



# Malnutrition and Clopidogrel Non-Use Worsen Prognosis of Critical Limb Ischemia Patients After Revascularization

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**Background:** Critical limb ischemia (CLI) patients have high risk for major adverse cerebrovascular and cardiovascular events. This study investigated the risk factors of cerebrovascular or cardiovascular death in CLI patients with concomitant coronary artery disease (CAD).

**Methods and Results:** The association between baseline characteristics and cerebrovascular or cardiovascular death  $\leq 2$  years after revascularization for CLI was investigated in 137 CLI patients who previously underwent successful revascularization for CAD before treatment for CLI. Twenty-three patients (17%) died. Geriatric nutritional risk index (GNRI) in the deceased group (DG) was significantly lower than in the surviving group (SG). On Cox proportional hazard multivariate analysis, hemodialysis (HD) and malnutrition (defined as GNRI  $< 92$ ) were significantly associated with cerebrovascular or cardiovascular death. Also, on Kaplan-Meier analysis, survival rate was significantly lower in CLI patients with either malnutrition or HD compared with patients without either malnutrition or HD, respectively. Furthermore, clopidogrel was less used in the DG than in the SG. The use of clopidogrel was associated with cerebrovascular or cardiovascular death. Especially, non-use of clopidogrel in the malnutrition group further increased the correlation with cerebrovascular or cardiovascular death.

**Conclusions:** Malnutrition is a crucial risk factor for cerebrovascular and cardiovascular death in CLI patients with CAD. Nutritional status intervention and use of clopidogrel may be an important strategy for CLI.

**Key Words:** Clopidogrel; Coronary artery disease; Critical limb ischemia; Malnutrition

Peripheral artery disease (PAD) is a manifestation of atherosclerosis, and PAD patients are known to have poor prognosis because of the high prevalence of concomitant vascular disease including coronary artery disease (CAD) and/or cerebrovascular disease (CVD).<sup>1</sup> Critical limb ischemia (CLI) is the most advanced form of PAD, and CLI patients have poor vascular condition due to severe arteriosclerosis.

Approximately one-half of CLI patients without revascularization will either die or undergo major amputation in  $\leq 1$  year.<sup>2,3</sup> However, even if CLI patients undergo revascularization, they still have very poor prognosis with a high mortality because of cardiovascular events. Therefore, it is important to identify the treatable factors in CLI patients in order to prevent major adverse cardiac and cerebral events.

According to the accumulated evidence, frailty and sarcopenia are important factors affecting the prognosis of

cardiovascular disease, especially of CAD and heart failure.<sup>4</sup> Malnutrition is the main factor causing frailty and sarcopenia.<sup>5,6</sup> Recently, malnutrition has also been found to negatively influence the prognosis of PAD. As a tool of assessment for nutritional status, serum albumin (Alb) level and body mass index (BMI) are often used in routine clinical practice. Serum Alb level, however, is influenced by several factors including inflammation, fluid status and renal dysfunction.<sup>7-9</sup> Similarly, BMI is also influenced by fluid status.<sup>10,11</sup> Hence, the geriatric nutritional risk index (GNRI) and controlling nutrition status (CONUT) are now widely used for simple screening of nutritional status. Shiraki et al, however, reported that GNRI, a simple screening of nutritional status using BMI and serum Alb, was independently associated with mortality and major amputation after endovascular therapy in CLI patients,<sup>12</sup> although the effect of factors including malnutrition assessed with GNRI, on cerebrovascular and/or cardiovascular

Received October 4, 2019; revised manuscript received November 27, 2019; accepted December 4, 2019; J-STAGE Advance Publication released online December 28, 2019 Time for primary review: 1 day

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death in CLI patients who had CAD, is unknown.

The purpose of this study was therefore to evaluate the treatable factors including malnutrition in CLI patients with CAD, in order to develop optimal recommendations for preventing cerebrovascular and/or cardiovascular death in CLI patients.

