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Stroke or left atrial thrombus prediction using antithrombin III and mean platelet volume in patients with non-valvular atrial fibrillation

조선대학교 대학원

의 학 과

최 서 원

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비판막성 심방세동 환자에서 안티트롬빈 Ⅲ와 평균 혈소판 부피를 이용한 뇌졸중 또는 좌심방 혈전 예측

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조선대학교 대학원

의학과

최 서 원

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지도교수 최 동 현

이 논문을 의학박사학위신청 논문으로 제출함.

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최 서 원

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위원장	조선대학교	교수	김동민	(인)
위 원	조선대학교	교수	김동훈	(인)
위 원	조선대학교	교수	신병철	(인)
위 원	조선대학교	교수	김원장	(인)
위 원	조선대학교	교수	최동현	(인)

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조선대학교 대학원

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Abstract

Stroke or left atrial thrombus prediction using antithrombin III and mean platelet volume in patients with non-valvular atrial fibrillation

Seo-Won Choi
Advisor: Prof. Dong-Hyun Choi, M.D.
Department of Medicine,
Graduate School Chosun University

Background- The aim of this study was to determine the association of antithrombin III (AT-III) deficiency and mean platelet volume (MPV) with the development of stoke or left atrial (LA) thrombus in patients with atrial fibrillation (AF). without clinically apparent CHD.

Methods and Results- AT-III and MPV were analyzed in 352 patients with AF. The primary endpoint was a composite of ischemic stroke event and incidental LA thrombus.

There were 50 events (14.2%; 32 ischemic stroke events and 16 incident LA thrombus, 2 patients had both events) during a mean of 35.4 months of follow up. Kaplan-Meier analysis revealed a significantly higher stroke or LA thrombus rate in low AT-III group (<70%) compared to the high AT-III group (≥70%). When the MPV cut-off level was set to 7.0 fL using the receiver operating characteristic

curve, the sensitivity was 84.0% and the specificity was 59.5% for differentiating between the group with stroke or LA thrombus and the group without stroke or LA thrombus. A significantly higher stroke or LA thrombus rate was observed in the high MPV group (≥7.0 fL) compared to the low MPV group (<7.0 fL). This value was more useful in patients with a high AT-III level. Furthermore, AF patients with an MPV over 7.0 fL and AT-III deficiency had higher stroke or LA thrombus risk than those with low MPV and high AT-III level. In the Cox proportional hazard analysis, high MPV was found to be independent predictor of stroke or LA thrombus risk (hazard ratio, 6.408; 95% confidence interval, 2.874-14.286). Although AT-III deficiency was not independent predictor of stroke or LA thrombus risk, a trend was observed.

Conclusions- The results of this study demonstrate that the high MPV and AT-III deficiency were predictive markers for stroke or LA thrombus; its predictive power for stroke was independent of antiplatelet treatment, anticoagulation therapy and high CHA_2DS_2-VASc score in patients with AF.

Key words: Antithrombin III; Mean platelet volume; Atrial fibrillation; Stroke; Left atrial thrombus

국 문 초 록

비판막성 심방세동 환자에서 안티트롬빈 Ⅲ와 평균 혈소판 부피를 이용한 뇌졸중 또는 좌심방 혈전 예측

최 서 원
지 도 교 수: 최 동 현
조선대학교대학원 의학과

배경: 안티트롬빈 III 의 결핍과 평균 혈소판 부피는 비판막성 심방세동 환자에서 허혈성 뇌졸중과 좌심방 혈전의 발생과 연관성이 있는 것으로 사료된다. 이 연구의 목적은 비판막성 심방세동 환자에서 뇌졸중이나 좌심방 혈전 발생과 안티트롬빈 III 결핍증과 평균 혈소판 부피와의 연관성을 규명하는 것이다.

방법과 결과: 비판막성 심방세동 환자 352 명의 환자에서 안티트롬빈 III와 평균 혈소판 부피의 측정치를 분석하였다. 일차 종료점은 허혈성 뇌졸중과 좌심방 혈전증 발생의 복합으로 정하였다. 35.4 개월의 평균 추적

