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Peripheral Arterial Occlusive Disease – PAOD

CHA_2DS_2-VASc Score and Risk of New-Onset Peripheral Arterial Occlusive Disease in Patients without Atrial Fibrillation

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Background: CHA_2DS_2-VASc score is a useful score to evaluate the risk of stroke in patients with atrial fibrillation (AF), and it has been shown to outperform $CHADS_2$ score. Our recent cross-sectional study showed that CHA_2DS_2-VASc score was associated with an ankle-brachial index < 0.9. The aim of the current study was to evaluate whether CHA_2DS_2-VASc score is a useful predictor of new-onset peripheral artery occlusive disease (PAOD) and whether it can outperform $CHADS_2$ and R_2CHADS_2 scores.

Methods: We used the National Health Insurance Research Database to survey 723750 patients from January 1, 2000 to December 31, 2001. $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc scores were calculated for every patient. Finally, 280176 (score 0), 307209 (score 1), 61093 (score 2), 35594 (score 3), 18956 (score 4), 11032 (score 5), 6006 (score 6), 2696 (score 7), 843 (score 8), and 145 (score 9) patients were studied and followed to evaluate new-onset PAOD. We further divided the study patients into six groups: group 1 (score 0), group 2 (score 1-2), group 3 (score 3-4), group 4 (score 5-6), group 5 (score 7-8), and group 6 (score 9).

Results: Overall, 24775 (3.4%) patients experienced new-onset PAOD during 9.8 years of follow-up. The occurrence rate of PAOD increased from 1.3% (group 1) to 23.4% (group 6). Subgroup analysis by gender also showed an association between CHA_2DS_2-VASc score and the occurrence rate of PAOD. After multivariate analysis, groups 2-6 were significantly associated with new-onset PAOD. CHA_2DS_2-VASc score also outperformed $CHADS_2$ and R_2CHADS_2 scores for predicting new-onset PAOD.

Conclusions: CHA_2DS_2-VASc score was a more powerful predictor of new-onset PAOD than $CHADS_2$ and R_2CHADS_2 scores in patients without AF.

Key Words: $CHADS_2$ score • CHA_2DS_2-VASc score • Peripheral arterial occlusive disease • R_2CHADS_2 score

INTRODUCTION

Peripheral arterial occlusive disease (PAOD) is one of the most common atherosclerotic vascular diseases, and shares similar risk factors to coronary artery disease and cerebrovascular disease.[1,2] Major risk factors for PAOD include advanced age, dyslipidemia, hypertension, diabetes mellitus, and cigarette smoking.[2,3] Furthermore, congestive heart failure, chronic kidney disease, stroke, race, elevated inflammatory markers, and obesity are also associated with the PAOD process.[1-8]

$CHADS_2$ score is a useful scoring system to assess

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the risk of stroke in patients with atrial fibrillation (AF).[9] A significant relationship between $CHADS_2$ score and the annual risk of stroke has been reported in AF patients.[10] In addition, $CHADS_2$ score has also been reported to predict future cardiovascular outcomes in non-AF populations.[11,12] R_2CHADS_2 score is another scoring system which combines $CHADS_2$ score and impaired renal function.[13] Because renal dysfunction is also a predictor of stroke and systemic embolization in patients with nonvalvular AF, Piccini et al. verified R_2CHADS_2 score in the ROCKET AF study and ATRIA study cohorts, and showed that R_2CHADS_2 score exhibited excellent predictive value for future stroke and systemic embolization in AF patients.[13]

Because older age, hypertension, diabetes, congestive heart failure, chronic kidney disease, and stroke are all risk factors for PAOD, our previous study showed that $CHADS_2$ score and R_2CHADS_2 score were significantly associated with an ankle-brachial index (ABI) < 0.9 in non-AF patients.[14,15] In addition, we also performed a nationwide cohort study using data from the National Health Insurance Research Database (NHIRD) and further confirmed the relationship between $CHADS_2$ score and PAOD.[16]

CHA_2DS_2-VASc score has been shown to be more useful than $CHADS_2$ score for predicting future stroke and systemic embolization in AF patients.[17-19] In our recent study, we also found that CHA_2DS_2-VASc score was significantly associated with an ABI < 0.9 in non-AF patients.[20] Hence, the aim of this study was to investigate whether CHA_2DS_2-VASc score is also a powerful predictor of new-onset PAOD in non-AF patients. In addition, we also wanted to further confirm whether CHA_2DS_2-VASc score can outperform $CHADS_2$ score and R_2CHADS_2 score.