## Methods

### Study Design and Informed Consent

We conducted a retrospective cohort study in a single center, of 152 consecutive CLI patients who were admitted to Kagoshima University Hospital from January 2014 to August 2016 to undergo revascularization for peripheral artery disease with an endovascular treatment or surgery.

This study was approved by the research and ethics committee of Kagoshima University Hospital and was carried out in accordance with the ethical principles stated in the 1975 Declaration of Helsinki. All patients provided written informed consent.

### Subjects

In this study, we excluded 4 patients (3%) who died from sepsis and pneumonia and 11 patients who were lost to follow-up. Given that this study focused on cerebrovascular and/or cardiovascular death, non-cardiac deaths such as death from infection were excluded from analysis. All patients were followed up at hospital or by their physician, and we investigated prognosis after revascularization.

Seventy-six CLI patients (55%) received endovascular therapy and 61 patients were given a combination of endovascular therapy and surgical bypass grafting (45%). Moreover, these patients had already undergone revascularization for the comorbidity of CAD, using percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) before the treatment for CLI. PCI had used second-generation drug-eluting stents. With regard to the revascularization for CAD, PCI was done 109 patients (80%); CABG in 19 (14%); and the combination of CABG and PCI in 9 (6%).

We investigated the association between baseline characteristics including medication at discharge and cerebrovascular or cardiovascular death  $\leq 2$  years after revascularization for CLI.

### Measurements

Blood samples were obtained at admission before the revascularization for CLI. Serum Alb, high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose (FPG), hemoglobin (Hb), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), uric acid (UA), and white blood cell (WBC) count were measured.

In addition, echocardiograms were measured on admission.

### Definitions

CLI was diagnosed when patients met at least one of the following criteria: (1) chronic ischemic foot rest pain with ankle pressure  $< 50$  mmHg, skin perfusion pressure  $< 30$  mmHg; (2) ischemic foot ulcer or gangrene with ankle pressure  $< 70$  mmHg; or (3) ischemic foot rest pain or ulcer/gangrene with critical ischemia indicated on other modalities.

BMI was calculated as bodyweight divided by height

squared ( $\text{kg}/\text{m}^2$ ). GNRI was also calculated using the following equation:  $\text{GNRI} = 14.89 \times \text{serum Alb [g/dL]} + 41.7 \times (\text{body weight in kg}/\text{ideal body weight})$ . Body weight/ideal body weight was set to 1 when body weight exceeded the ideal body weight. Ideal body weight was calculated using a BMI of 22. Patients with  $\text{GNRI} < 92$  were defined as having malnutrition based on previously published thresholds.<sup>13</sup> Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or the use of antihypertensive medication. Diabetes mellitus was defined as use of anti-hyperglycemic medication, FPG concentration  $> 126$  mg/dL, or glycosylated Hb concentration  $\geq 6.5\%$  (according to the National Glycohemoglobin Standardization Program). Dyslipidemia was defined as a  $\text{LDL-C} \geq 140$  mg/dL,  $\text{TG} \geq 150$  mg/dL,  $\text{HDL-C} < 40$  mg/dL, or anti-dyslipidemic medication use. Current smoking was defined as active smoking on admission for revascularization for CLI.

Cardiovascular death was defined as death due to CAD including acute coronary syndrome (ACS), and cerebrovascular death was defined as death due to cerebral infarction or cerebral hemorrhage.

### Endpoints

The primary outcome measure for adverse cardiovascular events was a composite of cerebrovascular and cardiovascular death  $\leq 2$  years after revascularization for CLI. In addition, an exploratory risk factor analysis related to the primary outcome measure was conducted.

