Aim: Originally developed for predicting the risk of stroke in patients with atrial fibrillation (AF), the CHA2DS2-VASc score also has the potential to predict the risk of other cardiovascular disease. This study aimed to investigate the prognostic value of the CHA2DS2-VASc score in patients with peripheral artery disease (PAD) requiring Femoral popliteal (FP) endovascular therapy (EVT).

Methods: This multicenter, retrospective study analyzed the clinical database of 2190 patients who underwent FP EVT for symptomatic PAD (Rutherford categories 2–4) between January 2010 and December 2018. We calculated the CHA2DS2-VASc score and then investigated the association between the score, as well as AF, and their prognosis. Outcome measures were major adverse cardiovascular events (MACEs) and major adverse limb events (MALEs).

Results: During a median follow-up of 3.0 years (interquartile range, 1.5–5.0 years), 532 MACEs and 562 MALEs occurred. The CHA2DS2-VASc score and AF were independently associated with an increased risk of MACEs; their adjusted hazard ratios [95% confidence intervals] were 1.28 [1.20–1.36] (P<0.001) per 1-point increase and 1.49 [1.06–2.09] (P=0.022), respectively. The CHA2DS2-VASc score was almost linearly associated with MACEs, without any clear threshold point. On the other hand, these variables were not associated with MALEs risk (P=0.32 and 0.48).

Conclusion: The CHA2DS2-VASc score and AF were independently associated with the increased risk of MACEs but not of MALEs in patients with symptomatic PAD who underwent FP EVT. The score might be useful in stratifying the MACEs risk in this type of patients.

Key words: Peripheral artery disease, Endovascular therapy, CHA2DS2-VASc score, Atrial fibrillation, Femoral popliteal artery lesion

Introduction

Peripheral artery disease (PAD) is a manifestation of systemic atherosclerotic disease and is one of the most serious global health problems, which have increased in prevalence in the aging society. Revascularization therapy is often required in symptomatic PAD cases refractory to conservative treatment. Advancements in endovascular techniques and devices have allowed more aggressive approaches to the treatment of femoral popliteal (FP) artery disease, with less invasiveness compared to bypass surgery. An increasing number of patients with PAD have now been treated with endovascular therapy.
Atrial fibrillation (AF) and PAD are equally associated with increasing morbidity and mortality\(^6\). These two diseases might be closely related to each other, whereas the causal relationship was not fully understood\(^7, 8\). In addition, the prognostic value of AF after EVT remains unknown.

The CHA\(_2\)DS\(_2\)-VASc score is a risk assessment tool used to predict stroke incidence in patients with AF and as a guide for anticoagulation therapy in clinical practice\(^6\). In this score, PAD is included as a main clinical risk factor\(^9\). The score also has the potential to predict the risk of other cardiovascular disease, especially in patients with cardiac diseases (e.g., coronary artery disease and heart failure)\(^10, 11\). However, its usefulness in patients with PAD remains unknown.

**Aim**

This study aimed to reveal the prognostic value of AF and the CHA\(_2\)DS\(_2\)-VASc score in patients with PAD after EVT for FP artery lesions.

**Methods**

**Study Design**

This retrospective, multicenter study analyzed the clinical database of consecutive symptomatic patients with PAD (Rutherford categories 2, 3, and 4) who underwent EVT for de novo FP (from the superficial femoral artery ostium to the proximal popliteal artery) lesions at five cardiovascular centers in Japan between 2010 and 2018 (University Hospital Medical Information Network Clinical Trial Registry: UMIN-CTR, no. 000045682). During this period, 2249 patients were recorded in the clinical database. However, 59 patients were excluded due to incomplete data; thus, 2190 patients were ultimately analyzed in this study. We calculated the CHA\(_2\)DS\(_2\)-VASc score and investigated the association of the score, as well as AF, with their prognosis. The baseline clinical and lesion characteristics and procedural data were collected from each hospital database. The hospital ethics committees approved the study protocol, and the study was performed in accordance with the Declaration of Helsinki.