기간 동안 50 명 (14.2%; 32 명의 허혈성 뇌졸중 사고와 16 명의 좌심방 혈전증, 이 중 2 명에서는 허혈성 뇌졸중 사고와 좌심방 혈전증 모두 발생)의 환자에서 일차 종료점 사건이 발생하였다. 카플란-메이어 분석을 통해 분석하였을 때 안티트롬빈 III 가 70% 이상으로 높은 군에 비애 낮은 환자군에서 유의하게 높은 뇌줄중이나 좌심방 혈전 발생률을 관찰할 수 있었다. 수신자 조작 특성 곡선을 이용하여 결정한 평균 혈소판 부피의 절단값을 7.0fL 로 하였을 때 민감도 84.0%와 특이도 59.5%로 뇌졸중이나 좌심방 혈전 발생군과 비발생군 사이의 차이를 둘 수 있었고 평균 혈소판 부피가 낮은 군에 비해 높은 높은 군에서 유의하게 높은 뇌졸중이나 좌심방 혈전 발생률을 보였다. 이 값은 안티트롬빈 III 가 높은 군에서 더 유용하게 작용하였다. 높은 평균 혈소판 부피와 안티트롬빈 III 결핍을 동시에 만족하는 환자군에서 이러한 위험도가 더욱 증가되는 것 또한 관찰할 수 있었다. 다변수 비례 위험 분석을 시행하였을 때 높은 평균 혈소판 부피가 뇌졸중이나 좌심방 혈전 위험을 예측하는 독립 예측 인자였다 (위험도 6.408; 95% 신뢰 구간, 2.874-14.286). 안티트롬빈 III 결핍은 통계적으로 유의한 독립 위험 인자가 아니었지만 예측 경향성을 보였다.

결론: 본 연구의 결론은 비판막성 심방세동 환자들에서 높은 평균 혈소판 부피와 안티트롬빈 결핍은 뇌졸중이나 좌심방 혈전에 대한 독립 예측

인자이고 이러한 예측력은 항혈소판제, 항응고 치료에 독립적인 예측 인자라는 것이다.

Introduction

Atrial fibrillation (AF) is the most common main arrhythmia in clinical practice; it is associated with substantial morbidity and mortality from stroke events.[1-3] At the present time, the risk for stroke and the indication for anticoagulant therapy in AF can be estimated by $CHADS_2$ and CHA_2DS_2-VASc score.[4] Left atrial (LA) thrombus is a risk factor for stroke in patients with AF; it is estimated that at least 2 third of stroke in patients with nonvalvular AF occur due to LA thrombus drop-off.[5]

The mean platelet volume (MPV), the most frequently used measure of platelet size, is a surrogate marker of platelet function and a potential linkage between thrombosis and inflammation.[6] It can be measured in an inpatient or outpatient situation and is a low-cost examination. Bigger platelets are metabolically and enzymatically further active and have greater prothrombotic potential. In addition, there are evidences demonstrating that MPV is an independent predictor of the risk of stroke among individuals with a history of stroke or TIA and with AF.[7, 8]

Antithrombin-III (AT-III) is a naturally occurring anticoagulant protein that play an key role in the control of thrombus development and spread.[9] AT-III is produced by the endothelium of blood vessels and in the liver, which have linking sites for heparin and thrombin. Once thrombin is produced, which is linked with AT-III and forms thrombin-antithrombin III complex, it impedes the thrombosis.[10] AT-III deficiency is associated with hypercoagulability, causing

deep vein thrombosis and pulmonary embolism.[11] However, the association of AT-III deficiency and MPV with the development of ischemic stroke event and incidental LA thrombus in patients with AF has not been investigated.

The aim of this study was to determine the association of AT-III deficiency and MPV with the development of ischemic stroke event and incidental LA thrombus in patients with AF.

Methods

Subjects

A total of 352 consecutive patients with AF who underwent measurement of AT-III activity and MPV between September 2009 and October 2014 were included in this study. This study was approved by the Chosun University Hospital Research Ethics Committee (CHOSUN 2014-09-011). The primary endpoint was a composite of ischemic stroke event and incidental LA thrombus.

Blood collection and measurement of biomarkers

Venous blood samples were collected in K2-EDTA tubes (Becton Dickinson, Franklin Lakes, NJ, USA). MPV value was analyzed using an Advia 2120 hematology analyzer (Siemens Healthcare Diagnostic GmbH, Eschborn, Germany) within two hours after sample collection. AT-III activity was measured with the HemosIL Liquid Antithrombin kit (Instrumentation Laboratory, Bedford, MA, USA). According to manufacturer recommendations, normal AT-III activities are 83-128%. Because the risk of a certain kind of hypercoagulability disorder, like venous thromboembolism (VTE), is generally documented in patients with AT-III levels < 70%,[12] we stratified our study population on the basis of AT-III levels as follows: low AT-III group (<70%) and high AT-III group (≥70%).

