Effect of Clopidogrel on the Rate and Functional Severity of Stroke Among High Vascular Risk Patients

A Prespecified Substudy of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) Trial

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Background and Purpose—Disabling stroke is costly and considered by some patients a fate worse than death. We aimed to determine whether clopidogrel reduces the rate and functional severity of stroke among high vascular risk patients, including patients with previous transient ischemic attack or ischemic stroke, who were enrolled in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial.

Methods—We randomly assigned 15,603 high vascular risk patients to receive clopidogrel (75 mg daily) or placebo in addition to background acetylsalicylic acid and followed them for a median of 28 months. The main outcome of this prespecified substudy was the functional severity of stroke outcome events as measured by the modified Rankin Scale (mRS) score at 3 months after the stroke outcome.

Results—During follow-up, 436 (2.8%) patients had a definite adjudicated stroke and a follow-up assessment of the mRS at 3 months poststroke, of whom 202 had been randomly assigned clopidogrel and 234 placebo (relative risk reduction 14%, 95% CI: −4% to 29%, P=0.12). There was no significant difference between the mean mRS scores at 3 months after stroke among patients assigned clopidogrel compared with placebo (mean mRS 3.6 [SD 2.4] clopidogrel versus 3.3 [SD 2.1] placebo; P=0.15). There was also no significant difference between the various categories of the mRS score at 3 months after stroke among patients assigned to clopidogrel compared with placebo. Among 4320 patients with a qualifying diagnosis of transient ischemic attack or ischemic stroke, 233 (5.4%) experienced a stroke during follow-up, of whom 103 were randomly assigned clopidogrel and 130 placebo (relative risk reduction 20%, 95% CI: −3% to 38%). There was no significant difference between the mean mRS scores at 3 months after stroke among patients with a qualifying transient ischemic attack or ischemic stroke who were assigned clopidogrel compared with placebo (3.4 [SD 2.1] clopidogrel versus 3.3 [SD 1.9] placebo; P=0.48).

Conclusion—The addition of clopidogrel to acetylsalicylic acid did not significantly alter the rate and functional severity of stroke outcome events among high vascular risk patients enrolled in the CHARISMA trial. (Stroke. 2010;41:1679-1683.)

Key Words: antiplatelet therapy ■ cerebrovascular disease/stroke ■ infarction ■ stroke prevention ■ stroke severity

M uch of the burden of stroke can be attributed to its high rates of case fatality (20%) and dependency (50% of survivors).1-3 Strategies for stroke prevention such as antiplatelet therapy are likely to be optimally effective if they can reduce fatal and disabling strokes at least as effectively as they prevent nondisabling strokes.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial was designed to explore the hypothesis that long-term treatment with a combination of clopidogrel and acetylsalicylic acid (ASA) may be more effective than ASA alone in preventing the occurrence of the composite of stroke, myo-
cardial infarction, or death due to vascular causes among a broad population of patients at high risk for vascular events.\(^4,5\)
The rate of stroke, myocardial infarction, or vascular death was 6.8% among patients assigned clopidogrel and 7.3% among patients assigned placebo (relative risk: 0.93, 95% CI: 0.83 to 1.05).\(^5\)

A secondary a priori hypothesis was that the addition of clopidogrel to ASA may reduce the severity of stroke outcome events, perhaps by minimizing the size of thrombus formed on ruptured/eroded atherosclerotic plaque and thus the size of emboli to the brain and resultant brain infarction. However, it was also possible that adding clopidogrel to aspirin could increase the severity of any hemorrhagic strokes.

In this prespecified substudy of the CHARISMA trial, we aimed to determine the effect of clopidogrel on the functional severity of stroke as measured by the modified Rankin Scale (mRS)\(^6,7\) among all high vascular risk subjects randomized in the CHARISMA trial and followed-up for the occurrence of stroke events. In addition to the prespecified analysis, we also assessed the rate and severity of stroke events in those patients recruited after a transient ischemic attack (TIA) or stroke.