### Statistical Analysis

Quantitative data are presented as mean  $\pm$  SD or median (IQR). Fisher's exact test was used to compare the incidence of categorical variables, and categorical variables are expressed as percentages. Continuous variables were compared between the surviving group (SG) and the deceased group (DG) using Student's t-test (normal distribution) or the Wilcoxon rank-sum test (non-normal distribution). The survival rates of patients with malnutrition, hemodialysis (HD), and according to aspirin or clopidogrel prescription were compared on Kaplan-Meier analysis evaluated with the log-rank test.

The independent association between cerebrovascular and cardiovascular death  $\leq 2$  years after revascularization for CLI and baseline patient characteristics was assessed on Cox proportional hazard analysis, and the results expressed as hazard ratios (HR) and 95% CI.  $P < 0.05$  was considered to indicate statistical significance. Variables with  $P < 0.05$  on univariate analysis were used in the multivariate analysis model. When comparing hs-CRP between patients according to malnutrition status, hs-CRP data are expressed as median (IQR). Statistical analysis was performed using JMP version 11.0 (SAS).

## Results

### Baseline Characteristics

Baseline patient clinical characteristics are listed in **Table 1**. Mean age was  $71 \pm 11$  years and 80 patients (58%) were men. Of 137 patients, 90% had hypertension, 67% had diabetes, and 75% had dyslipidemia, and 48 (35%) received HD.

Twenty-three patients (17%) died from cerebrovascular and cardiovascular events. Of these 23 deaths, 15 were due to ACS and 8 were due to cerebrovascular events. These cerebrovascular events were all ischemic stroke without

Table 1. CLI Patient Characteristics vs. Survival Status				
Variables	Over all (n=137)	Survival group (n=114)	Deceased group (n=23)	P-value
Age (years)	71±11	69±11	76±9	0.008
BMI (kg/m <sup>2</sup> )	22.8 (21.2–25.1)	22.9 (21.5–25.2)	21.7 (19–24.7)	0.048
Sex: male	80 (58)	66 (58)	14 (61)	0.82
Risk factors				
Hypertension	123 (90)	103 (90)	20 (87)	0.70
DM	92 (67)	74 (65)	18 (78)	0.33
Dyslipidemia	103 (75)	88 (77)	15 (65)	0.29
Current smoking	20 (15)	17 (15)	3 (13)	1.00
HD	48 (35)	35 (31)	13 (57)	0.029
History of stroke	16 (12)	12 (11)	4 (17)	0.47
History of MI	23 (17)	17 (15)	6 (26)	0.22
Medication				
Aspirin	90 (66)	71 (62)	19 (83)	0.09
Clopidogrel	68 (50)	63 (55)	5 (22)	0.005
DAPT	43 (31)	40 (35)	3 (13)	0.050
CCB	69 (50)	58 (51)	11 (48)	0.83
ACEI/ARB	73 (53)	65 (57)	8 (35)	0.067
β-blocker	36 (26)	33 (29)	3 (13)	0.131
Statin	123 (90)	102 (89)	21 (91)	0.89
PPI	80 (58)	63 (55)	17 (74)	0.112
GNRI	100.8 (91.5–110.2)	101.9 (93.4–111.3)	94 (84.9–104.9)	0.036
Malnutrition	34 (25)	23 (20)	11 (48)	0.008
WBC (/ $\mu$ L)	6,770 (5,265–8,265)	6,770 (5,265–8,222)	7,230 (5,250–8,890)	0.36
Hb (g/dL)	12.2 (10.6–13.6)	12.3 (10.6–13.6)	11.8 (10.5–13.3)	0.60
hs-CRP (mg/dL)	0.26 (0.09–1.11)	0.25 (0.08–1.00)	0.31 (0.11–3.03)	0.102
LDL-C (mg/dL)	88.5 (71–114.3)	87 (71–115)	87 (71–112)	0.83
HDL-C (mg/dL)	47.7±13.3	45.4±12.3	48.2±13.5	0.23
TG (mg/dL)	117 (83.5–156)	117.5 (81.8–158.8)	109 (89–128)	0.44
Alb (g/dL)	3.9 (3.4–4.2)	3.9 (3.4–4.3)	3.7 (3.4–4.1)	0.095
UA (mg/dL)	5.4±1.6	5.4±1.5	5.5±1.9	0.79
FPG (mg/dL)	113.5 (93–141.5)	111 (92.3–140)	126 (92.3–147.8)	0.46
LVEF (%)	64.5 (53.6–72.2)	64.7 (53.7–73.3)	63.9 (49.4–68)	0.21