**Procedures and Follow-Up**

Dual antiplatelet therapy (DAPT; 100 mg/day of aspirin and 75 mg/day of Clopidogrel) at least 2 days before the procedure was commonly recommended, although individual regimens of antiplatelet and anticoagulant drugs were determined at each physician’s discretion. A 5 or 6 Fr sheath was inserted into the common femoral artery, mostly using a contralateral approach. After 5,000 units of heparin was infused, a 0.035, 0.018, or 0.014 in. guidewire was inserted to cross the lesion. Thereafter, conventional balloon dilation was performed using an appropriately sized angioplasty balloon. The choice of bare metal stent (BMS), drug-eluting stent (DES), covered stent (CS), or drug-coated balloon (DCB) was at the operator’s discretion. Basically, DCB is indicated for cases with optimal dilation (no major flow-limiting dissection or residual stenosis <50%); for suboptimal dilation, stent implantation is commonly applied. The size of stents was approximately 1 mm larger than the vessel diameter. After stenting, post-dilation was routinely performed to achieve better stent expansion and apposition. However, no directional or rotational atherectomy devices were used because they were unavailable in Japan. The use of intravascular ultrasound during EVT was at the discretion of the operators. DAPT was prescribed for at least 1 month after procedures involving conventional balloon angioplasty, BMS implantation, or DCB angioplasty, but package insert instructions recommended continuing DAPT for at least 2 months after DES implantation and at least 6 months after CS implantation.

Follow-ups after discharge were scheduled at 1, 3, and 6 months, and thereafter, every 6 months. The follow-up assessment included clinical symptoms, ankle-brachial index, and duplex ultrasonography scan (DUS) images\(^12\).

**Outcomes and Definitions**

The outcome measures of this study were major adverse cardiovascular events (MACEs) and major adverse limb events (MALEs). MACEs was defined as a composite of all-cause mortality, stroke, and MI, and MALEs was defined as a composite of major amputation and any reintervention (either endovascular or surgical). Nonfatal MI was assessed according to the fourth universal definition of MI\(^13\). Stroke during follow-up was defined as an ischemic or hemorrhagic event necessitating hospitalization with symptoms lasting >24 h. Major amputation was defined as above-ankle amputation. Reintervention was performed for ≥50% stenosis (or >2.4 of peak systolic velocity ratio by DUS) with recurrent clinical symptoms\(^12\). The CHA\(_2\)DS\(_2\)-VASc scoring system assigned 1 point each for congestive heart failure (C), hypertension (H), diabetes mellitus (D), vascular
disease (V), and female sex category (Sc), whereas 2 points each for age $\geq$ 75 years (A) and history of stroke, transit ischemic attack, or thromboembolism (S). The sum of these points indicated the CHA2DS2-VASc score, with a possible range of 0–9 points.\(^6,9\) In the scoring system, congestive heart failure was defined as the signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction ($<40\%)$. Hypertension was defined as resting blood pressure $>140/90$ mmHg on at least two occasions or current antihypertensive treatment. Diabetes mellitus was defined as fasting glucose $>125$ mg/dL (7 mmol/L) or treatment with an oral hypoglycemic agent and/or insulin. Vascular diseases included coronary artery disease and PAD\(^9\), considering that this study included patients who had PAD, the minimum CHA2DS2-VASc score in the current study population was 1 point. AF was identified by an electrocardiogram performed during hospitalization and/or from medical records including past history. The severity of calcification in treated vessels was assessed according to the Peripheral Arterial Calcium Scoring System (PACSS)\(^1\). Meanwhile, below-the-knee runoff was assessed by angiography after the procedure.

### Statistical Analysis

Data are represented as means and standard deviations for continuous variables or as frequencies and percentages for discrete variables, if not otherwise mentioned. Moreover, $P<0.05$ was considered statistically significant, and 95% confidence intervals were reported when appropriate. The association of baseline characteristics, including the CHA2DS2-VASc score and AF, with clinical outcomes was investigated using the Cox proportional hazards regression model. All statistical analyses were performed using the R version 3.6.0 (R Development Core Team, Vienna, Austria).

