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석사학위논문

Stroke or coronary artery disease prediction from mean platelet volume in patients with diabetes mellitus

조선대학교 대학원

의 학 과

기 영 재

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당뇨병 환자에서 평균 혈소판 부피를 이용한
뇌졸중이나 관상동맥 질환의 예측

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의학과

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이 논문을 의학석사학위신청 논문으로 제출함.

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의학과

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

Abstract

Stroke or coronary artery disease prediction from mean platelet volume in patients with diabetes mellitus

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Background-Platelet size, measured as the mean platelet volume (MPV), is associated with platelet reactivity. MPV has been identified as an independent risk factor for future stroke and myocardial infarction. The aim of this study was to determine the association of MPV with the development of stoke or coronary artery disease (CAD) in diabetes mellitus (DM).

Methods and Results-MPV was analyzed in 200 patients with DM (mean age, 66 years; 50.5% male). The primary endpoint was composite of ischemic stroke /CAD events.

The mean MPV was 7.6±0.8 fL. There were 14 ischemic stroke events and 8 CAD events during a mean of 28.4 months of follow-up. The Kaplan-Meier analysis revealed that the higher tertile MPV group (≥7.9 fL) had a significantly higher stroke/CAD rate compared to the lower tertile MPV group (<7.3 fL) (29.9% vs. 3.9%, log-rank: $P < 0.001$). Higher MPV was an independent predictor of

stroke/CAD risk after adjusting for age, sex, hypertension and hemoglobin A1c (HbA1c) level (hazard ratio: 9.96, 95% CI 2.29-43.33, P = 0.002) in the Cox proportional hazard analysis. When the MPV cut-off level was set to 7.95 fL using the receiver operating characteristic curve, the sensitivity was 91% and the specificity was 80% for differentiating between the group with stroke/CAD and the group without stroke/CAD. This value was more useful in patients with hypertension. Furthermore, DM patients with an MPV over 7.95 fL had high stroke risk without aspirin, especially in the hypertension group (Log-Rank < 0.0001).

Conclusions-The results of this study show that MPV was a predictive marker for stroke/CAD; its predictive power for stroke/CAD was independent of age, gender, hypertension and HbA1c in patients with DM. These findings suggest that antiplatelet therapy with aspirin may be needed in hypertensive patients with a high MPV among patients with DM.

Key words: Mean platelet volume; diabetes mellitus; stroke; coronary artery disease

국 문 초 록

당뇨병 환자에서 평균 혈소판 부피를 이용한 뇌졸중이나 관상동맥 질환의 예측

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배경: 평균 혈소판 부피로 측정된 혈소판 크기는 혈소판의 반응성과 연관성이 있다. 평균 혈소판 부피는 뇌졸중과 심근경색증에 대한 독립적인 위험인자로 알려져 있다. 이 연구의 목적은 당뇨병 환자에서 뇌졸중이나 관상동맥 질환의 발생과 평균 혈소판 부피의 연관성을 알아내고자 한 것이다.

방법과 결과: 평균 혈소판 부피를 당뇨병 환자 200 명의 환자에서 분석하였다. 환자들의 평균 나이는 66 세였고 50.5%가 남성이었다. 일차 연구 종료점은 허혈성 뇌졸중과 관상동맥질환 사건의 복합으로 정하였다.

평균 혈소판 부피의 평균치는 7.6±0.8 fL 이었다. 14 건의 허혈성 뇌졸중 사건과 8 건의 관상동맥 질환 사건이 평균 28.4 개월의 추적 조사 기간 동안 발생하였다. Kaplan-Meier analysis 로 분석하였을 때 7.9 fL 이