Data given as mean±SD, median (IQR) or n (%). Alb, albumin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; CLI, critical limb ischemia; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HD, hemodialysis; hs-CRP, high-sensitivity C-reactive protein; FPG, fasting plasma glucose; GNRI, geriatric nutritional risk index; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PPI, proton pump inhibitor; TG, triglycerides; UA, uric acid; WBC, white blood cell.

cardiogenic embolism. In the ACS group, there was no definite or probable stent thrombosis in the early phase. Stent thrombosis was defined according to Academic Research Consortium criteria.<sup>14</sup> In this ACS group, 13 cases originated from new lesions different from previously treated lesions, and 2 patients had in-stent restenosis. Moreover, 17 ACS patients (12%) had undergone amputation after revascularization in this study.

#### Patient Characteristics According to Survival Status

**Table 1** shows the comparison of patient characteristics between the SG and DG. The DG was older than the SG (76±9 vs. 69±11 years, P=0.008). In the SG, BMI was higher than in the DG (median, 22.9 kg/m<sup>2</sup>; IQR, 21.5–25.2 kg/m<sup>2</sup> vs. median, 21.7 kg/m<sup>2</sup>; IQR, 19–24.7 kg/m<sup>2</sup>; P=0.048). There were no significant differences in hypertension, diabetes mellitus or dyslipidemia between the 2 groups. GNRI in the DG was significantly lower than in the SG (median, 94; IQR, 84.9–104.9 vs. median, 101.9; IQR,

93.4–111.3; P=0.036). Moreover, the rate of complication with malnutrition defined as GNRI <92 was significantly higher in the DG than in the SG (48 vs. 20%, P=0.008).

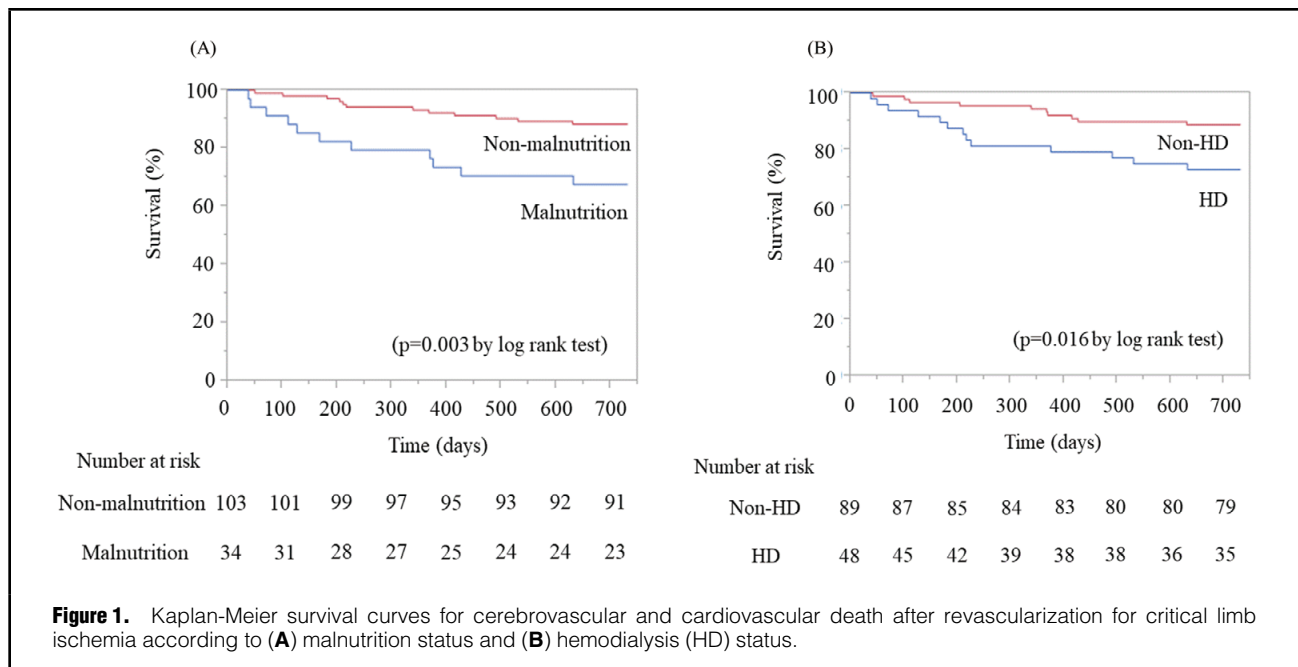
There were no differences in survival rate or amputation rate between endovascular therapy and the combination of endovascular therapy and CABG (82 vs. 86%, P=0.65; 17 vs. 7%, P=0.07, respectively).