Calculation of CHA_2DS_2-VASc score

We evaluated the CHA_2DS_2-VASc score which was calculated as follows: 2 points were assigned for a history of stroke or transient ischemic attack (TIA), or age ≥ 75 years; and 1 point was assigned for age 65-74 years, history of hypertension, diabetes mellitus, recent cardiac failure, vascular disease, and female sex.[4] The patient was considered as having diabetes if it was reported by a physician (or fasting blood glucose ≥ 126 or use of antidiabetic medication). Hypertension was determined according to the following conditions: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. The presence of heart failure and history of stroke/TIA was determined from the patients' medical records.

Detection of LA thrombus

Incidental LA thrombus was defined as a circumscribed homogeneous mass with a non-myocardial texture, which was detected by transesophageal echocardiography (TEE) or multidetector computed tomography (MDCT). TEE was performed with an iE33 system with a multiplane 5MHz probe (Philips Medical Systems, Bothell, WA, USA) or a VIVID E9 echocardiography system (GE Medical Systems, Horten, Norway). In CT, LA thrombus is seen a well circumscribed nodule with irregular margin and not enhanced. 16-(Sensation 16, Siemens Medical Systems, Erlangen, Germany), 128-(Ingenuity CT, Philips Healthcare, Best, The Netherlands), and 640-slice CT (Aquilion One, Toshiba Medical Systems Corporation, Japan)

scanners were used for detecting LA thrombus.

Outcomes

Clinical follow-up data were gotten from outpatient medical records or telephone interviews. The primary endpoint analyzed was a composite of ischemic stroke event and incidental LA thrombus.

Statistical analysis

All values are expressed as the mean ± SD/the median (IQR) or as a number (percentages). The baseline characteristics of the groups were compared using the Student's t-test for continuous variables and the χ^2 statistic for non-continuous variables.

The primary endpoint free survival according to AT-III and MPV was estimated using the Kaplan-Meier method, and outcomes were compared using the log-rank test. Cox proportional hazards regression was used for calculation of independent predictors of the primary endpoint. We entered into a forward stepwise multivariate Cox proportional hazards model aspirin therapy, warfarin therapy, CHA_2DS_2-VASc score, AT-III, and MPV. Receiver operating characteristic (ROC) analysis was performed for determination of sensitivity and specificity with 95% confidence interval (CIs) for the MPV at cutoff values. SPSS 12.0 (SPSS Inc., Chicago, Illinois, USA) was used to perform all statistical analyses and a *P* value of <0.05 was considered statistically significant.

Results

The cut-off value of MPV for the primary endpoint

The median MPV for the overall study population was 7.0 fL (IQR 6.6-7.6, normal range; 7.2~11.1 fL). The cut-off value for the MPV level predictive of the primary endpoint was evaluated by ROC analysis. When the MPV cut-off level was set to 7.0 fL using the ROC curve, the sensitivity was 84.0% (95% CI: 70.9-92.8) and the specificity was 59.5% (95% CI: 53.7-65.1) for differentiating between the group with the primary endpoint and the group without the primary endpoint (AUC = 0.800, $P < 0.001$) (Figure 1).

Clinical Characteristics

The mean MVP and AT-III activity for the overall study population were 7.3±1.1 fL (median, 7.0 fL, IQR 6.6-7.6, normal range; 7.2~11.1 fL) and 88.7±17.4 % (median 91.0%, IQR 78.3-101.0, normal range; >80%), respectively. Baseline clinical characteristics according to the cut-off value for the MPV are shown in Table 1. Overall clinical characteristics were generally comparable between the two groups except AT-III activity. CHA_2DS_2-VASc score was also similar between the two groups.

The majority of patients used more than one antithrombotic agent. Aspirin was the most frequently prescribed antithrombotic agent, followed by warfarin and clopidogrel.

Correlation between MPV and AT-III activities

There was a weak and negative correlation between MPV and AT-III activity (r = -0.135, *P* = 0.011). The mean AT-III activity was lower in participants with high MPV (87.0 vs. 90.7%, *P* = 0.045) than in those with low MPV. The mean MPV tended to be higher in participants with lower AT-III activity (7.52 vs. 7.21, *P* = 0.055) than in those with higher AT-III activity.

The primary endpoint-free survival according to AT-III activity

During the mean follow-up period of 35.4 months, 50 patients (14.2%) experienced the primary endpoint (32 ischemic stroke events and 16 incident LA thrombus, 2 patients had both events).

