Conclusions—Over a median follow-up of 19 months, ICH developed in 31 patients and extracranial hemorrhage developed in 77. Entry BP levels were similar among patients with ICH, those with extracranial hemorrhage, and those without hemorrhagic events. Both systolic and diastolic BP were relatively high during follow-up compared with the levels at entry in patients with ICH, whereas they showed plateaus in patients with extracranial hemorrhage and patients without hemorrhagic events. Average systolic BP levels between 1 and 6 months (hazard ratio, 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (hazard ratio, 1.47; 95% CI, 1.05 to 2.01) as well as average diastolic BP levels between 7 and 12 months (hazard ratio, 2.05; 95% CI, 1.15 to 3.62) were independently associated with development of ICH after adjustment for established ICH predictors. The optimal cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg using receiver operating characteristic curve analysis.

Methods—A total of 4009 patients taking oral antithrombotic agents for cardiovascular or cerebrovascular diseases (2728 men, 69±10 years old) were followed. Changes in systolic and diastolic BPs between entry and the last clinic visit before intracranial hemorrhage (ICH) or extracranial hemorrhage were assessed.

Results—Over a median follow-up of 19 months, ICH developed in 31 patients and extracranial hemorrhage developed in 77. Entry BP levels were similar among patients with ICH, those with extracranial hemorrhage, and those without hemorrhagic events. Both systolic and diastolic BP were relatively high during follow-up as compared with the levels at entry in patients with ICH, whereas they showed plateaus in patients with extracranial hemorrhage and patients without hemorrhagic events. Average systolic BP levels between 1 and 6 months (hazard ratio, 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (hazard ratio, 1.47; 95% CI, 1.05 to 2.01) as well as average diastolic BP levels between 7 and 12 months (hazard ratio, 2.05; 95% CI, 1.15 to 3.62) were independently associated with development of ICH after adjustment for established ICH predictors. The optimal cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg using receiver operating characteristic curve analysis.

Conclusions—An increase in BP levels during antithrombotic medication was positively associated with development of ICH, suggesting the importance of adequate BP control for avoiding ICH. BP levels did not appear to be associated with extracranial hemorrhage. (Stroke. 2010;41:1440-1444.)

Key Words: anticoagulation ■ antiplatelet therapy ■ hypertension ■ intracerebral hemorrhage ■ stroke

Antithrombotic therapy is regarded as an essential primary and secondary preventive strategy for cardiovascular diseases and stroke. However, bleeding events are inevitable complications of this therapy; in particular, intracranial hemorrhage (ICH) is a typical life-threatening event. Carefully regulated warfarin therapy to international normalized ratios between 2 and 3 doubles the risk of ICH, and aspirin increases the risk by approximately 40%.

Hypertension is a firmly established risk factor for ICH in the general population as well as in warfarin users. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), in which 72% of enrolled patients with stroke were receiving antiplatelets and 10% were receiving anticoagulants, ICH was reduced by half after mean blood pressure (BP) lowering by 9/4 mm Hg. Thus, adequate antihypertensive therapy seems to prevent ICH during antithrombotic therapy. This raises an essential issue: whether antithrombotic users who finally developed ICH and other bleeding events had high BP levels throughout follow-up as well as how such patients’ BP levels changed during follow-up.
To determine the incidence and severity of bleeding complications in patients with cardiovascular diseases and stroke treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study (the Bleeding with Antithrombotic Therapy [BAT] Study) was conducted. In its initial report of the overall results, adding antiplatelets to warfarin or single antiplatelet therapy doubled the risk of life-threatening or major bleeding events. Here, the association between these patients’ BP levels during follow-up and development of bleeding events was determined.

Patients and Methods
The BAT Study was a prospective, multicenter, observational cohort study on the incidence and severity of bleeding complications in antithrombotic users. A total of 4009 patients (2728 men, 69 ± 10 years [mean ± SD]) who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular diseases were consecutively enrolled from 19 stroke and cardiovascular centers that were balanced regionally in Japan and observed for 2 to 30 months between October 2003 and March 2006. The study protocol, inclusion/exclusion criteria, and general results were published previously. The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided written informed consent.