#### Influence of Baseline Characteristics

Cox proportional hazard analysis was performed to investigate the association between cerebrovascular and cardiovascular death ≤2 years after revascularization for CLI and baseline patient characteristics (**Table 2**). On univariate analysis, cerebrovascular and cardiovascular death were associated with age (HR, 1.06; 95% CI: 1.02–1.11, P=0.005), HD (HR, 2.66; 95% CI: 1.17–6.22; P=0.020) and malnutrition (HR, 3.21; 95% CI: 1.40–7.34, P=0.007). On multivariate analysis, HD (HR, 2.74; 95% CI: 1.19–6.48, P=0.017) and malnutrition (HR, 2.53; 95% CI: 1.09–5.79,

Table 2. Predictors of Cerebrovascular and Cardiovascular Death <sup>†</sup>				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.06 (1.02–1.11)	0.005	1.05 (1.00–1.10)	0.052
BMI	1.13 (0.99–1.31)	0.079		
Sex (male)	0.88 (0.35–2.18)	0.79		
Hypertension	1.50 (0.39–4.80)	0.52		
DM	1.94 (0.71–6.21)	0.22		
Dyslipidemia	1.81 (0.66–4.65)	0.23		
Current smoking	1.52 (0.46–6.85)	0.53		
HD	2.66 (1.17–6.22)	0.020	2.74 (1.19–6.48)	0.017
CCB	1.10 (0.48–2.52)	0.80		
ACEI/ARB	0.40 (0.15–1.00)	0.056		
$\beta$ -blocker	2.00 (0.74–6.19)	0.21		
Statin	0.51 (0.22–1.16)	0.118		
PPI	0.55 (0.22–1.29)	0.192		
Malnutrition	3.21 (1.40–7.34)	0.007	2.53 (1.09–5.79)	0.031
WBC count	1.00 (1.00–1.01)	0.61		
Hb	1.10 (0.93–1.29)	0.27		
hs-CRP	1.12 (0.85–1.21)	0.057		
LDL-C	1.00 (0.99–1.02)	0.78		
HDL-C	1.00 (0.97–1.03)	0.77		
TG	1.00 (0.99–1.01)	0.37		
Alb	1.82 (0.87–3.83)	0.101		
UA	0.98 (0.73–1.30)	0.88		
FPG	1.00 (0.98–1.06)	0.42		
LVEF	1.03 (0.99–1.06)	0.097		

<sup>†</sup>Cox proportional hazard analysis. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.