The Kaplan-Meier the primary endpoint-free survival curves of the patients according to AT-III activity are shown in Figure 2-A; < 70% (46 patients) and ≥ 70 % (306 patients). The primary endpoint rates showed a significant increase in the low AT-III activity group. Log-rank analysis showed a significant association of the low AT-III activity with the primary endpoint (23.9% vs. 12.7%, log-rank: *P* = 0.0287).

The primary endpoint-free survival according to MPV

The patients were stratified into two groups according to the cut-off values of baseline MPV (fL); < 7.0 (168 patients) and ≥ 7.0 fL (184 patients).

The Kaplan-Meier primary endpoint-free survival curves of the patients according to MPV are shown in Figure 2-B. The primary endpoint rates showed a significant increase in the high MPV group. Log-rank analysis showed a significant association of MPV with the primary endpoint (23.4% vs. 4.2%, log-rank: $P < 0.0001$). This value was more useful in patients with a high AT-III level (Figure 3).

Independent predictors of the primary endpoint

In multivariable analysis, after adjustment for aspirin therapy, warfarin therapy, CHA_2DS_2-VASc score, AT-III, and MPV, MPV was an independent risk factor of the primary endpoint (hazard ratio, 6.41; 95% confidence interval, 2.87-14.29; $P < 0.0001$; table 2). Even though low AT-III activity was not a significant independent risk factor of the primary endpoint, it showed a trend towards an increased risk for the primary endpoint (hazard ratio, 1.84; 95% confidence interval, 0.93-3.65; $P = 0.078$; table 2).

Combined effect of AT-III and MPV on primary endpoint

A combined analysis of primary endpoint according to both AT-III and MPV using the Kaplan-Meier event-free survival curve is shown in Figure 4, which demonstrated an exaggerated primary endpoint risk in the combined low AT-III activity and high MPV group.

Discussion

The main findings of the current observational study were that the high MPV and AT-III deficiency were predictive markers for stroke or LA thrombus in patients with AF, and its predictive power for these events was independent of antiplatelet treatment, anticoagulation therapy and high CHA_2DS_2-VASc score. Although AT-III deficiency is a modest predictor of stroke or LA thrombus, it might help to stratify the risk of these events in patients with AF. In our analysis, this relationship between MPV and the primary endpoint appeared to be more obvious in patients in the high AT-III group. Furthermore, stroke or LA thrombus risk was exaggerated in AF patients with an MPV over 7.0 fL and AT-III deficiency compared to those with low MPV and high AT-III level.

Many studies have reported on the association between MPV levels and stroke [7, 13-16] or LA stasis [17], especially in patients with AF.[8, 18-21] Moreover, some investigations have demonstrated the controversial relationship between AT-III and stroke.[22, 23] However, the association of AT-III deficiency and MPV with the development of ischemic stroke event and incidental LA thrombus in patients with AF has not been investigated. To the best of our knowledge, this is the first study to investigate the long-term (mean follow-up period of 3 years, with a maximum of 5.9 years) impact of AT-III deficiency and MPV level on the occurrence of stroke or LA thrombus in patients with AF.

Even though the prevalence of AT-III deficiency is 0.02 to 0.17% in the healthy population and 1.1% in patients with VTE [24, 25], AT-III deficiency has

been recognized as important thrombophilic conditions and is an established risk factor mainly for VTE.[26-30] In fact, there were no precise data about prevalence of AT-III deficiency in patients with AF. In this cohort, however, the prevalence of AT-III deficiency in patients with AF could be estimated that it would be somewhat high (13.1%). This finding needs to be validated by further studies.

Our data have some significant clinical implications in several important aspects. Systemic thromboembolism is a serious problem in patients with AF.[31] Over the preceding several years, numerous forms of risk stratification methods, such as the $CHADS_2$ and CHA_2DS_2-VASc scores have been settled for predicting the risk of embolic events in AF patients.[4, 32] However, in several studies, the $CHADS_2$ and CHA_2DS_2-VASc scores showed just a moderate discrimination ability to predict thromboembolic complications.[3, 33, 34] Actually, CHA_2DS_2-VASc is not an independent risk factor of ischemic stroke or LA thrombus in this study. In addition, 16 patients with low CHA_2DS_2-VASc scores had ischemic stroke or incidental LA thrombus during follow up in this study. The risk of ischemic stroke and LA thrombus in patients with low CHA_2DS_2-VASc scores should not be underestimated. In the present investigation, MPV and AT-III were independently predictive of ischemic stroke or incidental LA thrombus in multivariate analysis after adjusting for the CHA_2DS_2-VASc scores. It seemed that high MPV level and AT-III deficiency could potentially improve CHA_2DS_2-VASc scores in predicting ischemic stroke or LA thrombus.