Based on bleeding events during follow-up, the patients were divided into 3 groups: an “ICH group” for the patients developing any symptomatic ICH; an “extracranial hemorrhage (ECH) group” for those developing a life-threatening or major bleeding event other than ICH; and a “non-H group” for those without any life-threatening or major bleeding event. Bleeding events were classified according to the definition by the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study (MATCH). Briefly, life-threatening bleeding was defined as: any fatal bleeding event; a drop in hemoglobin of ≥50 g/L; hemorrhagic shock; symptomatic ICH; or transfusion of ≥4 U of red blood cells. Major bleeding was defined as significantly disabling, severe intraocular bleeding, or transfusion of ≥3 U of red blood cells. Secondary hemorrhagic transformation of an ischemic stroke was not regarded as a bleeding event. When the patients developed a life-threatening or major bleeding event, observation was discontinued.

Comorbidities (ischemic and hemorrhagic stroke, heart disease, neoplasms, and liver cirrhosis) and cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, hyperlipidemia, and use of warfarin) were assessed for the Cox proportional hazards regression analysis. BP levels at the last clinic visit of the observation period (the last visit before bleeding events for the ICH and ECH groups) and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit were assessed for the annual incidence and 95% CIs of ICH and the receiver operating characteristic (ROC) curves analysis. To compare baseline clinical characteristics and BP levels among the ICH, ECH, and Non-H groups, 1-way factorial analysis of variance with post hoc comparison by Dunnett test (with Non-H patients as control subjects) was used for continuous variables, and the χ² test was used for categorical variables. To examine the associations of BP levels and their changes with the development of ICH, a Cox proportional hazards regression analysis was performed using a forced entry method of established ICH predictors, including sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin. Goodness of fit of the statistical model was tested using the likelihood ratio in the Whole Model Test and Akaike information criterion. Finally, the optimal cutoff BP levels to predict impending development of ICH (in other words, to predict the last clinic visit before ICH) were determined using ROC curves based on all the BP measurements during follow-up. A probability value < 0.05 was considered statistically significant.

Results
Of 4009 enrolled patients, 1891 (47.2%) were taking single antiplatelet agents, 349 (8.7%) were taking dual antiplatelet agents, 1298 (32.4%) were taking warfarin, and 471 (11.7%) were taking warfarin plus antiplatelet agents. The main antiplatelet agents used in the enrolled patients were described previously. Briefly, aspirin monotherapy, ticlopidine monotherapy, and aspirin plus ticlopidine were the major choice for both antiplatelet users (1340, 394, and 220 patients, respectively) and warfarin plus antiplatelets users (336, 69, and 49 patients, respectively). At entry, the median international normalized ratio was 1.97 (interquartile range, 1.69 to 2.33) in warfarin users (taking warfarin alone or warfarin plus antiplatelets).

During the median observation period of 19 months (interquartile range, 13 to 23 months), 108 life-threatening or major bleeding events, including 31 ICH and 77 ECH, occurred. In warfarin users, the median international normalized ratio at entry was 2.06 (interquartile range, 1.95 to 2.30) in the ICH group, 2.06 (1.65 to 2.46) in the ECH group, and 1.96 (1.69 to 2.33) in the Non-H group (P = 0.149); and the median international normalized ratio at the last visit before bleeding events or on the day of the event was 2.28 (1.74 to 2.68) in the ICH group and 2.24 (1.75 to 3.06) in the ECH group (P = 0.993). Among the 3 groups, observation period (P < 0.001), age (P = 0.003), use of warfarin (P = 0.002), and neoplasm (P = 0.013) were significantly different (Table 1).

Figure 1 shows the time courses of the BP levels. Both SBP and DBP levels at entry were similar among the 3 groups (Table 1). During follow-up, both SBP and DBP were relatively high as compared with the levels at entry in the ICH group, and they plateaued in the ECH and Non-H groups. BP levels were not significantly different among the 3 groups in any BP measurements.