METHODS

Data source

We analyzed data from the NHIRD, which is published by the National Health Research Institute in Taiwan. The database contains 1000000 random subjects. The National Health Insurance (NHI) program offers a comprehensive and universal health insurance program to all citizens who have established a registered domicile for at least 4 months in Taiwan. The coverage includes inpatient and outpatient services, physical therapy, preventive health care, and home care. In 2004, 99% of the population of Taiwan were covered by the NHI program. The NHIRD is one of the most complete and also the largest population-based dataset in Taiwan. The patients' privacy is protected because the original identification numbers of the patients are encrypted in the NHIRD. The extremely large sample size in the NHIRD provided a good opportunity to evaluate CHA_2DS_2-VASc score in predicting new-onset PAOD.

Study population

In total, 723750 patients who were aged ≥ 18 years with no past history of PAOD, rheumatic heart disease, or AF were identified in the NHIRD from January 1, 2000 to December 31, 2001.

Calculation of $CHADS_2$ score, R_2CHADS_2 score, and CHA_2DS_2-VASc score

The $CHADS_2$ score was calculated for each patient based on a scoring system in which 2 points were assigned for a history of stroke or transient ischemic attack and 1 point was assigned for age ≥ 75 years, the presence of hypertension, diabetes mellitus, and congestive heart failure.[9,10] The R_2CHADS_2 score was calculated for each patient based on a scoring system in which 2 points were assigned for chronic kidney disease and a history of stroke, and 1 point was assigned for age ≥ 75 years, the presence of hypertension, diabetes mellitus, and congestive heart failure.[13] The modified CHA_2DS_2-VASc score was calculated for each patient based on a point system in which 2 points were assigned for age ≥ 75 years and a history of stroke, and 1 point was assigned for congestive heart failure, hypertension, age between 65 and 74 years, diabetes mellitus, female sex, and vascular disease (coronary artery disease including acute coronary syndrome).

We used the following international classification of disease (ICD) codes: congestive heart failure (ICD-9-CM: 428), hypertension (ICD-9-CM: 401-405), diabetes mellitus (ICD-9-CM: 250), stroke (ICD-9-CM: 430-438), chronic kidney disease (ICD-9-CM: 250.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 447.3, 572.4, 580-588, 642.1, 646.2), coronary artery disease including acute coronary syndrome (ICD-9-CM: 410-414), and PAOD (ICD-9-CM: 250.7, 443, 443.81, 443.9, 785.4, and 444.2). Further-

more, comorbidities including dyslipidemia and chronic obstructive pulmonary disease were also evaluated. The flowchart of the study patients is shown in Figure 1. In this study, 280176 (score 0), 307209 (score 1), 61093 (score 2), 35594 (score 3), 18956 (score 4), 11032 (score 5), 6006 (score 6), 2696 (score 7), 843 (score 8), and 145 (score 9) patients were enrolled. The study patients were further divided into 6 groups: group 1 (score 0), group 2 (score 1-2), group 3 (score 3-4), group 4 (score 5-6), group 5 (score 7-8), and group 6 (score 9). Medications of the patients including aspirin, β-blockers, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), diuretics, and statins were also obtained from the database.

Statistical analysis

Data are presented as the mean and standard deviation for normally distributed continuous variables and proportions for categorical variables. Differences in categorical variables between groups were compared using the chi-square test. Differences in continuous values between groups were compared using the unpaired t test for normally distributed continuous variables and Mann-Whitney rank-sum test for skewed variables. Covariates of risk factors and time to developing PAOD were modeled using Cox regression analysis. ROC curves were used to compare different scores to assess the predictive ability for the risk of PAOD. A higher area under the curve (AUC) was considered to be better. A p value less than 0.05 was considered to be statistically significant. All data processing and statistical analyses were performed with SAS 9.2 software.