The gold and traditional standard for ruling out an LA thrombus is TEE, but

this is somewhat invasive study and there are several contraindications for this technique, such as esophageal bleeding or recent surgery.[35] Hence, an alternative examination procedure for detecting the LA thrombus is required. MDCT is a potential alternative for the assessment of LA thrombus because appropriate temporal and spatial resolution can be attained with this method.[36-40] In addition, MDCT is a non-invasive invasive modality and can be applied to head area for diagnosing stroke with extended scan range. In most of other studies evaluating LA thrombus, TEE has been used for detecting LA thrombus.[17, 41-43] In this cohort, however, MDCT was used for detecting LA thrombus around 60% of patents. This is another unique aspect of our investigation.

Limitations

Current investigation has some limitations, commonly stemming from its relatively small sample size. In addition, this study was not a prospective study, and the results and conclusions are subject to the limitations inherent in these forms of investigations. Due to our original inclusion criteria (patients with AF who were all measured for MPV and AT-III activity), a selection bias was possible. This cohort has small number of patients with AT-III deficiency. However, the prevalence of AT-III deficiency is very low. In light of this, it can be considered relatively high proportion of patients with AT-III deficiency in this study population.

Conclusion

In conclusion, the results of this study demonstrate that the high MPV and AT-III deficiency were predictive markers for stroke or LA thrombus; its predictive power for stroke was independent of antiplatelet treatment, anticoagulation therapy and high CHA_2DS_2-VASc score in patients with AF. It seemed that high MPV level and AT-III deficiency could potentially improve the ability of CHA_2DS_2-VASc scores in predicting ischemic stroke or LA thrombus.

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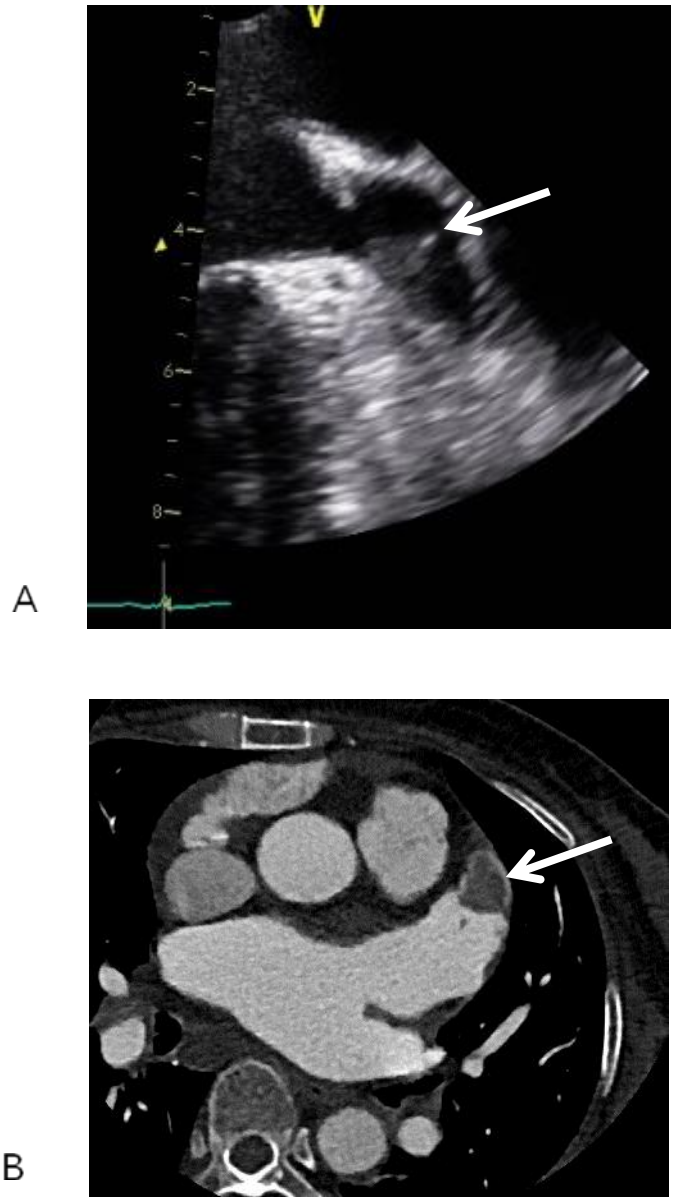


Figure 1. (A) 51-year-old man with left atrial appendage (LAA) thrombus (arrow) detected by transesophageal echocardiography. (B) 63-year-old woman with LAA thrombus; thoracic axial scan of MDCT shows a well demarcated thrombus without enhancement within tip of LAA (arrow).