The association of BP with the development of ICH was determined after adjustment for sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin (Table 2). Average SBP levels between 1 and 6 months (hazard ratio [HR], 1.45; 95% CI, 1.08 to 1.92 per 10-mm Hg increase) and between 7 and 12 months (HR, 1.47; 95% CI, 1.05 to 2.01) as well as average DBP levels between 7 and 12 months (HR, 2.05; 95% CI, 1.15 to 3.62) were independently associated with ICH. The probability value of likelihood ratio in the Whole Model Test after multivariate adjustment was 0.055 for SBP at entry, 0.007 for average SBP between 1 and 6 months, 0.014 for average SBP between 7 and 12 months, 0.114 for average SBP after 13 months, 0.066 for DBP at entry, 0.046 for average DBP between 1 and 6 months, 0.010

Statistical Methods
All analyses were performed using JMP 7 statistical software (SAS Institute Inc, Cary, NC). Average levels of systolic and diastolic BPs (SBP and DBP, respectively) between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry were assessed for the Cox proportional hazards regression analysis. BP levels at the last clinic visit of the observation period (the last visit before bleeding events for the ICH and ECH groups) and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit were assessed for the annual incidence and 95% CIs of ICH and the receiver operating characteristic (ROC) curves analysis. To compare baseline clinical characteristics and BP levels among the ICH, ECH, and Non-H groups, 1-way factorial analysis of variance with post hoc comparison by Dunnett test (with Non-H patients as control subjects) was used for continuous variables, and the χ² test was used for categorical variables. To examine the associations of BP levels and their changes with the development of ICH, a Cox proportional hazards regression analysis was performed using a forced entry method of established ICH predictors, including sex, age, hypertension, diabetes mellitus, current or previous smoking habit, alcohol consumption, prior cerebrovascular disease, and use of warfarin. Goodness of fit of the statistical model was tested using the likelihood ratio in the Whole Model Test and Akaike information criterion. Finally, the optimal cutoff BP levels to predict impending development of ICH (in other words, to predict the last clinic visit before ICH) were determined using ROC curves based on all the BP measurements during follow-up. A probability value < 0.05 was considered statistically significant.
for average DBP between 7 and 12 months, and 0.117 for average DBP after 13 months. Thus, SBP between 1 and 6 months, SBP between 7 and 12 months, and DBP between 7 and 12 months showed relatively good fitness. Akaike information criterion was 446.4, 438.1, 326.4, and 204.4 for each SBP measurement and 447.0, 443.3, 325.6, and 204.5 for each DBP measurement, respectively. Based on Akaike information criterion, SBP and DBP after 13 months were better than other BP measurements in regard to goodness of fit.

Because the observation was discontinued within 6 months or within 12 months for many patients, especially for those with ICH and ECH, the following analyses were performed using BP levels at the last clinic visit and the average BP levels of all the follow-up measurements except for the levels at entry and at the last visit. At the last visit, both SBP and DBP were higher in the ICH group than in the Non-H group (141.7 / 110.06 13.6/81.3 / 10.3 mm Hg versus 132.4 / 17.8 / 74.7 10.9 mm Hg, \( P = 0.011 \) for SBP and \( P = 0.003 \) for DBP).

Figure 1. Time courses of BP. Average levels of SBP and DBP between 1 and 6 months, between 7 and 12 months, and after 13 months as well as the levels at entry are plotted. ICH indicates patients developing any symptomatic ICH; ECH, patients developing a life-threatening or major bleeding event other than ICH; Non-H, patients without any life-threatening or major bleeding event. All patients are included at entry and during 1 and 6 months; 21 patients with ICH, 53 patients with ECH, and 3293 Non-H patients are included during 7 and 12 months; and 13 patients with ICH, 30 patients with ECH, and 2936 Non-H patients are included after 13 months.

![Figure 1](image)

Figure 2. Annual incidence of ICH according to SBP and DBP levels. Bars indicate 95% CI for BP at the last clinic visit. "BP during follow-up" means average BP levels of all the follow-up measurements except for the levels at entry and at the last visit.