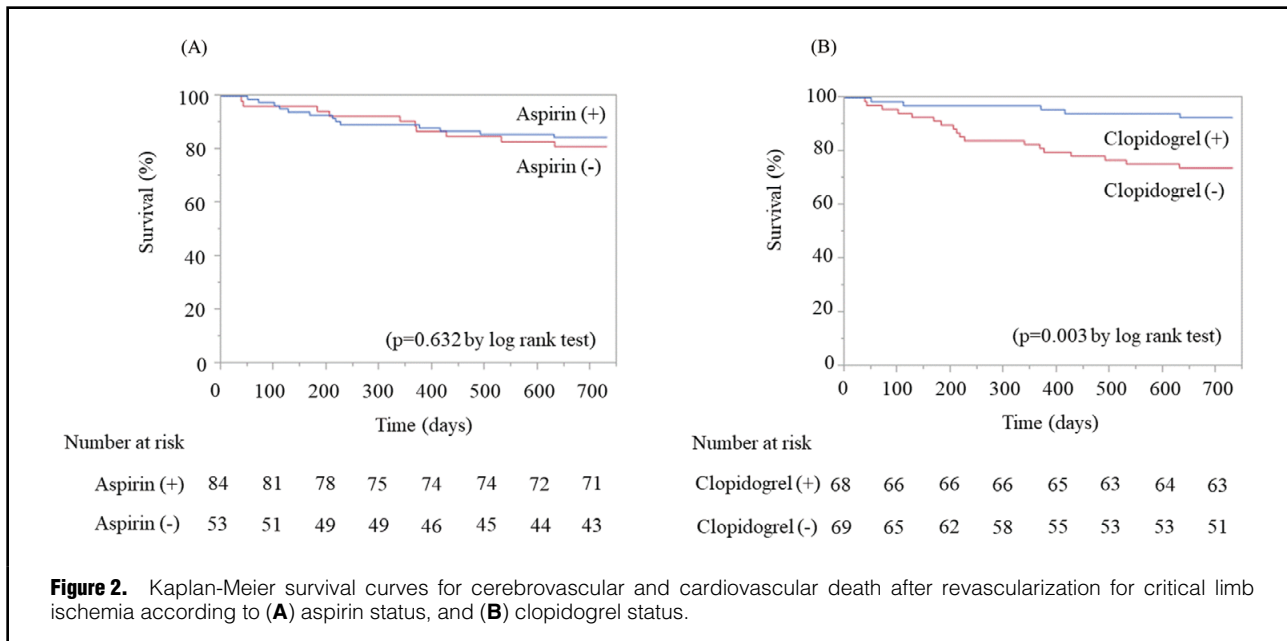
**Figure 1.** Kaplan-Meier survival curves for cerebrovascular and cardiovascular death after revascularization for critical limb ischemia according to (A) malnutrition status and (B) hemodialysis (HD) status.

P=0.031) were significantly associated with cerebrovascular and cardiovascular death. Kaplan-Meier analysis also showed that survival rate was significantly lower in CLI patients with either malnutrition or HD compared with that in patients without either malnutrition or HD, respectively

(Figure 1).

#### Malnutrition and the Association With Inflammation

On multivariate analysis, malnutrition was a significant risk factor for cerebrovascular and cardiovascular death.



**Table 3. HR for Non-Use of Clopidogrel and Incidence of Cerebrovascular and Cardiovascular Death**

	HR (95% CI)	P-value
Unadjusted	3.97 (1.47–10.68)	0.007
Model 1	3.12 (1.13–8.58)	0.028
Model 2	3.06 (1.11–8.41)	0.030
Model 3	3.02 (1.10–8.30)	0.032
Model 4	3.23 (1.18–8.88)	0.023

Model 1, adjusted for age; model 2, adjusted for variables in model 1 plus HD; model 3, adjusted for variables in model 1 plus malnutrition; model 4, adjusted for variables in model 1 plus HD and malnutrition. Abbreviations as in Tables 1,2.