RESULTS

Table 1 shows the baseline characteristics of the study population. The mean age of the study population was 42 ± 17 years old. Most of the patients had a CHA_2DS_2-VASc score of 1 (42.4%). During the period from January 2000 to December 2009 with a mean follow-up duration of 9.8 years, 24775 (3.4%) patients experienced new-onset PAOD. The occurrence rates of new-onset PAOD from score 0 to score 9 were 1.32%, 2.36%, 7.35%, 9.78%, 13.50%, 15.09%, 15.55%, 18.47%, 19.22%, and 23.45%, respectively (Figure 2A). In addition, the occurrence rates of new-onset PAOD from group

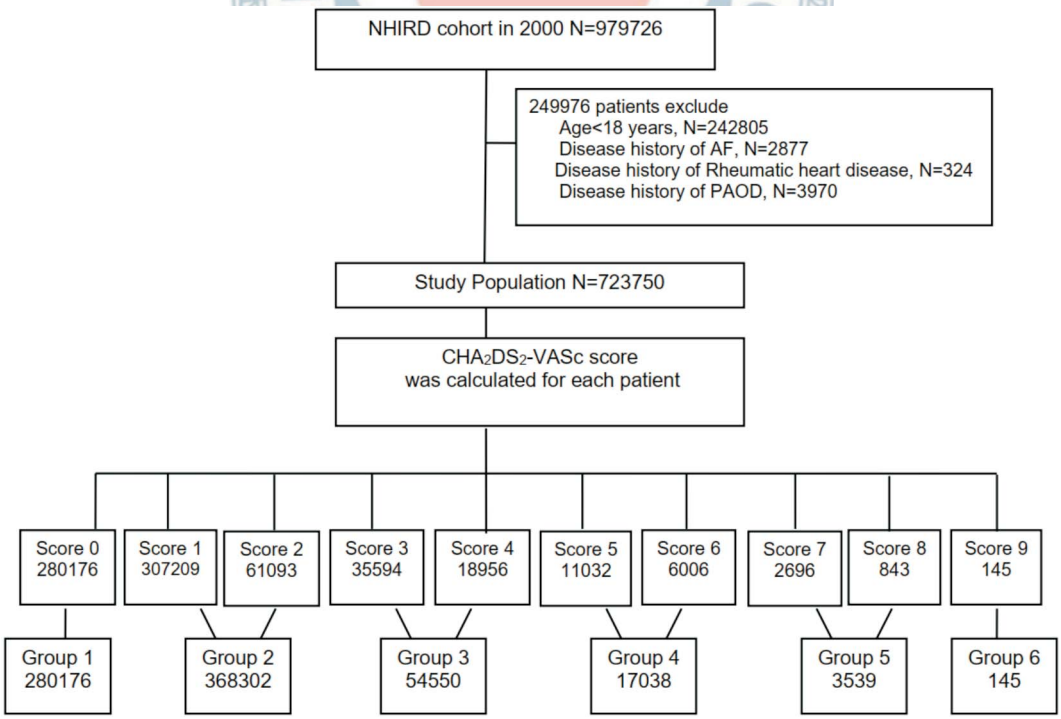

Figure 1. *The flowchart of the study population. AF, atrial fibrillation; NHIRD, National Health Insurance Research Database; PAOD, peripheral arterial occlusive disease.*

Table 1. The baseline characteristics of the study population

Variables	Study population
Age (years)	41.7 ± 16.8
Gender (female)	354327 (49.0%)
Newly-onset PAOD	24775 (3.4%)
Group 1 (score 0)	3709 (15.0%)
Group 2 (score 1-2)	11732 (47.4%)
Group 3 (score 3-4)	6041 (24.4%)
Group 4 (score 5-6)	2599 (10.5%)
Group 5 (score 7-8)	660 (2.7%)
Group 6 (score 9)	34 (0.1%)
Comorbidities	
Hypertension	96382 (13.3%)
Diabetes mellitus	48145 (6.7%)
Dyslipidemia	18366 (2.5%)
Cerebrovascular disease	26086 (3.6%)
Heart failure	10349 (1.4%)
Coronary artery disease	22258 (3.1%)
Chronic kidney disease	14809 (2.1%)
COPD	23964 (3.3%)
Medications	
Aspirin	4614 (0.6%)
β-blocker	26975 (3.7%)
CCB	44103 (6.1%)
ACEI	21460 (3.0%)
ARB	7248 (1.0%)
Diuretic	10208 (1.4%)
Statin	6391 (0.9%)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.