![Figure 2](image)
41.8%, and an area under the ROC curve of 0.659; the optimal cutoff DBP level was ≥81 mm Hg with a sensitivity of 53.6%, specificity of 74.2%, and an area under the ROC curve of 0.676. Both SBP3 ≥130 mm Hg (OR, 6.23; 95% CI, 2.16 to 26.35; \( P < 0.001 \)) and DBP3 ≥81 mm Hg (OR, 3.49; 95% CI, 1.64 to 7.52; \( P = 0.001 \)) were independently associated with ICH after adjustment for the 8 established ICH predictors.

**Discussion**

A major new finding of the present observational study was that BP levels during the follow-up, but not the level at entry, were independently associated with the development of ICH. In particular, ICH risk increased linearly as BP levels at the last clinic visit increased. The estimated cutoff BP level to predict impending risk of ICH was ≥130/81 mm Hg. BP levels did not appear to be associated with major systemic (excluding intracranial) bleeding events.

Hypertension is an established modifiable risk factor for ICH during warfarin therapy along with intensity of anticoagulation, concomitant use of antplatelets, and smoking and heavy drinking habits. However, major trials involving anticoagulant therapy failed to show entry BP level as a predictor for major bleeding events.\(^9^,\(^11^\) To resolve the contradiction, we designed the present study, which assessed BP levels during follow-up. The present antithrombotic users developing ICH had approximately 2 to 4 mm Hg higher entry SBP than those without bleeding events, which was not statistically significant. However, their SBP and DBP increased by an average of approximately 4 mm Hg at the follow-up as compared with at entry, and this increase may trigger ICH. Such an increase might result from careless BP management or resistance to antihypertensive therapy. Regardless of the cause, avoidance of a BP increase would lessen the risk for ICH.

Based on differences in average BP levels at the last visit between the ICH group and the other 2 groups, we hypothesized that the cutoff SBP level to predict impending development of ICH was roughly between 132 and 142 mm Hg, and the cutoff DBP level was roughly between 75 and 81 mm Hg. After ROC curve analyses, 130/81 mm Hg appears to be the cutoff level. Although the statistical power judged from the area under the ROC curve is not strong, this cutoff level seems to be reasonable, because recent guidelines from the European Society of Hypertension and the European Society of Cardiology and those from the Japanese Society of Hypertension advocated <130/80 mm Hg as the target BP level in diabetics and in high- or very-high-risk patients.\(^12^,\(^13^\)

Real target BP levels during antithrombotic therapy should be determined by systematic comparative trials.

Combination therapy with antithrombotics and antihypertensives appears to be preventive for ICH. In the interim report of the Secondary Prevention of Small Subcortical Strokes (www.sps3.org/), in which SBP was lowered to <149 mm Hg or <130 mm Hg, risk of ICH was less than expected in patients with stroke taking aspirin alone or aspirin plus clopidogrel (personal communication). Success in reducing ICH in PROGRESS, in which 82% of enrolled patients were receiving antithrombotics, was reviewed.\(^6^\) On the other hand, an angiotensin receptor blocker, telmisartan, did not reduce the risk of ICH for antiplatelet users who recently had ischemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study (HR, 0.81; 95% CI, 0.63 to 1.05)\(^14^\); the relatively small number of patients developing ICH may be a reason for this failure to show an effect.

Major systemic (not intracranial) bleeding events developed under identical BP levels as those in our patients without major bleeding events. This indicates that hypertensive damage to gastrointestinal, dermal, and other systemic circulations is milder than the damage to cerebral circulation. Preventive strategies other than antihypertensives, including proton pump inhibitors and H2 receptor antagonists, appear to be promising for reducing gastrointestinal bleeding.\(^15^,\(^16^\)

The limitations of the present study include the relatively short duration of the observation period and the small numbers of bleeding events as a result, which may affect the statistical results and make it difficult to perform subanalyses for patients with different clinical backgrounds and different antithrombotic regimens. Second, information on patients’ antihypertensive therapy was not given. Third, clopidogrel, a universal antiplatelet agent, was not used in our patients because the agent was approved for use in Japan in 2006, after the study was finished. Finally, data of many patients were not included in the analysis of the follow-up BP measurements during 7 and 12 months and after 13 months partly because of early discontinuance of the observation due to bleeding events. To overcome this limitation and to introduce a message that BP levels at the last clinic visit are important for ICH risk, we used the BP levels at the last visit for some analyses, including the ROC. However, it is not originally appropriate to use the last available measurement as a predictor of a bleeding event in a prospective study.