**Table 4. HR for Non-Use of Clopidogrel and Incidence of Cerebrovascular and Cardiovascular Death in the Malnutrition Group**

	HR (95% CI)	P-value
Unadjusted	3.42 (1.38–7.88)	0.010
Model 1	2.32 (1.12–3.52)	0.028

Model 1, adjusted for age. CI, confidence interval; HR, hazard ratio.

Given that malnutrition and inflammation have recently been shown to work together in the development of atherosclerosis,<sup>15</sup> we also investigated the relationship between inflammation assessed on hs-CRP, and malnutrition. In the malnutrition group, hs-CRP was significantly higher than in the non-malnutrition group (non-malnutrition group vs. malnutrition group: median, 0.17mg/dL; IQR, 0.07–0.56 mg/dL vs. median, 2.87 mg/dL; IQR, 0.32–5.89 mg/dL; P<0.001).

**Influence of Baseline Antiplatelet Therapy**

Given that antiplatelet therapy may affect cerebrovascular and cardiovascular death, we further investigated whether aspirin and/or clopidogrel (used as optimal antiplatelet therapy for CAD) were associated with cerebrovascular and cardiovascular death. In the present study, all patients had received antiplatelet therapy with aspirin and/or clopidogrel. Aspirin and clopidogrel were prescribed for 90 (66%) and for 68 patients (50%), respectively. Notably, clopidogrel was less used in the DG than in the SG (22 vs. 55%, P=0.005), whereas the use of aspirin was not significantly different between the 2 groups (83 vs. 62%, P=0.09). Use of dual antiplatelet therapy also was not significantly different between the 2 groups (13 vs. 35%, P=0.050;

**Table 1).** On Kaplan-Meier analysis, the survival rate was significantly lower in patients with non-use of clopidogrel, but use of aspirin was not significantly associated with survival rate (**Figure 2**). On Cox proportional hazard analysis modeling, the non-use of clopidogrel was significantly associated with cerebrovascular and cardiovascular death (**Table 3**). Notably, even in the malnutrition group, the non-use of clopidogrel was correlated with cerebrovascular and cardiovascular death (**Table 4**). Major bleeding events, defined according to Thrombolysis in Myocardial Infarction (TIMI) Risk Score bleeding classification,<sup>16</sup> did not occur during antiplatelet therapy in this study.

**Discussion**

The main findings of this study are as follows: (1) malnutrition, non-use of clopidogrel and HD were independent risk factors for cerebrovascular and cardiovascular death in CLI patients with a past history of CAD; and (2) malnutrition and non-use of clopidogrel further worsened prognosis.

CLI is associated with major adverse cardiac and limb events, including myocardial infarction (MI) and ischemic stroke, and CLI patients are known to have a high mortality due to cardiovascular events. In the present study, cerebrovascular and cardiovascular death comprised 85% of all-cause death. Therefore, it is important to prevent lethal cardiovascular and cerebrovascular events in the manage-

ment of CLI patients.<sup>17</sup>

In recent years, nutritional status has been found to influence overall prognosis. GNRI is universally adopted to evaluate nutritional state and is reported to be beneficial to estimate the prognosis for patients on HD, with chronic heart failure and with CAD.<sup>18,19</sup> Also, GRNI <92 may represent major nutrition-related risk.<sup>13</sup> In the present study, malnutrition, defined as GNRI <92, was an independent risk factor for cerebrovascular and cardiovascular death. Atherosclerosis is a widely accepted inflammatory disease and the concept of malnutrition-inflammation-atherosclerosis syndrome (MIAS) has been recently reported.<sup>15</sup> Given that CLI is the most advanced form of atherosclerosis, we investigated the relationship between inflammation assessed on hs-CRP, malnutrition and prognosis in CLI patients. hs-CRP was significantly higher in the malnutrition group than in the non-malnutrition group. Taken together, this indicates that malnutrition and inflammation might work together to increase the likelihood of cardiovascular events in CLI patients with CAD, leading to worsening of mortality.