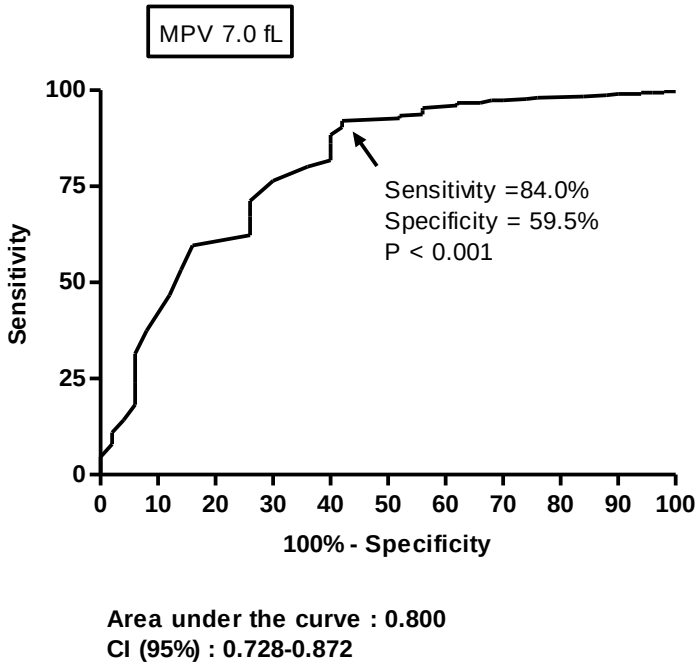
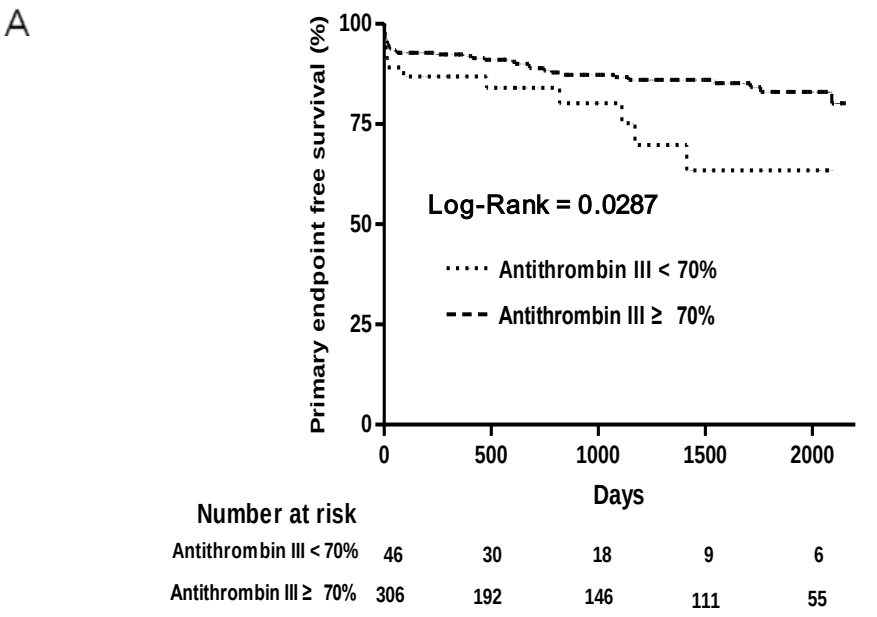