### Methods

#### Design

The methods of the CHARISMA trial have been described in detail elsewhere.\(^6,8\) Briefly, CHARISMA was a multicenter, multinational, randomized, parallel-group, double-blind trial of clopidogrel versus placebo in high-risk patients at risk of atherothrombotic events and who were receiving low dose ASA at the time of randomization. A total of 15 603 patients with either clinically established cardiovascular disease or multiple risk factors were randomly assigned to receive clopidogrel (75 mg per day) plus low-dose ASA (75 to 162 mg per day) or placebo plus low-dose ASA. Patients with a previous disabling condition such that they were bedridden or demented were excluded from the trial. Patients were followed-up prospectively at 1, 3, and 6 months, and every 6 months thereafter until the trial end. The median follow-up period was 28 months. The primary efficacy end point for the CHARISMA trial was a composite of stroke, myocardial infarction, or death from cardiovascular causes.

#### Subjects

The population for the substudy on stroke severity consisted of all high vascular risk patients randomized in the CHARISMA trial who experienced at least 1 adjudicated stroke end point during follow-up and underwent an assessment of the functional severity of the stroke outcome event at 3 months after the event.

#### Outcome Evaluation

The primary outcome measure was functional severity of the first stroke outcome event as defined by the mRS score at 3 months after the stroke.\(^6,7\)

All randomized subjects who experienced at least 1 stroke end point as determined by the investigator were evaluated using the mRS approximately 3 months (or at study end date or death if these occurred earlier) after the stroke to determine the severity of the stroke and the patient’s functional outcome. Assessments were made after each stroke end point, but only the assessment after the initial adjudicated stroke was used for the primary analysis.

The assessment and scoring of the mRS was done by the same observer immediately after the stroke and at the 3 months poststroke follow-up assessment. The mRS was assessed incorporating all activities that the patients could actually do, not what they thought they could do. The difference between a mRS score of 2 (independent) and 3 (dependent) was the need for assistance in any activities of daily living (eg, walking, bathing, dressing, grooming).

#### Statistical Methods

Data were analyzed on an intention-to-treat basis. Kaplan–Meier curves were generated to show time to first adjudicated stroke in each treatment group. The mRS score was summarized by treatment group using counts and percentage as well as mean, SD, minimum, and maximum.

In the patients who had an assessment of the mRS at 3 months after their stroke, analysis of variance was used to test the difference in mean scores between treatment groups. An adjusted analysis was also performed using analysis of variance because the population was chosen based on an end point and could not be assumed to be random. Adjustment factors included whether the patient was on the study drug at the time of stroke (yes/no), time from randomization to stroke (continuous days), and the initial mRS score. The poststroke mRS score was also assessed on patients who did not permanently discontinue the study drug before the functional outcome assessment.

Only observed values were used in the analysis and presentations, that is, no attempt was made to impute missing values.

#### Results

#### Study Patients

Among the 15 603 high vascular risk patients randomized to placebo (n=7801) or clopidogrel (n=7802), in addition to background ASA, and followed for a median of 28 months, 503 were reported by the investigator to have had a stroke. Of these, 441 strokes were adjudicated as a stroke. The Figure is a Kaplan–Meier curve showing the rate of stroke over the first 30 months of follow-up according to the random treatment allocation at Time 0. Among the 441 patients with adjudicated stroke, 436 had an assessment of the mRS 3 months after their stroke.
Stroke Outcomes According to Randomized Treatment Group
Among the 436 patients who had an adjudicated definite stroke during trial follow-up and underwent an assessment of functional stroke severity at 3 months poststroke, 202 had been randomly assigned clopidogrel and 234 assigned aspirin (relative risk reduction 14%, 95% CI: −4% to 29%, \( P=0.12 \), 2-tailed).

Baseline Demographic and Other Prognostic Factors
Table 1 shows that there were no significant differences in the prevalence or level of baseline demographic and other prognostic factors between the two treatment groups of patients who experienced a stroke during follow-up.

Duration of Study Drug Treatment
The 234 patients assigned placebo (who subsequently experienced a stroke) were treated with study drug for 17.1 months (median) compared with 16.1 months (median) for the 202 patients assigned clopidogrel (\( P=0.43 \)).

Time Between First Adjudicated Stroke and Follow-Up Assessment of Functional Stroke Severity
The median time between stroke and follow-up assessment of functional stroke severity was 163 days for patients on clopidogrel versus 130 days for patients on placebo (\( P=0.03 \)).