상의, 높은 삼분위군에서 7.3 fL 미만으로 낮은 삼분위군과 비교하였을 때 뇌졸중/관상동맥질환의 발생이 유의하게 높았다 (29.9% vs. 3.9%, log-rank: $P < 0.001$). 높은 평균혈소판 부피는 Cox proportional hazard 분석을 이용하여 나이, 성별, 고혈압, 헤모글로빈 A1c 수치로 보정하였을 때 뇌졸중/관상동맥 질환 위험에 대한 독립적인 예측 인자였다 (hazard ratio: 9.96, 95% CI 2.29-43.33, $P = 0.002$). 수신자 조작 특성 곡선을 이용하여 평균혈소판부피의 절단점을 7.95 fL 로 하여 뇌졸중/관상동맥질환이 발생한 군과 발생하지 않은 군을 분별하고자 하였을 때 민감도는 91%, 특이도는 80%였다. 이 절단점은 특히 고혈압이 동반된 환자에서 더 유용하였다. 더욱이 평균혈소판 부피가 7.95 fL 이상인 당뇨병 환자가 아스피린을 복용하지 않은 경우 뇌졸중 발생 위험이 높았는데, 특히 고혈압이 동반된 경우 그러했다 (Log-Rank < 0.0001).

결론: 본 연구의 결론은 평균혈소판부피가 당뇨병 환자에서 뇌졸중/관상동맥질환을 예측하는 표지자인데, 이것은 나이, 성별, 고혈압, 헤모글로빈 A1c 와 독립적인 예측력을 보유한다는 것이다. 이러한 결과는 당뇨병 환자 중 평균 혈소판부피가 높으면서 고혈압이 동반된 환자에서는 아스피린과 같은 항혈소판 치료가 필요하다는 것을 제시하는 결과라고 할 수 있겠다.

Introduction

Morbidity from diabetes mellitus (DM) can result from cardiovascular (CV) disease including stroke, coronary artery disease (CAD), and peripheral arterial disease[1]. The challenge faced by clinicians is to correctly recognize the patient at the highest risk and to develop an overall CV risk diminution plan. The ADA/AHA/ACCF recently provided new recommendations on the use of aspirin in patients with DM[2]. The board recommended the use of low-dose (75-162 mg/day) aspirin for prevention in adults with DM. However, aspirin can cause higher rates of bleeding and gastrointestinal complications[3]. Therefore, individual risk should be considered when clinical decisions are made regarding aspirin in those with DM.

Appropriate selection of candidates for aspirin treatment among patients with DM is a matter of debate. A number of factors promote accelerated atherosclerosis in persons with DM, including endothelial dysfunction, impaired fibrinolysis, augmented platelet aggregation, plaque instability, dysfunctional arterial remodeling, and fibrotic and calcified coronary arteries[4]. Increasing evidence indicates that platelets of DM patients are bigger and hyperreactive, showing increased adhesion and aggregation, with increased platelet-dependent thrombin production[5].

The mean platelet volume (MPV), the most commonly utilized measure of platelet size, is a surrogate indicator of platelet function and a possible connection between inflammation and thrombosis[6]. It can be determined on an inpatient or outpatient basis and is a low-cost examination. Larger platelets are metabolically and enzymatically more active and have greater prothrombotic potential. An increased MPV is related to other markers of platelet activity, including amplified platelet aggregation, increased thromboxane synthesis and β-thromboglobulin release, as well as increased expression of adhesion molecules[7]. Furthermore,

an elevated MPV is observed in patients with DM, hypertension, hypercholesterolemia, inflammatory disorders and obesity[6, 8-11]. In addition, there is evidence that MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or transient ischemic attack[12]. Nevertheless, the association between CV disease and MPV levels in patients with DM has not been determined.

The aim of this study was to determine the association of MPV with the development of stroke or CAD in patients with DM. To our knowledge, this is the first study to investigate the predictive values of MPV for CV disease in patients with DM.

Methods

Study population

A total of 288 consecutive patients with DM who had their MPV determined between October 2007 and December 2007 were enrolled in this study with approval from the Chosun University Hospital Research Ethics Committee (approval 11P-257). Patients followed for less than two months were excluded; 200 patients were thus included. They were followed to evaluate MPV for the prediction of stroke or CAD associated with DM.