Figure 2. Receiver operating characteristic curve of mean platelet volume



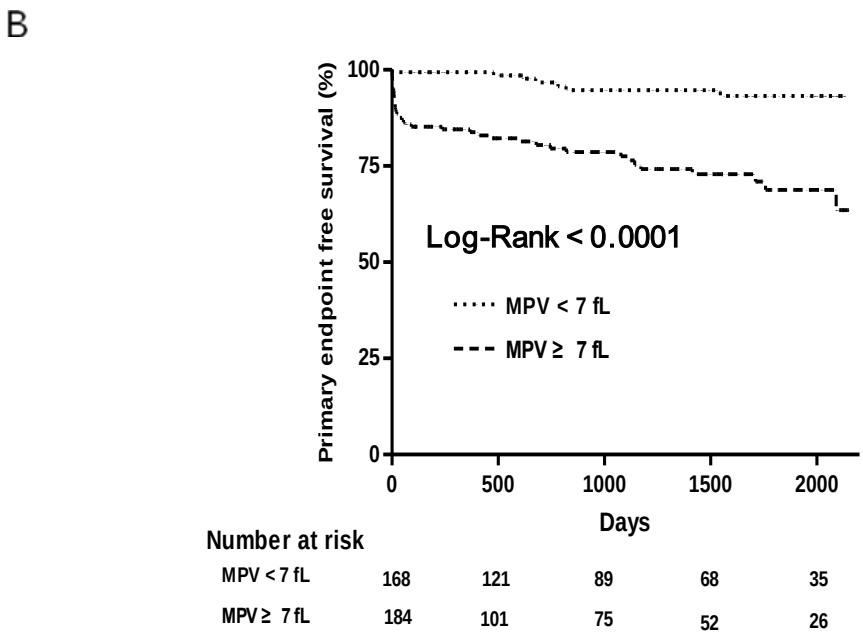


Figure 3. Primary endpoint-free survival according to (A) antithrombin III activity and (B) mean platelet volume

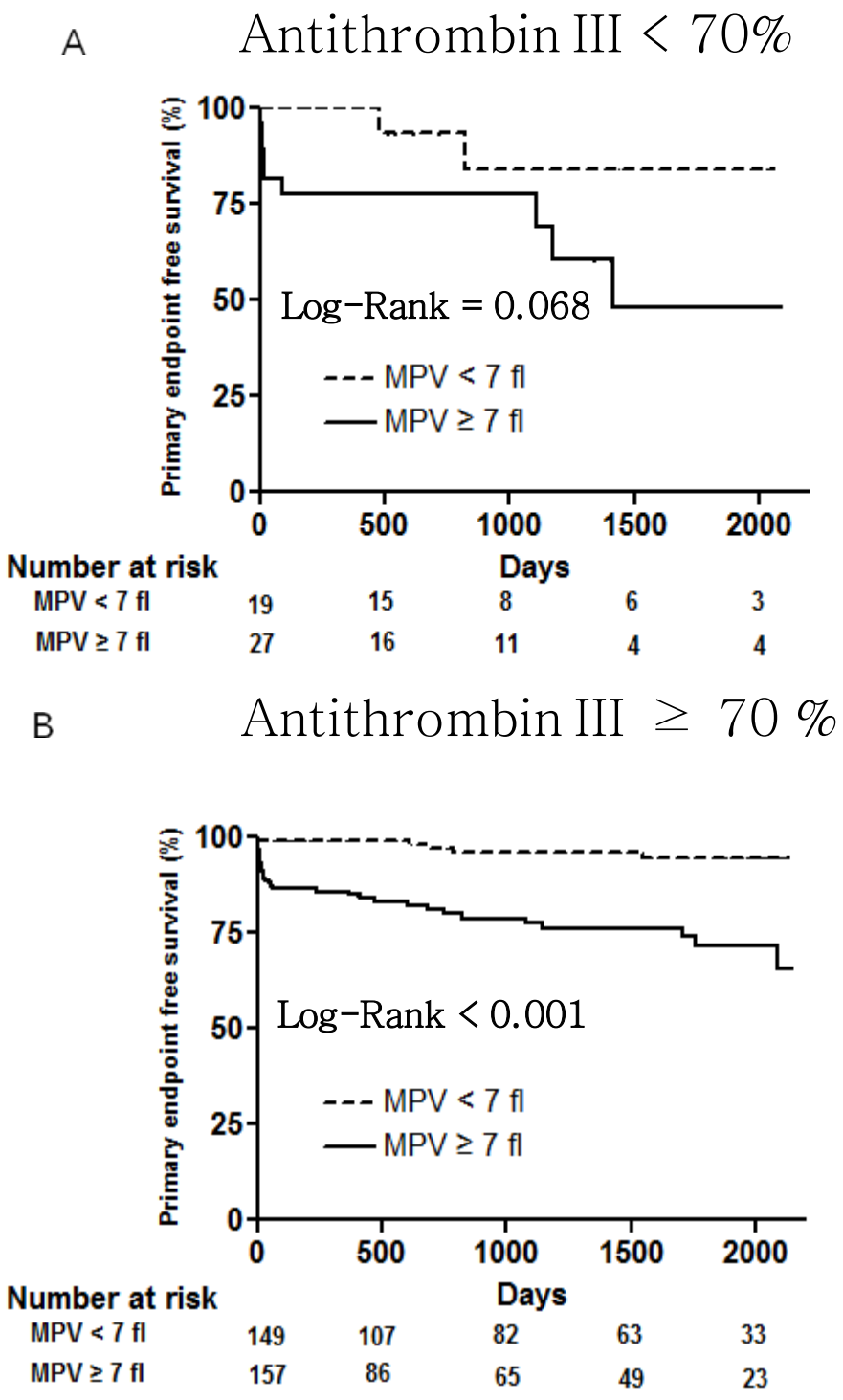
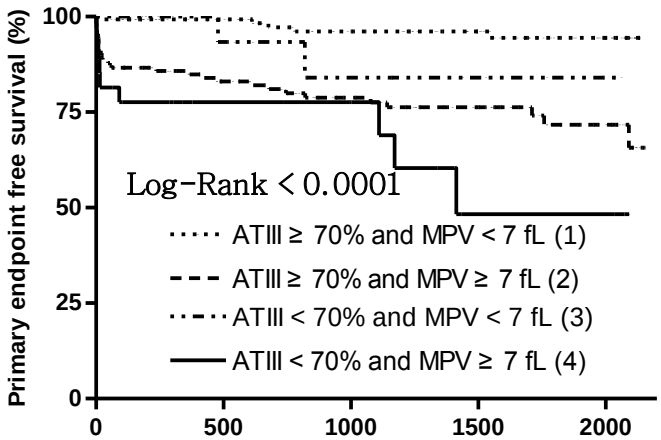