Because ischemic events are much more common than bleeding events, the use of antithrombotic agents has been increasing. The present study suggests that one should be careful to avoid BP elevations in antithrombotic users, and it is important to lower their BP adequately to avoid ICH.

**Appendix**

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Disclosures
None.

References
Blood Pressure Levels and Bleeding Events During Antithrombotic Therapy: The Bleeding With Antithrombotic Therapy (BAT) Study
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on behalf of The Bleeding With Antithrombotic Therapy (BAT) Study Group

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抗栓治疗中的血压水平与出血事件：抗栓相关出血研究 (BAT 研究)

Stroke. 2010;41:1440-1444. 赵璐 秦洁 译 许予明 校

Kazunori Toyoda, Masahiro Yasaka, Shinichiro Uchiyama, Takehiko Nagao, Jun Gotoh, Ken Nagata, Yukihiro Koretsune, Tomohiro Sakamoto, Kazunori Iwade, Masahiro Yamamoto, Jun C. Takahashi, Kazuo Minematsu and on behalf of The Bleeding With Antithrombotic Therapy (BAT) Study Group

背景与目的：为了阐明主要出血事件与血压水平的关系，在随访接受抗栓治疗的患者中进行了一项前瞻性、多中心、观察性的队列研究。

方法：4009例口服抗栓药物的心脑血管疾病患者 (2728例男性，平均年龄 69±10岁) 接受了随访，评估入组时与颅内外出血前最后一次门诊复诊时收缩压及舒张压的变化。

结果：平均19个月的随访中，31例颅内出血，77例颅外出血。发生颅内出血、颅外出血及未发生出血事件的患者入组时的血压水平是相似的。颅内出血患者随访时收缩压与舒张压相比入组时相对增加，而发生颅外出血和未发生出血事件的患者血压无明显变化。在校正了已知颅内出血的预测因子后，1-6月的平均收缩压 (HR 1.45; 95% CI, 1.08-1.92 每上升10 mmHg) 及7-12月的平均收缩压 (HR, 1.47; 95% CI, 1.05-2.01) 和舒张压 (HR, 2.05; 95% CI, 1.15-3.62) 与颅内出血的发生独立相关。受试者工作特征曲线分析显示：预测发生颅内出血的血压的最佳截断点是130/81 mmHg。

结论：抗栓治疗中颅内出血的发生与血压升高呈正相关，提示血压的有效控制对避免颅内出血具有重要意义。颅外出血与血压水平可能无关。

关键词：抗凝，抗血小板治疗，高血压，颅内出血，卒中
根据在随访中出血事件的发生情况，患者可分类为3组：颅内出血组 (ICH组)，即发生了致命性脑出血的患者；颅外出血组 (ECH组)，即发生了以外伤性脑出血或主要出血事件的患者；非出血组 (non-H组)，即未发生任何致死性或大出血事件的患者。出血事件是根据 MATCH 的定义来分类的。简单来说，致死性出血定义为：任何致命性出血事件；颅内出血定义为：死亡或大出血事件，严重的眼内出血，或者输入红细胞≥4 U。大出血事件被定义为严重的致残性出血事件，严重的眼内出血，或者输入红细胞≥3 U。缺血性卒中继发的出血事件不作为出血事件。非出血组发生出血事件之前的最后一次随访，使用二联抗血小板治疗者。纳入患者使用的抗血小板剂已在先前描述。本次研究列出的合并症包括高血压、糖尿病、高胆固醇血症、低胆固醇血症 [纳入标准为血清总胆固醇≤200 mg/dL]、吸烟史、每天饮酒≥2 drinks) 与先前研究一致。