HD is an important predictor of mortality, cardiovascular events and major amputation in CLI patients.<sup>20,21</sup> HD patients are also constantly exposed to oxidative stress and chronic inflammation.<sup>22</sup> The present study confirms that HD is an independent risk factor for cerebrovascular and cardiovascular death in CLI patients with CAD. Although GNRI is a predictor of cardiovascular death in patients undergoing HD, evidence that either BMI or serum Alb alone predicts outcome in patients undergoing HD is limited.<sup>23</sup> Given these previous reports and the present data, GNRI is thought to more accurately reflect the nutritional status of CLI patients who undergo HD than BMI and Alb, and is a useful index to predict cerebrovascular and cardiovascular death in CLI patients with CAD.

Antiplatelet therapy is the mainstay of treatment in CAD, ischemic CVD and PAD. Low-dose aspirin was also found to reduce the incidence of vascular events in the Critical Leg Ischemia Prevention Study trial.<sup>24</sup> The first-line antiplatelet therapy in PAD is aspirin despite a paucity of evidence that it reduces cardiovascular events.<sup>25</sup> Conversely, the CAPRIE study demonstrated that clopidogrel is more effective than aspirin in reducing cardiovascular events in PAD.<sup>26</sup> Apart from the beneficial effect of antiplatelet therapy, it has also been reported that the use of antiplatelet agents increases bleeding risk in low body weight and low nutrition patients. Yoshida et al found that low GNRI and hs-CRP were predictors of bleeding risk in patients requiring antiplatelet therapy after PCI.<sup>27</sup> Katsanos et al showed that clopidogrel monotherapy was associated with the most favorable harm-benefit profile without being associated with an increased risk of severe bleeding in PAD patients.<sup>28</sup> Furthermore, a recent study also reported that clopidogrel therapy extended beyond 12 months was associated with decreased risk of all-cause death or non-fatal MI in DM patients after second-generation drug-eluting stent implantation in PCI.<sup>29</sup> These several studies seem to support the present clinical data. Current guidelines give a class IA recommendation for aspirin or clopidogrel as a monotherapy in patients with symptomatic PAD, prior MI or stroke. In the present study, however, use of clopidogrel in CLI patients with CAD was more effective in the prevention of cerebrovascular and cardiovascular death regardless of low nutritional status, and there was no severe bleeding. Therefore,

we believe that clopidogrel should be used early, even in CLI patients with malnutrition and who may be at risk of MIAS.

### Study Limitations

Several limitations of this study must be considered. First, we found an independent association between cerebrovascular/cardiovascular death and malnutrition (which is associated with frailty and sarcopenia). We could not, however, investigate the relationship between other frailty/sarcopenia factors such as muscle strength, and outcome of CLI patients. Second, the effect and the optimal methods of intervention with regard to nutrition status were unclear, even though malnutrition is a risk factor for cerebrovascular and cardiovascular death. Third, this study was retrospective and involved a relatively small number of patients, and we could not analyze all patients who received the procedure due to loss to follow-up.

These data suggest that management of nutrition status is a novel therapeutic target in CLI patients with CAD. In future, we must assess cerebrovascular and cardiovascular death in CLI patients with and without CAD, using a longer time interval after revascularization in a large-scale prospective study.

### Conclusions

Malnutrition, non-use of clopidogrel and HD are risk factors for cerebrovascular and cardiovascular death in CLI patients with CAD. In addition, the non-use of clopidogrel in patients with malnutrition further increased the correlation with cerebrovascular and cardiovascular death.

### Grant Support

This work was supported in part by the Japan Society for the Promotion of Science KAKENHI (Grant No. 16H070890).

### Acknowledgments

We thank the staff of the Department of Cardiovascular Medicine and Hypertension for their assistance with data processing.

### Disclosures

M.O. is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

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