Definition of diabetes mellitus

DM was defined if formerly diagnosed or was newly defined by the following criteria: in the presence of classic symptoms if fasting glucose was ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL; in the absence of DM associated symptoms if fasting glucose was ≥ 126 mg/dL on two different days or if non-fasting glucose was ≥ 200 mg/dL on two different days of if glucose values reached ≥ 200 mg/dL 2h after oral glucose tolerance test.

Blood collection and measurement of MPV

Venous blood samples were collected in K_2-EDTA and serum separator blood-drawing tubes (Franklin Lakes, NJ, USA). MPV was analyzed using an Advia 2120 hematology analyzer (Siemens Healthcare Diagnostic GmbH, Eschborn, Germany) within two hours after sample collection. The patients were stratified into tertiles according to their baseline MPV (< 7.3, 7.3-7.9, ≥ 7.9 fL).

Outcomes

Clinical follow-up data were obtained from outpatient records or telephone interviews. The primary end point analyzed was cardiovascular events (CVE), the composite of ischemic stroke or CAD event.

Statistical analysis

Participants were subdivided into tertiles according to their baseline MPV levels. All values are expressed as the mean ± SD/the median (IQR) or as a number (percentages). The baseline characteristics of the groups were compared by one-way ANOVA for continuous variables and by the χ^2 statistic for non-continuous variables.

The CVE-free survival according to MPV tertiles was estimated using the Kaplan-Meier method, and outcomes were compared using the log-rank test. Independent predictors of stroke were calculated using Cox proportional hazards regression. Baseline clinical and biochemical factors with a *P* value < 0.1 were then entered into a forward stepwise multivariate Cox proportional hazards model. Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity with 95% confidence interval (CIs) for the MPV at cut-off values. All statistical analyses were performed using SPSS, Version 15 for Windows (SPSS Inc., Chicago, Illinois, USA), and a *P* value of <0.05 was considered statistically significant.

Results

Clinical Characteristics

The mean MVP for the overall study population was 7.6±1.0 fL (median, 7.6 fL, IQR 7.2-8.0, normal range; 7.2~11.1 fL). The patients were stratified into three groups according to the tertile values of baseline MPV (fL); < 7.3 (51 patients), 7.3 to 7.8 (82 patients), ≥ 7.9 fL (67 patients). Baseline clinical characteristics and biochemical data on the basis of MPV are described in Table 1. The highest tertile of MPV was associated with previous stroke or transient ischemic attack (TIA).

Event-free survival according to MPV tertiles

CVE during the median follow-up of 29.8 months (interquartile range; 16-42.4 months, mean follow-up 28.4±14.5 months) developed in 22 patients (11%): 14 ischemic strokes and 8 CAD events.

The Kaplan-Meier CVE-free survival curves of the patients at the median follow-up, according to the MPV tertiles, are shown in Figure 1. The CVE rates increased significantly in the highest MPV tertile group. Log-rank analysis showed a significant association of the MPV with CVE (29.9% vs. 3.9%, log-rank: $P < 0.001$). The stroke event rates and CAD rates also increased significantly in the highest MPV tertile group (19.4% vs. 2.0%, log-rank: $P < 0.001$; 10.4% vs. 2.0%, $P = 0.005$, respectively).

Independent predictors of CVE

The univariate analysis showed that 10-year risk ≥ 10%, hypertension, dyslipidemia,

previous stroke or TIA history and MPV level (≥ 7.9 fL) were significantly associated with CVE in the cohort. The Cox proportional hazards model included the significant univariate variables. From this model, the variable that remained an independent risk factor of stroke events was the highest tertile of the MPV level (≥ 7.9 fL) (Table. 2).

The cut-off value of MPV for prediction of CVE

The cut-off value for the MPV level predictive of CVE was evaluated by ROC analysis. The ROC analysis indicated a cut-off value of 7.95 fL for the MPV with a 91% sensitivity (95% CI: 70.8-98.9) and 80% specificity (95% CI: 73.1-85.4) (AUC = 0.879, $P < 0.001$) for CVE prediction (Figure 2).