### Results

The baseline characteristics of the study population are summarized in Table 1. Their mean age was $73 \pm 9$ years, and 14.2% had AF. The mean CHA2DS2-VASc score was $4.6 \pm 1.4$ points (Fig. 1). During a median follow-up of 3.0 years (interquartile range, 1.5–5.0 years), 532 MACEs (431 deaths, 117 strokes, and 57 MIs) and 562 MALEs (553 reinterventions and 24 major amputations) were identified.

Table 2 demonstrates the association of baseline clinical characteristics with the MACEs and MALEs risks. A higher CHA2DS2-VASc score and the presence of AF, as well as earlier year of EVT, lower body mass index, end-stage renal disease, no statin use, PACSS classification grades 2 and 4 (i.e., arterial calcification $\geq 5$ cm), and no below-the-knee runoff, were independently associated with increased MACEs risk. The adjusted hazard ratios of the CHA2DS2-VASc score and AF were 1.28 (1.20–1.36) per 1-point increase ($P<0.001$) and 1.49 (1.06–2.09) ($P=0.022$), respectively. However, the CHA2DS2-VASc score and

| Table 1. Baseline characteristics of the study population |
|-----------------------------------------------|
| Age (years) | $73 \pm 9$ |
| Male sex | 1561 (71.3\%) |
| Current smoking | 816 (37.3\%) |
| Body mass index (kg/m$^2$) | $22.6 \pm 3.4$ |
| Atrial fibrillation | 311 (14.2\%) |
| Hypertension | 1875 (85.6\%) |
| Diabetes mellitus | 1195 (54.6\%) |
| End-stage renal disease | 524 (23.9\%) |
| Coronary artery disease | 1299 (59.3\%) |
| Heart failure | 327 (14.9\%) |
| History of stroke | 436 (19.9\%) |
| Dual antiplatelet therapy | 1904 (86.9\%) |
| Warfarin use | 230 (10.5\%) |
| Reason of administration |
| Atrial fibrillation | 164 (7.5\%) |
| Post prosthetic valve implantation | 19 (0.9\%) |
| Venous thrombosis | 5 (0.2\%) |
| Post coronary artery bypass grafting | 42 (1.9\%) |
| DOAC use | 99 (4.5\%) |
| Reason of administration |
| Atrial fibrillation | 93 (4.2\%) |
| Venous thrombosis | 6 (0.3\%) |
| Statin use | 1097 (50.1\%) |
| Rutherford classification |
| Category 2 | 729 (33.3\%) |
| Category 3 | 1259 (57.5\%) |
| Category 4 | 202 (9.2\%) |
| Ankle-brachial index | $0.64 \pm 0.21$ |
| Iliac revascularization | 551 (25.2\%) |
| Distal reference vessel diameter (mm) | $5.2 \pm 0.9$ |
| Chronic total occlusion | 879 (40.1\%) |
| Lesion length (mm) | $146 \pm 99$ |
| PACSS classification |
| Grade 0 | 787 (35.9\%) |
| Grade 1 | 402 (18.4\%) |
| Grade 2 | 310 (14.2\%) |
| Grade 3 | 228 (10.4\%) |
| Grade 4 | 463 (21.1\%) |
| No below-the-knee runoff | 193 (8.8\%) |
| Bare metal stent use | 1045 (47.7\%) |
| Covered stent use | 112 (5.1\%) |
| Drug-eluting stent use | 205 (9.4\%) |
| Drug-coated balloon | 249 (11.4\%) |

Abbreviations: DOAC, direct oral anticoagulant; PACSS, Peripheral Arterial Calcium Scoring System

Continuous data are presented as mean $\pm$ standard deviation. Categorical data are presented as the number (percentage).
Abbreviations: EVT, endovascular therapy; DOAC, direct oral anticoagulant; MACEs, major adverse cardiovascular events; MALEs, major adverse limb events; PACSS, Peripheral Arterial Calcium Scoring System.