Pathological Subtype of Stroke Outcomes
Among the 436 patients who had a stroke outcome, 369 (85%) were ischemic (171 [84.7%] among patients assigned clopidogrel versus 198 [84.6%] among patients assigned placebo), 41 (9%) were hemorrhagic (20 [9.9%] clopidogrel versus 21 [9.0%] ASA), and 26 (6%) were of uncertain pathological type (11 [5.4%] clopidogrel versus 15 [6.4%] ASA).

Functional Outcome 3 Months After the First Stroke Outcome Event
Table 2 shows that there was no significant difference between the mean mRS scores at 3 months after stroke among patients assigned clopidogrel compared with placebo (3.6 [SD 2.3] clopidogrel versus 3.3 [SD 2.1] placebo; \( P=0.15 \)). After adjusting for treatment group, on study drug at the time of stroke, time from randomization to stroke, and initial mRS score, similar results remained with no difference between treatment groups.

Table 3 shows that there was also no significant difference between the various categories of the mRS score at 3 months after stroke among patients assigned to clopidogrel compared with placebo. Although patients assigned clopidogrel showed a small trend toward more severe stroke than placebo in each comparison, it is highly probable that this finding reflects random error (chance). These results were consistent in patients who did not permanently discontinue the study drug (n=261; clopidogrel: n=122, placebo: n=139) before the poststroke functional outcome assessment (\( P=0.09 \)).
Patients With Qualifying TIA or Ischemic Stroke

Among the 15,603 high vascular risk patients randomized in the main CHARISMA trial, 4,320 patients were enrolled with a qualifying diagnosis of documented cerebrovascular disease (TIA \( n=1,233 \) or ischemic stroke \( n=3,245 \); 158 patients with ischemic stroke also had a history of TIA), of whom 2,163 were assigned placebo and 2,157 clopidogrel.

An adjudicated first stroke during follow-up (ie, a recurrent stroke for patients who qualified with stroke) occurred in 233 patients, of whom 103 were randomly assigned clopidogrel and 130 to placebo (relative risk reduction 20\%, 95\% CI: −3\% to 38\%). Most strokes were ischemic \( n=202 \) of 233 [87\%]; 91 patients assigned clopidogrel versus 113 on placebo). A few strokes were hemorrhagic \( n=19 \) of 236 [8\%]; 10 clopidogrel versus 9 placebo). Only 12 strokes were of unknown type.

Table 4 shows that there was no significant difference between the mean mRS scores 3 months after (recurrent) stroke among patients with a qualifying TIA or ischemic stroke who were assigned clopidogrel compared with placebo.
Table 4. Summary of Functional Outcome as Measured by the mRS Score at 7 Days or at Hospital Discharge After the First Adjudicated Stroke Outcome Event (Initial mRS Score) and 3 Months After the First Adjudicated Stroke (Follow-Up mRS Score) Among Patients With a Qualifying TIA or Ischemic Stroke

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=103/2157</th>
<th>N=130/2163</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial mRS score, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, no symptoms at all</td>
<td>13 (13)</td>
<td>12 (9)</td>
<td>0.93</td>
</tr>
<tr>
<td>2, no significant disability despite symptoms</td>
<td>24 (23)</td>
<td>35 (27)</td>
<td></td>
</tr>
<tr>
<td>3, slight disability</td>
<td>20 (19)</td>
<td>26 (20)</td>
<td></td>
</tr>
<tr>
<td>4, moderate disability</td>
<td>16 (15)</td>
<td>25 (19)</td>
<td></td>
</tr>
<tr>
<td>5, moderately severe disability</td>
<td>16 (15)</td>
<td>16 (12)</td>
<td></td>
</tr>
<tr>
<td>6, severe disability</td>
<td>10 (10)</td>
<td>12 (9)</td>
<td></td>
</tr>
<tr>
<td>7, death</td>
<td>4 (4)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Follow-up mRS score, mean (SD)</td>
<td>3.4 (1.7)</td>
<td>3.4 (1.6)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

were not eligible for study entry if they were severely disabled, thus minimizing the potential for important imbalance in stroke severity at baseline.

Third, the mRS was assessed later after the stroke end point among patients assigned clopidogrel than those assigned placebo (163 days median for patients assigned clopidogrel versus 130 days for patients assigned placebo, P=0.03), introducing the possibility of bias favoring the outcome of patients assigned clopidogrel (ie, longer time to recover between stroke end point and functional assessment).