统计方法

所有的分析均在 JMP 类统计软件 (SAS Institute, Cary, NC) 上进行。1-6月、7-12月、13月后以及入组的平均收缩压及舒张压 (SBP及DBP) 进行Cox 回归分析。用观察期最后一次门诊随访 (在ICH组和ECH组发生出血事件之前的最后一次随访) 的血压水平以及除外入选及未次血压的随访期的平均血压评估ICH年发病率、95%可信区间及受试者工作特征 (ROC) 曲线分析。比较ICH、ECH及Non-H组的基线临床特征及高血压水平，连续变量进行单因素方差分析，用 Dunnett 检验进行均数间多重比较 (Non-H组患者作为对照组)，分类变量进行χ²检验。为检验血压水平及其变化与颅内出血的关系，采用颅内出血已知预测因子强行进入法进行Cox 回归分析，已知的预测因子包括性别、年龄、高血压、糖尿病、或既往吸烟史及饮酒、既往脑血管病、使用华法林等。采用似然比检验方法和赤池信息准则 (Akaike information criterion) 对整个模型进行拟合优度检验，基于随访血压值的 ROC 曲线确定预测发生颅内出血的血压最佳截断点。P<0.05 有统计学意义。

结果

纳入的4009例患者中，1891例(47.2%)使用单一抗血小板剂，349例(8.7%)使用单二联抗血小板治疗，1298(32.4%)例患者使用华法林，471(11.7%)例患者使用华法林联合抗血小板剂。纳入患者使用的抗血小板剂已在先前描述。简单来说，单用阿司匹林、单用噻氯匹定以及阿司匹林加噻氯匹定是抗血小板治疗者 (分别为1340、394、220例患者)。在华法林联合抗血小板治疗者 (分别为336、69、49例患者) 的主要选择。入选时，华法林治疗者 (单独或联合华法林)的中位INR是1.97(四分间距，1.69-2.33)。

在19个月(四分间距，13-23个月)的中位观察期内，共发生108例致死性或主要出血事件，占31例颅内出血及77例颅外出血。在华法林使用者中，ICH组入组时的中位INR为2.06(四分间距，1.95-2.30)，ECH组为2.06(1.65-2.46)。Non-H组为1.96(1.69-2.33)，P=0.149。在出血事件发生前或当日的最后一次随访时的中位INR如下：ICH组为2.28(四分间距，1.74-2.68)，ECH组为2.24(四分间距，1.75-3.06)，P=0.993。在三组中，观察期限(P<0.001)，年龄(P=0.003)，使用华法林(P=0.002)以及肿瘤(P=0.013)有显著差异 (表1)。

图1显示了血压水平的时间变化。入选时三组的收缩压与舒张压水平无明显差异。三组的血压水平在任何血压测量值无显著差异。

校正性别、年龄、高血压、糖尿病、或既往吸烟史、饮酒史、脑血管病史及华法林的使用等因素后 (表2)，确立血压与颅内出血的关系。1-6月的平均收缩压(HR，1.45；95% CI，1.08-1.92)增加10 mmHg，7-12月的平均收缩压(HR，1.47；95% CI，1.05-2.01)和舒张压(HR，2.05；95% CI，1.15-3.62)与颅内出血独立相关。在多变量调整后对整体模型进行检验，似然比检验的P值分别如下：0.055(入选时的收缩压)，0.007(1-6月的平均收缩压)，0.014(7-12月的平均收缩压)，0.114(13月后的平均收缩压)，0.066(入选时的舒张压)，0.046(1-6月的平均舒张压)，0.010(7-12月的平均舒张压)，0.117(13月后的舒张压)。因此，1-6月的收缩压、7-12月的收缩压、7-12月的舒张压显示出更好的关联性。