Data represent the hazard ratios [95% confidence intervals] (P values). Adjusted hazard ratios were derived from the multivariate model in which all the variables listed in the table were entered. Asterisks indicate \( P < 0.05 \).
the presence of AF were not associated with the MALEs risk ($P=0.32$ and $P=0.48$, respectively). The MALEs risk increased with end-stage renal disease (adjusted hazard ratio, 1.88 [1.53–2.32]; $P<0.001$), Rutherford classification (1.23 [1.07–1.43]; $P=0.005$), lesion length (1.26 [1.14–1.38] per 100 mm increase; $P<0.001$), and no below-the-knee runoff (1.35 [1.04–1.75]; $P=0.025$), but it decreased with ankle-brachial index (0.94 [0.90–0.98] per 0.1 unit increase; $P=0.002$), reference vessel diameter (0.80 [0.72–0.88] per 1 mm increase; $P<0.001$), BMS use (0.61 [0.49–0.76]; $P<0.001$), CS use (0.31 [0.18–0.53]; $P<0.001$), DES use (0.66 [0.48–0.90]; $P=0.009$), and DCB use (0.53 [0.35–0.82]; $P=0.004$). As illustrated in Fig. 2, the CHA\(_2\)DS\(_2\)-VASc score was almost linearly associated with the MACEs risk, without any clear threshold point. Table 3 presents the association between baseline
characteristics and each component of MACEs and MALEs. The CHA2DS2-VASc score and AF were independently associated with the risk of all-cause mortality but not with that of reintervention.

Discussion

This study demonstrated that the CHA2DS2-VASc score and AF were independently associated with the MACEs risk but were not associated with the MALEs risk in patients with PAD who underwent EVT for FP artery lesions. The association of the CHA2DS2-VASc score with the MACEs risk was almost linear, without any clear threshold.

Meanwhile, AF was independently associated with the MACEs risk after EVT for FP artery lesions. A subgroup analysis of the Reduction of Atherothrombosis for Continued Health (REACH) registry reported that 10% of patients with PAD had AF, with a higher 2-year risk of cardiovascular events than those without AF\textsuperscript{15}. In addition, Moussa Pacha et al. stated that patients who underwent limb revascularization and had AF had worse in-hospital outcomes than those without AF\textsuperscript{16}. In analyzing a longer-term prognosis (a median follow-up of 3.0 years), our study findings were consistent with these previous reports. Meanwhile, AF was not associated with MALEs, of which most were reinterventions. The lack of association was also suggested by the REACH registry, although the registry reported that PAD patients with AF had a higher 2-year risk of amputation (either major or minor) than those without AF\textsuperscript{16}. Moussa Pacha et al. also described that in-hospital major amputation was higher in patients with AF (5.2% vs. 3.9%)\textsuperscript{16}. Their findings were apparently different from ours in which AF was not significantly associated with major amputation. However, the incidence of major amputation in the current study population was relatively low (24 events were observed, and the estimated cumulative incidence rate was 0.6% at 3.0 years). The statistical power would affect the findings. Given that major amputation after FP EVT for PAD other than ischemic tissue loss is currently rare in clinical practice, the difference of the risk would become clinically unimportant.

This study further revealed that a higher CHA2DS2-VASc score was independently associated with the MACEs risk. The relationship was almost linear, with no any clear threshold point. The potential of the CHA2DS2-VASc score for predicting cardiovascular outcomes was suggested by recent studies on patients with coronary artery disease and heart failure\textsuperscript{10, 11}. As histological analyses indicated, patients with PAD are subject to progressive atherosclerosis\textsuperscript{17}. Notably, a clear, linear relationship was observed between the CHA2DS2-VASc score and the MACEs risk even in patients with progressive atherosclerosis. Patients with PAD are consistent and powerful independent predictor of cardiovascular event and mortality. Therefore, estimating their prognosis is clinically important after EVT. Accordingly, some risk prediction tools have been developed\textsuperscript{18, 19}; however, these tools often target a limited population, such as patients with chronic limb-threatening ischemia (CLTI), and focus on outcomes other than MACEs. The CHA2DS2-VASc score is simple and well known and can be easily calculated in clinical practice. The score would serve as a practically useful tool for evaluating the MACEs risk in patients with PAD free from ischemic tissue loss.