Stratification according to the components of ADA/AHA/ACCF recommendations

The patients were divided into two subgroups according to the component of ADA/AHA/ACCF recommendations[2] (10-year risk of CVD events over 10% or not, hypertension or not, dyslipidemia or not, albuminuria or not), and subgroup analysis was carried out to determine which group was a better predictor of CVE at the MPV cut-off value. Subgroup analyses according to age, smoking, and family history of premature CVD could not be conducted because of the small subgroup in this cohort (overall old population; mean 66 years, smoking 11%, family history of premature CVD 1%). The survival curve analysis revealed a good prediction for CVE at the MPV cut-off value in overall subgroups (data not shown).

To confirm that aspirin is warranted in diabetic patients with high MPV for prevention of CVE/ischemic stroke/CAD, we plotted survival curves of low MPV levels without aspirin, low

MPV level with aspirin, high MPV level without aspirin, and high MPV level with aspirin groups. The high MPV level without aspirin had a worse stroke-free survival trend than the other groups (Figure 3-A); however, aspirin had no significant effects on CVE- and CAD-free survival.

We conducted subgroup analyses according to the component of ADA/AHA/ACCF recommendations[2] (10-year risk of CVD events over 10%, hypertension, dyslipidemia, albuminuria) in the same way to determine the effectiveness of aspirin in preventing ischemic stroke in some subgroups at the MPV cut-off value. The high MPV level without aspirin had worse stroke-free survival in the hypertension subgroup (Figure 3-B). Subgroups of dyslipidemia and 10-year risk over 10% showed worse trends of stroke-free survival in high MPV level without aspirin (Figure 3-C, D, respectively). The albuminuria subgroup demonstrated no significant difference (data not shown).

Discussion

The main finding of the present study was that the MPV level was an independent predictor of CVE in patients with DM. Even after adjustment for 10-year risk over 10%, hypertension, dyslipidemia and previous stroke or TIA history, the hazard ratio was still significant in the high MPV group. Previously, we reported that MPV was a predictive marker for ischemic stroke in patients with atrial fibrillation; its predictive power for stroke was independent of age, gender, and other $CHADS_2$ score components[13]. However, there was no report on the association between MPV levels and stroke or CAD in patients with DM. To our knowledge, this is the first study to investigate the predictive values of MPV as a biomarker for CVE including ischemic stroke and CAD in patients with DM. In addition, if the patients had a high MPV level (cut-off value of 7.95 fL) without low-dose aspirin therapy, they were at risk for ischemic stroke, especially in cases with hypertension, dyslipidemia and 10-year risk over 10%.

MPV increases with storage time in EDTA and the results become increasingly unreliable after four hours[14, 15]. The measurements of MPV in this study were performed within two hours of sampling. Thus, we can exclude the possibility of storage-related errors.

The ADA/AHA/ACCF has provided new recommendations on the use of aspirin in patients with DM[2]. The board recommends the use of low-dose (75-162 mg/day) aspirin for prevention in adults with DM. The components of the risk stratification system mainly used in this recommendation are 10-year risk of CVD events over 10%, and smoking/hypertension/dyslipidemia/family history of premature CVD/albuminuria in men >50 years or women >60 years.

The results of this study suggest that biomarkers such as platelet activity have predictive

value for ischemic stroke or CAD in patients with DM. A high MPV level was an independent predictor of ischemic stroke or CAD events in patients with DM; these findings show the clinical relevance of MPV for risk stratification of stroke or CAD in patients with diabetes, as an additional component to the ADA/AHA/ACCF recommendations for low-dose aspirin use in patients with DM. The findings suggest that aspirin therapy may be needed in patients with high MPV levels, especially in patients with hypertension, dyslipidemia, or 10-year risk over 10%.

As a result, an easy blood examination for MPV is an ideal approach for selecting aspirin treatment for DM patients at risk for ischemic stroke.

