurement			
Age (yr)	65.3 ± 10.3	68.4 ± 10.0	0.076
Male sex (%)	82.4	79.5	0.676
Coronary risk factors			
Hypertension (%)	92.6	95.5	0.516
Dyslipidemia (%)	80.9	79.5	0.846
Diabetes (%)	56.6	50.0	0.443
Nonsmoker (%)	37.5	45.5	0.348
Family history of CAD (%)	25.0	22.7	0.760
Dyslipidemia-related variables			
Serum total cholesterol (mg/dL)	176 ± 37.5	175 ± 36.2	0.875
Serum triglyceride (mg/dL)	172 ± 129	150 ± 69.8	0.150
Serum HDL-C (mg/dL)	48.2 ± 12.7	55.5 ± 15.9	0.006
Serum LDL-C (mg/dL)	103 ± 32.0	100 ± 31.9	0.590
apo-A1 (mg/dL)	120 ± 25.1	129 ± 25.1	0.039
apo-B (mg/dL)	57.0 ± 21.8	55.0 ± 22.9	0.610
CEC	0.76 ± 0.16	1.20 ± 0.19	< 0.001
Statin administration (%)	64.0	75.0	0.177
Other laboratory variables			
Serum Ht (%)	41.6 ± 4.9	41.9 ± 5.1	0.732
Serum Cr (mg/dL)	0.91 ± 0.43	0.95 ± 0.28	0.488
Serum BNP (pg/dL)	106 ± 282	158 ± 326	0.342
Baseline cardiovascular characteristics			
Left ventricular dysfunction (%)	12.5	4.5	0.136
CABG (%)	6.6	2.3	0.274
Number of diseased coronary vessel	1.98 ± 0.80	1.68 ± 0.71	0.018
Diseased left main coronary artery (%)	4.4	6.8	0.524
PAD (%)	5.1	4.5	0.874

The baseline 23 variables are shown. The variables in impaired CEC group were compared to those in enhanced CEC group. Abbreviations are described in the text.

Table 2. Clinical outcomes in impaired CEC group and enhanced CEC group

(*n*)	Impaired CEC group 136	Enhanced CEC group 44	*p*-values
Clinical observational interval after CEC measurement (day)	2110 ± 888	2252 ± 685	0.268
Clinical outcomes			
All-cause death (%)	11.0	9.1	0.716
MACE (%)	16.9	2.3	0.013
Cardiac death (%)	2.9	0	0.250
Non-fatal myocardial infarction (%)	1.5	0	0.419
Target lesion revascularization (TLR) (%)	14.0	2.3	0.032
Late TLR (%)	5.9	2.3	0.340
Non-culprit TLR (%)	9.6	0	0.033

The clinical outcomes-related variables are shown. The variables in impaired CEC group were compared to those in enhanced CEC group. Abbreviations are described in the text.

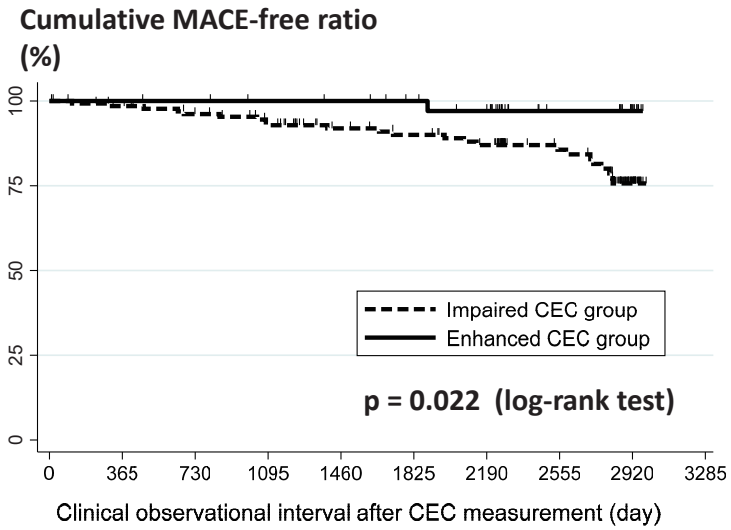

Fig. 1. Cumulative MACE-free ratios in impaired CEC group and enhanced CEC group

The cumulative MACE-free ratios in the 2 groups were determined by Kaplan-Meier curves. The cumulative MACE-free ratio in impaired CEC group (broken line) was significantly lower than that in enhanced CEC group (solid line) ($p=0.022$, log-rank test). The vertical axis shows the cumulative MACE-free ratio (%), while the horizontal axis shows the interval for clinical observation after CEC measurement (days).

Table 3. Predictors of MACE

	Hazard ratio	95%C.I.	*p*-values
PAD	32.3	4.60-226	<0.001
Enhanced CEC	0.11	0.013-0.879	0.038
Total cholesterol	1.09	0.996-1.19	0.061
Diabetes	2.79	0.945-8.26	0.063
Triglyceride	0.99	0.977-1.001	0.077
HDL-C	0.91	0.817-1.01	0.077
BNP	1.00	0.999-1.002	0.079
Family history of CAD	0.33	0.085-1.31	0.116
LDL-C	0.94	0.853-1.03	0.154
apo-B	0.98	0.939-1.02	0.285
Male sex	2.41	0.445-13.1	0.307
apo-A1	1.02	0.984-1.05	0.316
Serum Cr	1.43	0.615-3.31	0.407
Age	1.02	0.968-1.08	0.428
Diseased left main coronary artery	0.40	0.027-6.02	0.510
Ht	1.04	0.925-1.16	0.539
CABG	1.59	0.261-9.74	0.613
Statin administration	1.35	0.405-4.51	0.624
Hypertension	0.57	0.061-5.36	0.626
Nonsmoker	1.24	0.410-3.74	0.705
Left ventricular dysfunction	0.94	0.207-4.30	0.939
Number of diseased coronary vessel	0.99	0.463-2.10	0.975

The predictors of MACE in the entire cohort were shown according to the *p*-values calculated by a Cox proportional hazard model. The upper two variables including CEC were significant. Abbreviations are described in the text.