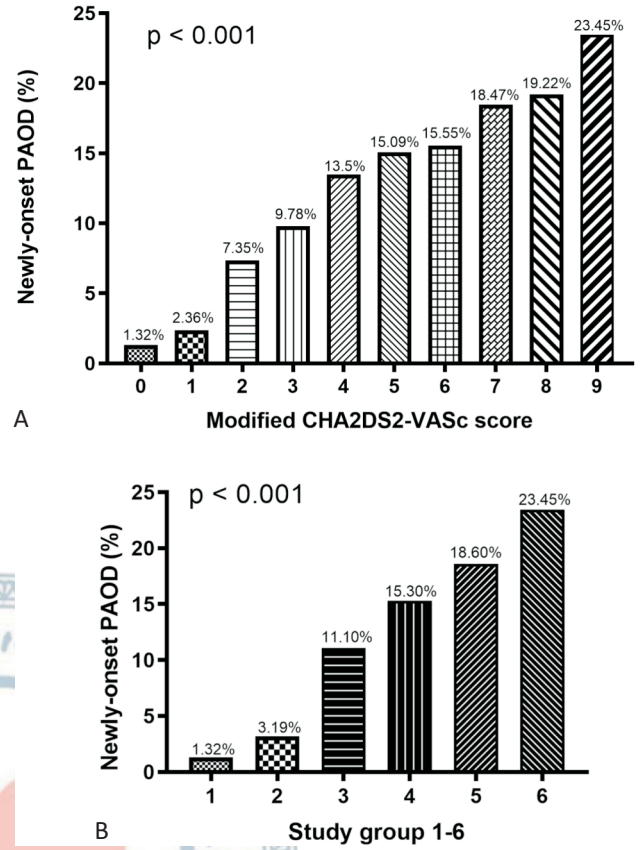

Figure 2. *The occurrence rate of newly-onset peripheral arterial occlusive disease (PAOD) progressively increased from CHA_2DS_2-VASc score 0 to 9 (A) and from study group 1 to group 6 (B).*

1 to group 6 were 1.32%, 3.19%, 11.10%, 15.30%, 18.60%, and 23.45%, respectively (p < 0.001) (Figure 2B). We further performed subgroup analysis by gender to evaluate CHA_2DS_2-VASc score and the occurrence rate of new-onset PAOD. In the male patients, the occurrence rates of new-onset PAOD from group 1 to group 5 were 1.32%, 6.72%, 11.86%, 15.17%, and 18.45%, respectively (p < 0.001) (Figure 3A). In the female patients, the occurrence rates of new-onset PAOD from group 2 to group 6 were 2.46%, 10.65%, 15.30%, 18.71%, and 23.45%, respectively (p < 0.001) (Figure 3B). Due to gender issues, none of the males did had a score of 9 (group 6), and none of the females had a score of 0 (group 1).

Table 2 shows the multivariate Cox regression analysis for the prediction of new-onset PAOD. After adjusting for chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, and medications (aspirin, ACEIs, ARBs, β-blockers, CCBs, diuretics, and statins), chronic kidney disease, dyslipidemia, chronic obstructive pulmonary disease, the use of ACEIs, beta-blockers, CCBs, diuretics and statins, and group 2 to 6 (p < 0.001) were significantly associated with new-onset PAOD.

In addition, we further performed subgroup analysis by gender using Cox regression analysis for the prediction of new-onset PAOD, and the results are shown in Table 3. In the male patients, group 1 (score 0) was regarded as the baseline, and the hazard ratio (HR) showed a gradual increase from group 2 to group 5 (p < 0.001). In the female patients, group 2 (score 1-2) was regarded as the baseline, and the HR showed a gradual increase from group 3 to group 6 (p < 0.001). In both gender subgroups, CHA_2DS_2-VASc score was significantly associated with new-onset PAOD.

The AUCs for $CHADS_2$ score, R_2CHADS_2 score, and CHA_2DS_2-VASc score for the prediction of new-onset