Figure 4. Primary endpoint-free survival according to mean platelet volume based on antithrombin III activity



Number at risk

(1)	149	107	82	63	33
(2)	157	86	65	49	23
(3)	19	15	8	6	3
(4)	27	16	11	4	4

Log-Rank between groups

	(1)	(2)	(3)
(2)	<0.0001		
(3)	0.1146	0.2636	
(4)	<0.0001	0.1535	0.0683

Figure 5. Primary endpoint-free survival according to a combination of antithrombin III activity and mean platelet volume

Table 1. Baseline characteristics and medication data on the basis of treatment strategy of atrial fibrillation

Characteristic	***Total (N=352)***	***MPV < 7 fL (N=168)***	***MPV ≥ 7 fL (N=184)***	***P-value***
Age (years)	68.4±12.1	68.3±12.1	68.5±12.2	0.860
Female sex (%)	42.6	42.3	42.9	0.899
Hypertension (%)	50.9	52.4	49.5	0.584
Diabetes (%)	19.0	17.3	20.7	0.418
Antithrombin III activity (%)	88.7±17.4	90.7±17.0	87.0±17.7	0.045
Antithrombin III <70% (%)	13.1	11.3	14.7	0.350
Mean platelet volume (fL)	7.25±1.00	6.53±0.30	7.92±0.94	< 0.001
LVEF (%)	55.4±12.4	56.0±11.6	54.9±13.0	0.391
LVEF < 35% (%)	7.7	5.4	9.8	0.119
Previous stroke or TIA (%)	4.5	5.4	3.8	0.485
Vascular disease history (%)	6.5	4.8	8.2	0.199
Any antithrombotic agents (%)	87.2	85.7	88.6	0.420

Aspirin (%)	48.9	47.0	50.5	0.509
$P2Y_{12}$ inhibitor (%)	10.2	9.5	10.9	0.677
Dual antiplatelet therapy (%)	9.7	8.3	10.9	0.421
Warfarin (%)	44.6	44.0	45.1	0.841
CHA_2DS_2-VASc score	2.3±1.6	2.3±1.6	2.4±1.6	0.531
High (score≥2, %)	63.1	60.1	65.8	0.273
Follow up duration (days)	1063±756	1130±757	1002±752	0.113

LVEF denotes left ventricular ejection fraction; TIA, transient ischemic attack; CHA_2DS_2-VASc, **C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes Mellitus, **S**troke, **V**ascular disease, **A**ge 65 to 74 years, **S**ex **C**ategory.

Table 2. Multivariate Cox proportional hazard analyses determining the significant and independent predictors for the primary endpoint

Factor	P value	HR (95% CI)
Aspirin therapy	0.880	0.95 (0.46-1.96)
Warfarin therapy	0.910	1.04 (0.50-2.16)
CHA_2DS_2-VASc score ≥2	0.725	1.11 (0.61-2.03)
Antithrombin III <70%	0.078	1.84 (0.93-3.65)
Mean platelet volume ≥ 7.0 fL	< 0.001	6.41 (2.87-14.29)

CHA_2DS_2-VASc indicates **C**ongestive heart failure, **H**ypertension, **A**ge≥75 years, **D**iabetes Mellitus, **S**troke, **V**ascular disease, **A**ge 65 to 74 years, **S**ex **C**ategory.

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