Endler et al. reported that mean platelet volume is an independent risk factor for myocardial infarction but not for CAD[16]. Kilicli et al., however, demonstrated that high MPV is an independent risk factor for coronary atherosclerosis and MI[17]. Similarly, in this study, CAD rates increased significantly in the highest MPV tertile group. Even so, aspirin had no significant effects on CAD-free survival in patients with high MPV levels. Although it is unclear why aspirin therapy was not associated with prevention of CAD in patients with high MPV levels in this study, this result may be explained by the small number of myocardial infarction (MI) events in this population; there were only three cases of MI among eight CAD events.

Aspirin cab cause higher rates of bleeding and gastrointestinal complications[3]. Therefore, individual risk is significant in clinical decision-making regarding aspirin in those with DM. Our data can be extrapolated such that the measurement of biochemical markers, such as MPV, may satisfy the unmet need for better selection of unnecessary aspirin therapy in patients with DM.

Limitations

This study was limited by the relatively small sample size. In addition, this investigation was not a prospective study; consequently, the outcomes and conclusions are subject to the limitations inherent in these types of analyses. Because of our original inclusion criteria (patients with DM for whom MPV was measured were included, and patients followed for less than two months were excluded) a selection bias was possible. Moreover, the relatively short follow-up duration was another limitation of this study.

Conclusion

A high MPV level (cut off value > 7.95 fL) was an independent predictor of ischemic stroke or CAD in patients with DM. The results of this study suggest that low dose aspirin therapy may be needed in patients with DM and a high MPV level to prevent ischemic stroke, especially in cases with hypertension, dyslipidemia and 10-year risk over 10%. Further study is needed to confirm these findings.

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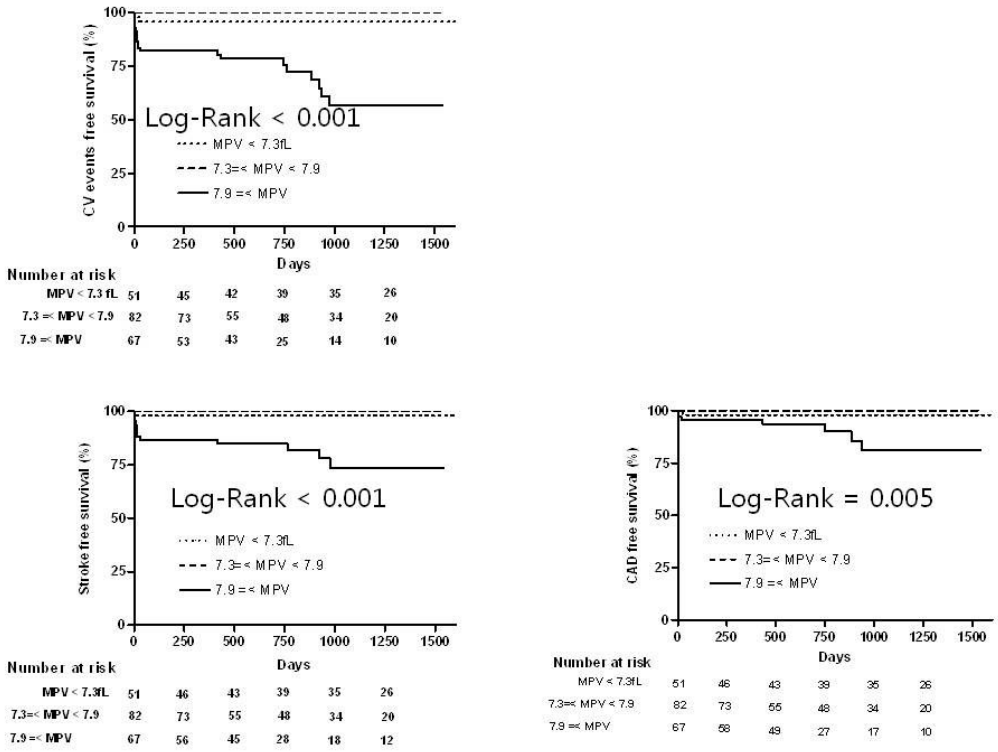

Figure 1. Event- free survival on the basis of MPV tertiles.