Fourth, the mRS is quite insensitive to small, but sometimes clinically meaningful, changes in functional status.6

Fifth, the mRS was assessed by a wide range of health professionals, some of whom may not have been well trained in, or familiar with, its use. Many were not stroke physicians. However, many studies have shown that the mRS has high interobserver reliability.6

Finally, the study is likely to have been underpowered to reliably identify or exclude a modest but clinically important effect of combination antiplatelet therapy on stroke severity compared with monotherapy.

This trial fails to provide evidence that adding clopidogrel to ASA significantly reduces the severity of stroke outcome events, as measured by the mRS, 3 months after stroke.

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Effect of Clopidogrel on Stroke Among High Vascular Risk Patients: A Prespecified Substudy of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) Trial

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Background and Objective: Stroke disability incurs a severe economic burden, and for some stroke patients, this outcome is worse than death. To clarify whether clopidogrel could reduce the stroke incidence and functional severity in patients with vascular risk factors such as prior transient ischemic attack (TIA) and prior ischemic stroke, we studied the prespecified subgroup of patients from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) clinical trial.

Methods: We randomly assigned 15,603 patients with vascular risk factors to receive clopidogrel (75 mg daily) or placebo, both groups also received aspirin; median follow-up was 28 months. The primary prognostic outcome of this subgroup study was functional severity 3 months after stroke, as measured by modified Rankin score (mRS).

Results: During follow-up, 436 (2.8%) patients had a stroke and completed mRS measurements at 3 months, 202 in the clopidogrel group and 234 in the placebo group (relative risk reduction, 14%; 95% CI, −4% to 29%; P=0.12). Among patients with vascular risk factors who developed stroke after randomization, 233 (5.4%) patients had TIAs or strokes in the placebo group and 103 (4.0%) patients had TIAs or strokes in the clopidogrel group (relative risk reduction, 20%; 95% CI, −3% to 38%). The mRS scores were similar between the two groups (clopidogrel group, 3.4 [standard deviation 2.1]; placebo group, 3.3 [standard deviation 1.9]; P=0.48).

Conclusion: For patients with vascular risk factors randomized to receive clopidogrel, the addition of clopidogrel to aspirin did not significantly improve the stroke incidence or functional severity.

Keywords: Antiplatelet treatment, Cerebrovascular disease / Stroke, Ischemic, Stroke prevention, Stroke severity

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期联用氯毗格雷与阿司匹林 (ASA) 是否比单用 ASA 更有效地预防卒中和心肌梗塞的发生以及血管疾病造成的死亡 [4,5]。氯毗格雷组的卒中、心肌梗塞和血管性死亡的发生率为 6.8%，安慰剂组为 7.3%（相对风险度 0.93, 95% CI: 0.83-1.05）[5]。

基于上述发现，我们进一步推测在 ASA 基础上添加氯吡格雷治疗可能降低卒中后功能损害的严重程度，其可能通过缩小破裂的动脉粥样斑块上的血栓和进入脑内栓子的大小，从而减少梗塞面积。然而，氯吡格雷与 ASA 联用也可能会增加出血性卒中的严重程度。

本亚组研究，通过随访 CHARISMA 研究中高血管风险患者卒中事件的发生，采用改良 Rankin 评分（mRS），评价氯吡格雷治疗对卒中功能损害严重程度的影响 [6,7]。此外，我们还对该亚组中既往有短暂性脑缺血发作 (TIA) 或卒中史的患者，评估他们的卒中发生率及功能损害的严重程度。

方法

研究设计

CHARISMA 临床研究的设计在之前文献中已有详细描述 [4,5]。简而言之，CHARISMA 是一项多中心、多国参与的随机、平行对照、双盲研究，在小剂量阿司匹林治疗的高血管风险患者中，比较氯吡格雷与安慰剂在预防动脉粥样硬化血栓形成方面的作用。该研究共纳入 15 603 例患者，均经临床确诊发生了心血管事件或存在多个血管危险因素，随机分组接受氯吡格雷（每天 75 mg）联合小剂量 ASA（每天 75-162 mg）治疗或安慰剂联合小剂量 ASA 治疗。排除既往存在致残情况的患者，如卧床，痴呆等。在第 1, 3, 6 个月以及之后每六个月前瞻性随访患者，直至研究结束。随访时间的中位数为 28 个月。CHARISMA 研究的复合终点事件包括卒中、心梗及心血管疾病造成的死亡。