CEC on CAD has been consistent[2, 3], and the prognostic impact of CEC on ASCVD has been previously documented among asymptomatic healthy subjects[4]. To the best of our knowledge, the present study is the first to demonstrate the prognostic impact of baseline CEC level, but not HDL-C or apo-A1 levels, on MACE in patients with CAD with the longest clinical observational interval. The frequency of MACE was quite different at a border CEC level of 1 with the large reduction of the frequency of non-culprit TLR (the development of de novo lesion) in enhanced CEC group, supporting the atheroprotective effects of CEC against the atherosclerotic coronary stenosis[2-4]. Therefore, the present study showed 1) the prognostic impact of baseline CEC on long-term clinical outcomes during secondary prevention of CAD, 2) a useful therapeutic goal of CEC level of 1 for secondary prevention of CAD, and 3) CEC as the single significant predictor of MACE in patients with CAD among conventional lipid-related variables.

The long-term clinical outcome in the cohort with CEC more than 1 (enhanced CEC group) was favorable in a few percentages of MACE (only one case of late TLR) during a mean clinical observation interval of more than 6 years **(Table 2, Fig. 1)**. The present low frequency of MACE in enhanced CEC group was similar to that of ASCVD at approximately 6 years follow-up in the cohort with CEC more than 1 in healthy young subjects[4]. However, in enhanced CEC group, there were several adverse baselines for MACE, such as a higher tendency of mean age than impaired CEC group[8], percentage of diabetes[9] as high as 50%, mean baseline BNP level more than 150 (pg/dL), and several percentages of the prevalence of PAD[10] **(Table 1)**. All of the significantly higher CEC, HDL-C, and apo-A1 levels in enhanced CEC group than those of impaired CEC group were the atheroprotective variables **(Table 1)**. However, CEC remained to be the significant predictor of MACE by a Cox proportional hazard model **(Table 3)**. Thus, CEC was the single significant predictor of MACE in patients with CAD among not only lipid-related variables, but also other conventional coronary risk factors. Therefore, the present favorable clinical outcome of enhanced CEC group is dependent upon the significantly higher CEC. As described above, the TLR was inversely related to CEC **(Table 2)**. Several predictors of late TLR after sirolimus-eluting stent placement in patient, lesion, and procedure characteristics were reported (j-Cypher Registry)[6]. In addition, several predictors related to atherosclerotic coronary plaque for non-culprit TLR were reported (PROSPECT study)[11]. Thus, the atheroprotective effects of CEC played a significant role for, particularly, reducing the non-culprit TLR, i.e. development of de novo stenotic lesions **(Table 2)**. Accordingly, the baseline CEC predicts the incidence of MACE, in particular, of coronary revascularization, in patients with CAD, including the boarder baseline CEC level of 1. Several interventions recommended as the optimal secondary preventions of CAD have been described and function to improve CEC level up to 1; these include pharmacological interventions by rosuvastatin[12], ezetimibe[13], eicosapentaenoic acid[14], and intensive cardiac rehabilitation, including smoking cessation[15] and improvement of diabetes state[9].

On the other hand, the frequency of MACE in impaired CEC group was as high as 16.9% in a mean observational interval of 5.78 years (approximately 7.3 hold higher compared to enhanced CEC group, **Table 2, Fig. 1**). The present frequency of MACE in impaired CEC group was similar to the Japanese large-scale multicenter RESET trial (approximately 20% to 23% in a 7-year follow-up)[16]. This frequency of MACE was several times higher than that of ASCVD, which ranged from approximately 2% to 4% at a 6-year clinical follow-up in the relatively lower values of CEC in healthy young subjects[4]. Therefore, as described above, the CEC level of 1, the boarder of the normal range of CEC, exerted an important prognostic impact on MACE in patients with CAD. In the present patients with CAD, PAD predicts the incidence of MACE beyond baseline CEC level **(Table 3)**, although the percentages of the patient with PAD were approximately 5% **(Table 1)**. Patients with CAD concurrent with PAD have a high risk for MACE, and are recommended intensive lipid lowering treatment[10]. Accordingly, in the CAD cohorts with CEC level less than 1, the impact of CEC on MACE with further intensive lipid-lowering therapy should be examined.

The present study had several limitations; these included a small population, retrospective observational study, factors related to the coronary stenotic lesion and the PCI procedure, achievement of CEC after secondary prevention, and the impact of other factors and underlying confounders potentially related to MACE during a long-term interval.

Conclusion

The present study demonstrated that 1) the baseline CEC level more than 1 in patients with CAD brought favorable long-term clinical outcomes, 2) CEC is a useful prognostic surrogate for the secondary prevention of CAD, and 3) CEC is the single significant predictor of MACE among not only lipid-related variables, but also conventional coronary risk factors.

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All of the authors have no conflict of interest, financial or otherwise.

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