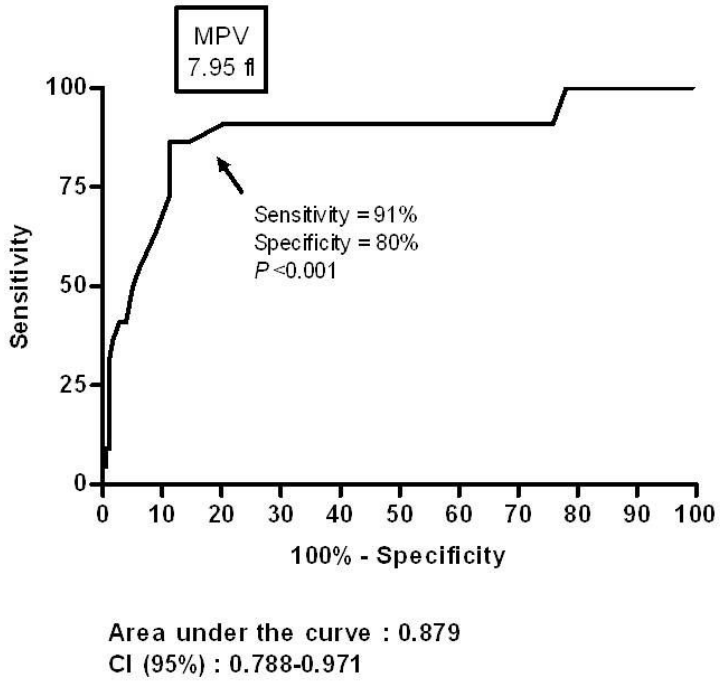

Figure 2. ROC curve of MPV.

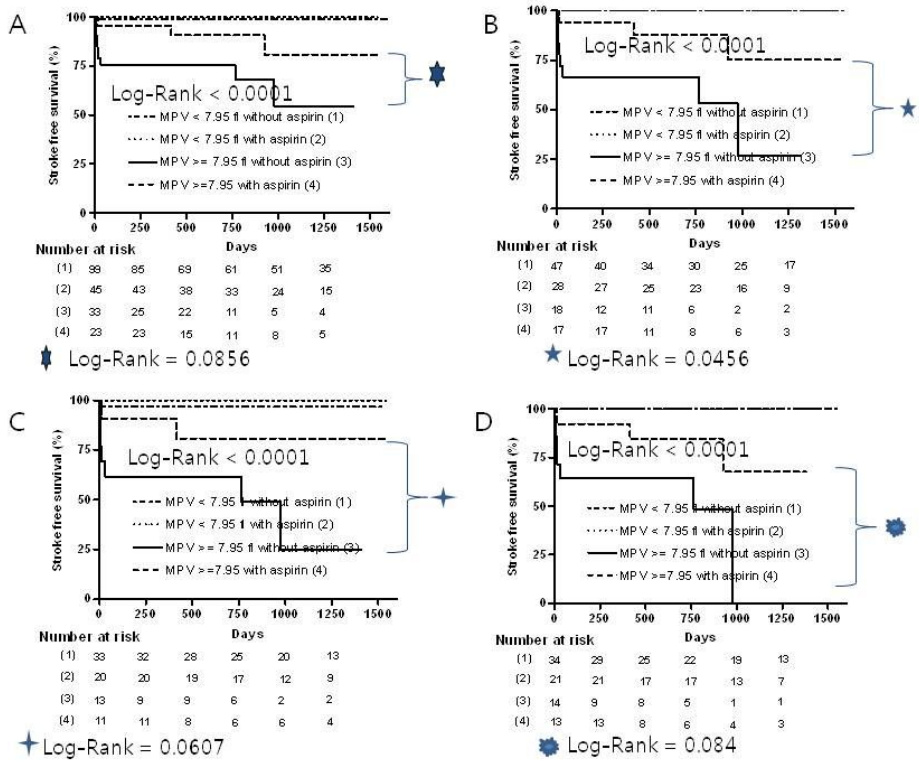

Figure 3. Stroke-free survival of the study groups. Group 1, patients with MPV < 7.95 fL without aspirin; group 2, patients with MPV < 7.95 fL with aspirin; group 3, patients with MPV ≥ 7.95 fL without aspirin; group 4, patients with MPV ≥ 7.95 fL with aspirin. (A. whole population, B. hypertension group, C. dyslipidemia group, D. 10-year risk over 10% group).