研究对象

CHARISMA 临床研究中，所有随机的高血管风险患者纳入本亚组分析。该组患者在随访过程中至少发生一次确诊的卒中终点事件，且在事件发生后 3 个月内进行了功能损害的严重程度评估。

预后评价

主要的预后评价定义为首次卒中的功能损害严重程度，即卒中后 3 个月时 mRS 评分 [6,7]。所有经研究者明确的，至少发生了一次卒中终点事件的随机对象，在 3 个月左右（或研究结束时，或患者死亡时，如果这二者在之前发生）进行 mRS 评分，以评估卒中中的严重程度和患者的功能预后。每次卒中终点事件后都进行评估，但仅将首次确诊卒中后的评估纳入本次分析。

同一个研究者在患者卒中即时及卒中后 3 个月的随访时进行 mRS 评分，mRS 评分是根据患者实际能够完成的所有日常活动进行综合评定，而不是根据想象。mRS 评分 2 分（有独立生活能力）与 3 分（无法独立生活）的区别在于患者完成日常生活所必要的那些动作是否需要帮助（例如行走、洗澡、穿衣以及梳理）。

统计方法

研究数据采用意向治疗模式进行分析。Kaplan-Meier 曲线可显示各治疗组从随机到发生首次确诊卒中事件的时间。统计各治疗组 mRS 评分的各分值计数、所占百分比、平均数、标准差、最小值及最大值。

比较各组卒中后 3 个月时 mRS 评分，其平均数采用方差分析明确是否存在组间差异。由于本研究是基于终点事件选择研究对象，存在研究人群的选择偏移，因此也进行了方差分析的校正检验。校正因素包括患者在卒中时是否服用研究药物（是或否），随机至卒中发生的时间（连续性数据）及首次 mRS 评
分。在完成功能预后评估前间断服用研究药物的患者，也进行了卒中后 mRS 评分。

分析和发表的数据均为实测值，减少了信息缺失造成的偏移。

研究人群
15 603 名高血管风险患者在 ASA 治疗的前提下，随机分为安慰剂组 (n=7801) 或氯吡格雷组 (n=7802)，随访时的中位数为 28 个月。研究人员报告了 503 例患者发生卒中，其中 441 例被确诊。

随机治疗组的卒中在 436 例确诊发生卒中的患者中，436 例患者在卒中发生 3 个月后进行了 mRS 评分。随机治疗组的卒中在 436 例确诊发生卒中并且在卒中后 3 个月的随访期间进行了功能障碍严重程度评估的患者中，202 例为氯吡格雷组，234 例为安慰剂组 (相对风险度降低 14%，95% CI: -4% - 29%，P=0.12，双侧)。

基线人口学特征及其它预后因素
如表 1 所示，随访期间发生卒中的两组患者在基线人口学特征及其它预后因素方面，没有显著差异。

研究药物的治疗时间
安慰剂组 234 例患者（随访期间发生卒中）在第 17.1 个月（中位数），而氯吡格雷组 202 例的治疗时间为 16.1 个月（中位数）(P=0.43)。

首次确诊卒中至功能障碍随访评估的时间
首次确诊卒中到卒中功能障碍随访评估的中位数时间，氯吡格雷组为 163 天，而安慰剂组为 130 天 (P=0.03)。

不同病理亚型的卒中预后
436 例卒中患者中，369 例(85%) 为缺血性卒中(氯吡格雷组 171 例 [84.7%]，安慰剂组 198 例 [84.6%])，41 例 (9%) 为出血性卒中 (氯吡格雷组 20 例 [9.9%]，安慰剂组 21 例 [9.0%])，26 例 (6%) 为不确定病理类型 (氯吡格雷组 11 例 [5.4%]，安慰剂组 15 例 [6.4%])。

首次卒中后 3 个月的 mRS 评分
如表 2 所示，氯吡格雷组与安慰剂组相比，卒中后 3 个月时 mRS 评分的平均值无显著差异 (氯吡格雷组 3.6 [标准差 2.3]，安慰剂组 3.3 [标准差 2.1]；P=0.15)。对卒中发生时使用的研究药物、随机至发生卒中的时间及首次 mRS 评分进行校正后，两组比较仍无显著差异。