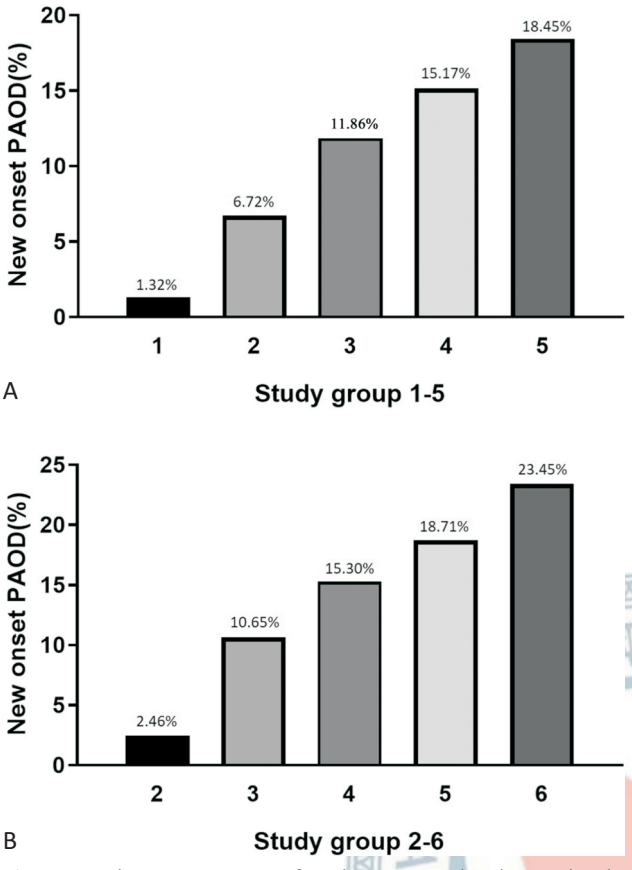

Figure 3. *The occurrence rate of newly-onset peripheral arterial occlusive disease (PAOD) progressively increased from study group 1 to group 5 in male subgroup (A) and from study group 2 to group 6 in female subgroup (B).*

PAOD were 0.709, 0.713, and 0.726, respectively. There were significant differences in the AUC between R_2CHADS_2 score and $CHADS_2$ score, CHA_2DS_2-VASc score and R_2CHADS_2 score, and CHA_2DS_2-VASc score and $CHADS_2$ score (all $p < 0.001$, Table 4).

DISCUSSION

There were three major findings in this nationwide cohort study. First, the occurrence rate of new-onset PAOD progressively increased from the patients with a CHA_2DS_2-VASc score 0 to score 9 and from group 1 to group 6 (1.32% to 23.45%). Second, CHA_2DS_2-VASc score was a useful tool in predicting new-onset PAOD in non-AF patients not only in the whole population but also in subgroup analysis of males and females. Third, CHA_2DS_2-VASc score outperformed $CHADS_2$ score and R_2CHADS_2 score for predicting the risk of new-onset PAOD.

Table 2. Multivariate Cox regression analysis for prediction of newly-onset PAOD

Variable	HR	Lower 95% CI	Upper 95% CI	p value
Chronic kidney disease	1.53	1.30	1.79	< 0.001
Dyslipidema	1.65	1.39	1.96	< 0.001
COPD	1.32	1.15	1.51	< 0.001
Medication				
Aspirin	1.21	0.88	1.66	0.247
ACEI	1.29	1.07	1.55	0.007
ARB	0.91	0.69	1.18	0.463
β-blocker	1.58	1.35	1.86	< 0.001
CCB	1.68	1.44	1.96	< 0.001
Diuretic	1.38	1.13	1.69	0.002
Statin	1.47	1.14	1.91	0.003
Group of CHA_2DS_2-VASc score				
Group 1 (score = 0)	1	-	-	-
Group 2 (score 1-2)	1.89	1.78	2.01	< 0.001
Group 3 (score 3-4)	4.21	3.75	4.72	< 0.001
Group 4 (score 5-6)	5.69	4.77	6.78	< 0.001
Group 5 (score 7-8)	7.61	5.77	10.04	< 0.001
Group 6 (score 9)	8.21	2.61	25.89	< 0.001

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PAOD, peripheral arterial occlusive disease.

Table 3. Cox regression analysis for prediction of newly-onset PAOD in subgroup of male and female

Variable	HR	Lower 95% CI	Upper 95% CI	p value
Group of male				
Group 1 (score = 0)	1	-	-	-
Group 2 (score 1-2)	5.23	5.00	5.46	< 0.001
Group 3 (score 3-4)	9.55	9.06	10.06	< 0.001
Group 4 (score 5-6)	12.64	11.77	13.57	< 0.001
Group 5 (score 7-8)	16.01	13.60	18.85	< 0.001
Group 6 (score 9)	-		-	-
Group of female				
Group 2 (score 1-2)	1	-	-	-
Group 3 (score 3-4)	4.55	4.37	4.73	< 0.001
Group 4 (score 5-6)	6.79	6.44	7.17	< 0.001
Group 5 (score 7-8)	8.58	7.85	9.39	< 0.001
Group 6 (score 9)	11.42	8.15	15.99	< 0.001

CI, confidence interval; HR, hazard ratio; PAOD, peripheral arterial occlusive disease.