图2显示了不同血压水平的颅内出血发病率。颅内出血危险性随着最后一次门
诊随访的收缩压与舒张压的升高而线性增加，并不随着入选时及随访过程中的血压升高而线性增加。

为预测颅内出血，使用ROC曲线确定收缩压最佳截断点是≥130 mmHg，敏感性89.3%，特异性41.8%，ROC曲线下面积为0.659；舒张压最佳截断点是81 mmHg，敏感性为53.6%，特异性为74.2%，ROC曲线下面积为0.676。校正已知的8个颅内出血预测因子后，SBP≥130 mmHg (OR, 6.23; 95% CI, 2.16-26.35, P=0.001) 和 DBP≥81 mmHg (OR, 3.49; 95% CI, 1.64-7.52, P=0.001) 与颅内出血独立相关。

讨论

这项观察性研究的一个主要新发现是随访的血压水平，而非入选时的血压水平，与颅内出血独立相关。尤其是颅内出血的危险性随着最后一次门诊随访血压的增加而增加。预测发生颅内出血的血压最佳截断点为≥130/81 mmHg。血压水平似乎和主要系统性(除外颅内出血)出血事件关系不大。

在华法林治疗中，高血压是一项确定可调控的颅内出血危险因子，其他还有抗凝治疗强度、联用抗血小板药物、吸烟及酗酒[4]。然而，试验未能证明入选时的血压水平是大出血事件的预测因子[9-11]。为了解决这个矛盾，我们设计了这个评估随访时血压水平的试验。抗栓治疗患者中，发生颅内出血患者的入组收缩压比未发生出血事件的高约2-4 mmHg，但无统计学意义。然而，随访时收缩压与舒张压较纳入时增加大约4 mmHg，这可能增加颅内出血风险。血压的升高有可能是因为不注意血压调控或不愿接受降压治疗。不考虑这些原因，避免血压升高能降低颅内出血的风险。

基于ICH组与其他两组在最后一次随访中的平均血压水平的差异，我们假设能预测颅内出血的收缩

表1 患者的基线临床特征

<table>
<thead>
<tr>
<th>患者数</th>
<th>颅内出血组</th>
<th>颅外出血组</th>
<th>非出血组</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>观察期(月)</td>
<td>31</td>
<td>77</td>
<td>3901</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>年龄(岁)</td>
<td>73±7</td>
<td>71±10</td>
<td>69±10</td>
<td>0.003</td>
</tr>
<tr>
<td>男性</td>
<td>81%</td>
<td>75%</td>
<td>69%</td>
<td>0.173</td>
</tr>
<tr>
<td>使用华法林*</td>
<td>61%</td>
<td>61%</td>
<td>44%</td>
<td>0.002</td>
</tr>
<tr>
<td>合并症</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>冠状性卒中</td>
<td>68%</td>
<td>44%</td>
<td>55%</td>
<td>0.060</td>
</tr>
<tr>
<td>出血卒中</td>
<td>6%</td>
<td>1%</td>
<td>2%</td>
<td>0.122</td>
</tr>
<tr>
<td>心脏病、心律失常</td>
<td>77%</td>
<td>77%</td>
<td>67%</td>
<td>0.217</td>
</tr>
<tr>
<td>肺病</td>
<td>19%</td>
<td>12%</td>
<td>7%</td>
<td>0.013</td>
</tr>
<tr>
<td>肝硬化</td>
<td>6%</td>
<td>4%</td>
<td>2%</td>
<td>0.197</td>
</tr>
<tr>
<td>危险因素</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>高血压</td>
<td>65%</td>
<td>57%</td>
<td>61%</td>
<td>0.746</td>
</tr>
<tr>
<td>糖尿病</td>
<td>26%</td>
<td>34%</td>
<td>26%</td>
<td>0.296</td>
</tr>
<tr>
<td>高血脂症</td>
<td>36%</td>
<td>32%</td>
<td>42%</td>
<td>0.173</td>
</tr>
<tr>
<td>心脏病、心律失常</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>0.152</td>
</tr>
<tr>
<td>抗栓药</td>
<td>19%</td>
<td>10%</td>
<td>14%</td>
<td>0.269</td>
</tr>
<tr>
<td>既往吸烟史</td>
<td>29%</td>
<td>47%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>饮酒史</td>
<td>10%</td>
<td>6%</td>
<td>5%</td>
<td>0.413</td>
</tr>
<tr>
<td>入选时收缩压(mmHg)</td>
<td>134.6±13.2</td>
<td>130.8±18.5</td>
<td>132.5±17.9</td>
<td>0.597</td>
</tr>
<tr>
<td>入选时舒张压(mmHg)</td>
<td>74.8±12.3</td>
<td>74.5±10.4</td>
<td>75.6±11.0</td>
<td>0.672</td>
</tr>
</tbody>
</table>
| 观察期 | 以中位数(四分间距)表示，年龄与血压以均值±标准差表示，其他以百分数表示。