如表 3 所示，比较氯吡格雷组与安慰剂组卒中后 3 个月时 mRS 评分，发现两组 mRS 评分的不同分值均无明显差异。尽管每个分值都发现氯吡格雷组患者卒中程度稍严重，但这很有可能是随机误差造成的 (偶然性)。在完成功能预后评估前间断服
表 2 确诊卒中后 7 天或出院时 ( 首次 mRS) 以及卒中后 3 个月时 ( 随访 mRS) mRS 评分功能预后总结

<table>
<thead>
<tr>
<th>治疗分组</th>
<th>氯吡格雷与 ASA 联合</th>
<th>安慰剂与 ASA 联合</th>
<th>mN=202/7802</th>
<th>mN=234/7801</th>
<th>P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>入组时 mRS 评分 % (n)</td>
<td>N=201</td>
<td>N=231</td>
<td>24 (12)</td>
<td>19 (8)</td>
<td></td>
</tr>
<tr>
<td>1. 无任何症状</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>2. 轻度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>3. 中度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>4. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>5. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>6. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>7. 死亡</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>首次 mRS 评分平均值 (标准差)</td>
<td>3.6 (1.8)</td>
<td>3.4 (1.7)</td>
<td>0.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>随访 mRS 评分 % (n)</td>
<td>N=202</td>
<td>N=234</td>
<td>24 (12)</td>
<td>19 (8)</td>
<td></td>
</tr>
<tr>
<td>1. 无任何症状</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>2. 轻度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>3. 中度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>4. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>5. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>6. 重度残疾</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>7. 死亡</td>
<td></td>
<td></td>
<td>31 (15)</td>
<td>50 (22)</td>
<td></td>
</tr>
<tr>
<td>随访 mRS 评分平均值 (标准差)</td>
<td>3.6 (2.3)</td>
<td>3.3 (2.1)</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>校正 mRS 评分, 最小二乘均数 (标准差)</td>
<td>3.5 (0.1)</td>
<td>3.4 (0.1)</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 经 t 检验得出 P 值

使用研究药物的患者 (n=261；氯吡格雷组：n=122，安慰剂组：n=139) 中，也得到相似的结果 (P=0.09)。

既往有 TIA 或缺血性卒中的患者

CHARISMA 临床研究纳入的 15603 例高血管风险患者中，4320 例患者存在明确的脑血管病症 (TIA [n=1233] 及缺血性卒中 [n=3245]；且 158 例缺血性卒中患者有 TIA 及干预，其中 2163 例纳入安慰剂组，2157 例纳入氯吡格雷组。

233 例患者随访中发生明确诊断的首次卒中 ( 对于有卒中史的患者为一次复发卒中)，其中 103 例为氯吡格雷组，130 例为安慰剂组 (相对危险度减少 20%，95% CI: -3% - 38%)。大多数属于缺血性卒中 (n=202/233 [87%]；91 例为氯吡格雷组，113 例为安慰剂组)，少数为出血性卒中 (n=19/236 [8%]；10 例为氯吡格雷组，9 例安慰剂组)。仅 12 例卒中无法分型。

如表 4 所示，比较氯吡格雷组与安慰剂组有 TIA 或卒中史患者 ( 再发) 卒中后 3 个月的 mRS 评分，无显著差异 ( 氯吡格雷组 3.4 [标准差 2.1]，安慰剂组 3.5 [标准差 2.5]，P=0.59)。

表 3 确诊卒中后 3 个月时 mRS 评分的二分法总结

<table>
<thead>
<tr>
<th>治疗分组</th>
<th>氯吡格雷与 ASA 联合</th>
<th>安慰剂与 ASA 联合</th>
<th>(N=202/7802)</th>
<th>(N=234/7801)</th>
<th>P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 评分</td>
<td>1-2 分和 3-7 分</td>
<td>88 (44)</td>
<td>108 (46)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>1-2 分</td>
<td>无症状或无明显残疾</td>
<td>114 (56)</td>
<td>126 (54)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>3-7 分</td>
<td>轻度残疾至死亡</td>
<td>117 (58)</td>
<td>135 (65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 评分</td>
<td>1-3 分和 4-7 分</td>
<td>85 (42)</td>
<td>81 (35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 分</td>
<td>无症状或轻度残疾</td>
<td>137 (68)</td>
<td>175 (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 评分</td>
<td>4-7 分和 5-7 分</td>
<td>65 (32)</td>
<td>59 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-7 分</td>
<td>中度残疾或死亡</td>
<td>65 (32)</td>
<td>59 (25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 经卡方检验得出 P 值