Moreover, the score might be clinically useful to identify patients who will benefit the most from intensive treatment against the progression and evolution of atherothrombosis. Although the best medical therapy was recommended in the guideline, especially the data in terms of heart failure in patients with PAD was limited\textsuperscript{2, 20}. Therefore, further results of newer drugs [angiotensin receptor–neprilysin inhibitor (ARNI), inhibitors of sodium–glucose cotransporter 2 (SGLT2)] in patients with PAD are awaited.

AF and the CHA2DS2-VASc score were crudely associated with the risk of each component of MACEs. Although their adjusted association with stroke and MI was not evaluated due to the small number of events, these two variables were found to be independently associated with the risk of all-cause mortality. Patients with a high CHA2DS2-VASc score together with AF might need a more careful monitoring and follow-up due to their high incidence rate of cardiovascular events and all-cause mortality. Meanwhile, the CHA2DS2-VASc score was not associated with the MALEs risk. The score might not reflect limb prognosis after FP EVT. The risk of MALEs was rather increased with the lesion severity, a major risk factor for patency loss after FP EVT\textsuperscript{21}. Moreover, the use of BMS, CS, DES, and DCB was associated with decreased MALEs risk, indicating that these devices might have a key role in reducing the MALEs risk.

Limitations

This study has several limitations. First, this study is a retrospective analysis, despite being a large-scale, multicenter database. Hence, the results would
be affected by relevant biases. Second, patients with CLTI (Rutherford categories 5 and 6) were not included in this study, because the risk stratification tool for the CLTI population has already reported\textsuperscript{18, 19}. Also, this study did not include patients with PAD who underwent bypass surgery and EVT for aortoiliac lesion, whereas the outcomes of these patients may be different from FP artery lesions\textsuperscript{22). Further investigation is needed to confirm the validity of these findings in such patients. Third, patients with undiagnosed AF were categorized as those without AF in the current study. Although the AF prevalence in this study (14.2%) was similar to that in the previous registry\textsuperscript{15}, we did not perform aggressive AF screening in clinical practice; thus, patients that had undiagnosed paroxysmal AF but presented sinus rhythm at EVT might be potentially overlooked. Clinical impact of such silent AF remained unknown.

Fourth, we did not distinguish the clinical phenotypes of AF (i.e., paroxysmal, persistent, and permanent) in this study. Fifth, we did not collect the data on the history of treatment for AF, including whether catheter ablation was performed for AF. Sixth, medication compliance was not monitored. Seventh, we included the cases with anticoagulant therapy according to the package insertion in Japan; therefore, the proportion of anticoagulation therapy was relatively low. This may have affected the outcomes. Although recent clinical trials reported that low-dose rivaroxaban was favorable outcomes than aspirin, the patients with AF required anticoagulant drugs and end-stage renal disease was excluded in these clinical trials\textsuperscript{23, 24). Therefore, further real-world clinical data will be needed. Finally, the proportion of patients on statin administration was relatively low because this data was between 2010 and 2018, although recent guideline was proposed that patients with PAD were considered as a very high cardiovascular risk\textsuperscript{2). These are the research tasks from now on.

Conclusion

The CHA\textsubscript{2}DS\textsubscript{2}-VASc score and AF were independently associated with the MACEs risk but were not associated with the MALEs risk in patients with PAD who underwent EVT for FP artery lesions. The CHA\textsubscript{2}DS\textsubscript{2}-VASc score might be a useful tool to stratify their cardiovascular prognosis.

Acknowledgements

The authors would like to acknowledge the catheterization laboratory medical staff, and thank to Enago (www.enago.jp) for the English language review.

Financial Support

None.

Disclosures

None.

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