*单独使用华法林或华法林加抗血小板药。

表2 发生颅内出血的多变量调整的HR及血压指数的95%可信区间

<table>
<thead>
<tr>
<th>HR</th>
<th>95%可信区间</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>收缩压</td>
<td></td>
<td></td>
</tr>
<tr>
<td>入选时水平</td>
<td>1.09</td>
<td>0.88-1.34</td>
</tr>
<tr>
<td>1-6月的均值</td>
<td>1.45</td>
<td>1.08-1.92</td>
</tr>
<tr>
<td>7-12月的均值</td>
<td>1.47</td>
<td>1.05-2.01</td>
</tr>
<tr>
<td>13月后的均值</td>
<td>1.29</td>
<td>0.93-1.76</td>
</tr>
<tr>
<td>舒张压</td>
<td></td>
<td></td>
</tr>
<tr>
<td>入选时水平</td>
<td>0.97</td>
<td>0.68-1.39</td>
</tr>
<tr>
<td>1-6月的均值</td>
<td>1.28</td>
<td>0.78-2.13</td>
</tr>
<tr>
<td>7-12月的均值</td>
<td>2.05</td>
<td>1.15-3.62</td>
</tr>
<tr>
<td>13月后的均值</td>
<td>1.50</td>
<td>0.89-2.53</td>
</tr>
</tbody>
</table>

*每升高10毫米汞柱，调整了性别、年龄、高血压、糖尿病、最近或以前吸烟史、饮酒、脑血管病史以及使用华法林等。
在减少颅内出血的发生上获得了成功。进入分析。为了克服这一缺陷，并为表明最后一次病患者的靶目标中患者发生颅内出血的危险性比预想的要低。在预防作用。皮层下小卒中的二级预防研究的中期报告显示:收缩压降到7-12而且，未能显示出结果的原因1.05)。抗栓治疗联合抗高血压治疗似乎对颅内出血有防作用。皮层下小卒中的二级预防研究的中期报告显示:收缩压降到149 mmHg或130 mmHg以下，单独服用阿司匹林或服用阿司匹林加氯吡格雷的卒中患者发生颅内出血的危险性比预想的要低。在PROGRESS研究中，82%的纳入患者接受抗栓治疗，在减少颅内出血的发生上获得了成功8)。另一方面，ProFESS(Prevention Regimen for Effectively Avoiding Second Strokes)研究显示:血栓紧张素受体拮抗剂(替米沙坦)并不减少近期缺血性卒中接受抗小板治疗患者的颅内出血风险(HR,0.81;95% CI,0.63-1.05);发生颅内出血的患者数目相对较少可能是导致未能显示出结果的原因14)。发生全身性(不包括颅内)大出血事件与未发生大出血事件的血压相同。这表明高血压对消化道、皮肤以及其他系统损害轻于对脑循环损害。保护策略除了抗高血压外，还包括质子泵抑制剂与H2受体阻滞剂，似乎对减少消化道出血很有效15,16)。 本次研究的不足之处包括观察期相对较短以及因此导致的相对较少的出血事件，这将影响到统计结果，并使对不同临床背景及不同抗栓策略的患者进行亚组分析变得困难。其次，没有提供患者抗高血压治疗的使用正在增加。本研究提示应用抗栓治疗患者应避免血压升高，合理降压能避免颅内出血。 参考文献