Table 1. Baseline characteristics and biochemical data on the basis of MPV

Characteristic	***Total (N=200)***	***MPV < 7.3 fl (N=51)***	***7.3 ≤ MPV < 7.9 (N=82)***	***7.9 ≥ MPV (N=67)***	***P-value***
Age (years)	66.2±9.7	67.3±8.6	64.4±9.8	67.7±10.2	0.091
Male gender (%)	50.5	52.9	48.8	50.7	0.896
Hypertension (%)	55.0	51.0	53.7	59.7	0.609
Dyslipidemia (%)	38.5	33.3	40.2	40.3	0.680
Family history of CVD (%)	1.0	2.0	1.2	0	0.551
Smoking (%)	11.0	11.8	11.0	10.4	0.975
Hemoglobin (g/dL)	13.3±1.9	13.5±1.8	13.3±1.9	13.2±1.9	0.615
Creatinine (mg/dL)	1.15±0.5	1.17±0.7	1.19±0.6	1.09±0.3	0.520
LVEF (%)	64.1±11.3	63.2±12.5	63.8±7.4	64.9±13.6	0.833
Previous stroke or TIA (%)	7.5	5.9	1.2	16.4	0.002
HbA1C (%)	7.84±2.0	7.62±1.7	8.22±2.2	7.54±1.8	0.074
Total-Cholesterol (mg/dL)	177±40.4	168±37.4	180±40.3	180±42.2	0.164
HDL-Cholesterol (mg/dL)	46.4±11.9	47.5±11.5	46.1±11.3	46.0±13.0	0.769
hsCRP (mg/dL)	0.69±1.47	0.60±0.66	0.74±1.60	0.69±1.47	0.898
Albuminuria (%)	24.5	17.6	25.6	28.4	0.389
Aspirin (%)	33	25.5	34.1	37.3	0.384

$P2Y_{12}$ inhibitor (%)	8	11.8	7.3	6	0.494
Dual antiplatelet therapy (%)	4	2	7.3	1.5	0.135
HMG-CoA reductase inhibitor (%)	30	23.5	35.4	28.4	0.328
10 year risk (%)	9.4±7.0	9.5±6.1	8.6±6.9	10.3±7.8	0.356
Follow up duration (median, days)	894 (IQR 480-1271)	1239 (IQR 696-1339)	905 (IQR 378-1219)	687 (IQR 498-1033)	

* 'Smoking' means active smokers as well as ex-smokers, in whom smoking is stopped less than 1 year before enrollment.

LVEF denotes left ventricular ejection fraction; CVD, cardiovascular disease; TIA, transient ischemic attack; HbA1C, hemoglobin A1C; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; MPV, mean platelet volume.

Table 2. Univariate and multivariate Cox proportional hazard analyses determining the significant and independent predictors for stroke, respectively

Factor	Univariate HR (95% CI), P value	Multivariate HR (95% CI), P value
MPV ≥ 7.9 fL	10.97 (2.54-47.45), 0.001	9.01 (2.02-40.16), 0.004
10 year risk ≥ 10%	3.14 (1.28-7.71), 0.012	2.11 (0.80-5.55), 0.130
Hypertension	3.70 (1.25-10.94), 0.018	2.07 (0.65-6.64), 0.222
Dyslipidemia	2.15 (0.92-5.03), 0.079	1.66 (0.68-4.04), 0.264
Previous stroke or TIA history	4.10 (1.51-11.12), 0.006	1.17 (0.42-3.27), 0.764

MPV indicates mean platelet volume; TIA, transient ischemic attack. Reference group was as follows: MPV < 7.3 fL, 10 year risk < 10%.

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