组 3.3 [标准差 1.9]； P=0.48。

讨论

本 CHARISMA 亚组研究的重要发现是，在长达 28 个月 ( 中位数) 的随访期间，氯吡格雷 ( 联合阿司匹林) 或安慰剂 ( 联合阿司匹林) 治疗对高血管风险患者的卒中发生率及严重程度 (mRS 评分方面) 没有统计学差异。

本研究的优势是这项大样本随机对照双盲研究，在大样本高血管风险人群中观察到大量卒中发生。

本研究的缺点在于尽管研究假说和分析方法是预先设定的，它只是一项亚组研究而非临床试验的主要目标。基于终点事件纳入分析患者的卒中严重程度，因此无法假定两治疗组之间重要的预后因素是平衡的 ( 即治疗效应不随机)。然而，如表 1 所示，两组患者的基线人口学特征及其它影响卒中严重程度的重要预后因素没有显著差异。

第二个潜在的缺点是随机分组时没有进行 mRS 评估 ( 如基线时)，因此患者随机分组时，有可能存在基线功能情况的不均衡。然而，若患者存在严重功能障碍不会被纳入本研究，因此最大程度降低了基线时卒中严重程度不均衡的可能。

第三，发生卒中终点事件后，氯吡格雷组进行 mRS 评估的时间较安慰剂组晚 (氯吡格雷组中位数时间为 163 天，安慰剂组为 130 天， P=0.03)，因此，可能导致氯吡格雷组患者的预后更好 ( 即发生卒中至评估的康复时间更长)。

第四，mRS 评分对某些临床意义的小差异不够敏感，如功能状态的变化 [6]。
表4 既往有TIA或卒中史患者首次确诊卒中事件后7天或出院时（首次mRS）与卒中后3个月时（随访mRS）mRS评分的功能预后总结

<table>
<thead>
<tr>
<th>mRS评分</th>
<th>治疗分组</th>
<th>ASA联合（N=103/2157）</th>
<th>ASA联合（N=130/2163）</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>首次mRS评分，n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1，无任何症状</td>
<td>13 (13)</td>
<td>12 (9)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>2，虽有症状，但没有残疾</td>
<td>24 (23)</td>
<td>35 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3，轻度残疾</td>
<td>20 (19)</td>
<td>26 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4，中度残疾</td>
<td>16 (15)</td>
<td>25 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5，中重度残疾</td>
<td>16 (15)</td>
<td>16 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6，重度残疾</td>
<td>10 (10)</td>
<td>12 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7，死亡</td>
<td>4 (4)</td>
<td>4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>首次mRS评分，平均值（标准差）</td>
<td>3.4 (1.7)</td>
<td>3.4 (1.6)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>随访mRS评分，n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1，无任何症状</td>
<td>20 (19)</td>
<td>23 (18)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>2，虽有症状，但没有残疾</td>
<td>22 (21)</td>
<td>31 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3，轻度残疾</td>
<td>22 (21)</td>
<td>30 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4，中度残疾</td>
<td>12 (12)</td>
<td>18 (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5，中重度残疾</td>
<td>5 (5)</td>
<td>8 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6，重度残疾</td>
<td>2 (2)</td>
<td>3 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7，死亡</td>
<td>20 (19)</td>
<td>17 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>随访mRS评分，平均值（标准差）</td>
<td>3.4 (2.1)</td>
<td>3.3 (1.9)</td>
<td>0.48</td>
<td></td>
</tr>
</tbody>
</table>

第五，mRS评分是由大量卫生专业人员操作的，但也许某些人没有经过严格的培训或不熟悉评分的方法，其中许多还并不是卒中医师。然而，很多研究证实mRS评分在不同评分人员之间的可靠性较高[8]。

最后，本次研究可能检验效力不够，无法支持或否定抗血小板联合治疗较单药治疗更有益于减轻卒中的严重程度。这个假设虽然看似简单，但对于临床工作则十分重要。

本研究采用卒中后3个月时mRS评分，无法证实氯吡格雷联合ASA治疗能有效降低卒中的严重程度。

参考文献