Table 4. Comparison of AUC between $CHADS_2$ score, R_2CHADS_2 score, and CHA_2DS_2-VASc score

	Comparison of AUC	p value
CHA_2DS_2-VASc score vs. $CHADS_2$ score	0.726 vs. 0.709	< 0.001
R_2CHADS_2 score vs. $CHADS_2$ score	0.713 vs. 0.709	< 0.001
CHA_2DS_2-VASc score vs. R_2CHADS_2 score	0.726 vs. 0.713	< 0.001

AUC, area under curve.

$CHADS_2$ score, R_2CHADS_2 score, CHA_2DS_2-VASc score and the risk of new-onset PAOD

PAOD is a systemic atherosclerotic process which is associated with high morbidity and mortality, especially in patients with acute limb ischemia or critical limb ischemia.[21-24] Although new medications such as rivaroxaban and advances in endovascular therapy have improved the outcomes of PAOD,[25-27] PAOD is still associated with extremely high rates of morbidity and mortality. Risk factors for PAOD include older age, hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, chronic kidney disease, congestive heart failure, stroke, elevated inflammatory markers, and other vascular bed diseases.[1-8] $CHADS_2$ score is regarded as a useful score to assess the risk of stroke in patients with AF.[9,10] However, some recent studies have extended the usage of $CHADS_2$ score to patients without AF, such as those with coronary artery disease and acute coronary syndrome.[11,12] Because PAOD is also a vascular disease which shares similar risk factors with coronary artery disease, $CHADS_2$-related scores such as $CHADS_2$, R_2CHADS_2 and CHA_2DS_2-VASc score might also be associated with the risk of PAOD. An ABI < 0.9 has been reported to be a reliable diagnostic tool for PAOD, and our previous studies found that these three scores were all associated with an ABI < 0.9.[14,15,20]

In the present study, we found that CHA_2DS_2-VASc score could not only predict the risk of new-onset PAOD in non-AF patients, it also outperformed $CHADS_2$ score and R_2CHADS_2 score for the risk prediction of PAOD. In the modified CHA_2DS_2-VASc score in our study, vascular disease was defined as coronary artery disease including acute coronary syndrome. Because we aimed to predict the future risk of PAOD, we did not include PAOD in the component of vascular disease, which is similar to our previous cross-sectional study.[20]

Another important finding of our study was related to gender. Compared to the men, the women had higher rates of PAOD despite having fewer risk factors for cardiovascular disease. Hiramoto et al. reported that although men and women shared similar risk factors for an ABI ≤ 0.9, women were more likely to have an ABI ≤ 1.0 and ABI ≤ 0.9 compared to men (all p < 0.001).[28] Kumakura et al. also showed sex-related differences in Japanese patients with PAOD. In their study, women more frequently had critical limb ischemia and diabetes mellitus, and below the knee lesions were more severe in women than in men.[29] In Taiwan, Chang et al. also reported that young and middle-aged female patents with diabetic and those on a low income had a tendency to undergo amputation due to PAOD.[30] Our previous nationwide cohort study evaluating $CHADS_2$ score and the risk of new-onset PAOD also showed that female gender was significantly associated with the risk of new-onset PAOD after multivariable analysis.[16] Furthermore, subgroup analysis by gender also showed that CHA_2DS_2-VASc score was significantly associated with new-onset PAOD in the current study.

Our results confirmed that $CHADS_2$ score, R_2CHADS_2 score, and CHA_2DS_2-VASc score were significantly associated with new-onset PAOD. Furthermore, AUC analysis of the three scoring systems showed that CHA_2DS_2-VASc score had a better predictive value than $CHADS_2$ score and R_2CHADS_2 score for the prediction of new-onset PAOD.

Study limitations

There are several limitations to this study. First, personal information such as cigarette smoking, body mass index, and physical activity was not available from the NHIRD, and these factors might be correlated with PAOD. Second, disease misclassification and inadequate diagnostic coding were possible in the NHIRD. The occurrence of PAOD was also based on the diagnostic code registered by the physicians responsible for the treatment of the patients.

CONCLUSION

Our study of patients without AF demonstrated that

CHA_2DS_2-VASc score was independently associated with new-onset PAOD, and that CHA_2DS_2-VASc score outperformed $CHADS_2$ score and R_2CHADS_2 score for predicting the risk of new-onset PAOD. Hence, CHA_2DS_2-VASc score is a more powerful tool in predicting the development of PAOD in non-AF patients.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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