Circulation

ORIGINAL RESEARCH ARTICLE

Time Course for Benefit and Risk of Clopidogrel and Aspirin After Acute Transient Ischemic Attack and Minor Ischemic Stroke

A Secondary Analysis from the POINT Randomized Trial

BACKGROUND: In patients with acute minor ischemic stroke or high-risk transient ischemic attack enrolled in the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke [POINT] Trial), the combination of clopidogrel and aspirin for 90 days reduced major ischemic events but increased major hemorrhage in comparison to aspirin alone.

METHODS: In a secondary analysis of POINT (N=4881), we assessed the time course for benefit and risk from the combination of clopidogrel and aspirin. The primary efficacy outcome was a composite of ischemic stroke, myocardial infarction, or ischemic vascular death. The primary safety outcome was major hemorrhage. Risks and benefits were estimated for delayed times of treatment initiation using left-truncated models.

RESULTS: Through 90 days, the rate of major ischemic events was initially high then decreased markedly, whereas the rate of major hemorrhage remained low but relatively constant throughout. With the use of a model-based approach, the optimal change point for major ischemic events was 21 days (0–21 days hazard ratio 0.65 for clopidogrel-aspirin versus aspirin; 95% CI, 0.50–0.85; *P*=0.0015, in comparison to 22–90 days hazard ratio, 1.38; 95% CI, 0.81–2.35; *P*=0.24). Models showed benefits of clopidogrel-aspirin for treatment delayed as long as 3 days after symptom onset.

CONCLUSIONS: The benefit of clopidogrel-aspirin occurs predominantly within the first 21 days, and outweighs the low, but ongoing risk of major hemorrhage. When considered with the results of the CHANCE trial (Clopidogrel in High-Risk Patients With Non-disabling Cerebrovascular Events), a similar trial treating with clopidogrel-aspirin for 21 days and showing no increase in major hemorrhage, these results suggest that limiting clopidogrel-aspirin use to 21 days may maximize benefit and reduce risk after high-risk transient ischemic attack or minor ischemic stroke.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00991029.

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Clinical Perspective

What Is New?

- In secondary analysis of patients with minor ischemic stroke or high-risk transient ischemic attack in the POINT randomized trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke [POINT] Trial), reduction in major ischemic events with clopidogrel combined with aspirin in comparison with aspirin alone was greatest with 21 days of treatment rather than the full 90-day treatment in the trial, and risk of major hemorrhage was less during this period.
- Models suggested that treatment initiated as late as 3 days after symptom onset may still be beneficial.

What Are the Clinical Implications?

- After minor ischemic stroke or high-risk transient ischemic attack, 21 days of treatment with clopidogrel combined with aspirin may maximize benefit and reduce risk of hemorrhage.

Patients who experience a transient ischemic attack (TIA) or a minor ischemic stroke are at high short-term risk of subsequent stroke.[1–7] Trials of clopidogrel in combination with aspirin in cardiovascular and cerebrovascular disease suggest that the combination reduces risk of ischemic events but slightly increases risk of major hemorrhage.[5,6,8] The POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke [POINT] Trial) was an international, randomized, placebo-controlled, double-blind trial that evaluated the efficacy and safety of 90 days of combination clopidogrel-aspirin versus aspirin alone in patients with high-risk TIA or minor acute ischemic stroke.[5] In comparison with aspirin alone, clopidogrel-aspirin reduced major ischemic events but was associated with a small increase in major hemorrhage. A similar trial in a Chinese population, the CHANCE trial (Clopidogrel in High-Risk Patients With Non-disabling Cerebrovascular Events), demonstrated a benefit of clopidogrel-aspirin when used for 21 days without an increased bleeding risk.[6] The CHANCE trial performed a time-course analysis and concluded that the benefit of clopidogrel-aspirin exceeded the risk for up to 2 weeks of treatment.[9] In the primary analysis of the POINT trial, the proportional hazards assumption for the primary outcome was not satisfied, which suggested that the benefit of clopidogrel-aspirin varied over time. The objective of this secondary analysis of the POINT trial is to assess the time course of benefit and risk for clopidogrel-aspirin versus aspirin alone in patients with TIA or minor stroke to provide additional information about the optimal duration of treatment.

METHODS

The authors will make the data, detailed methods, and all other study materials available to researchers who wish to reproduce the analysis in this article. We performed a secondary analysis of the POINT trial, a randomized double-blind trial funded by the National Institute for Neurological Disorders and Stroke. The design, protocol, statistical analysis plan, and primary results have been published elsewhere.[5,10] In brief, a total of 4881 patients were enrolled at 269 sites in North America, Europe, Australia, and New Zealand between May 2010 and December 2017. Patients with minor ischemic stroke (National Institutes of Health Stroke Scale score ≤3) or high-risk TIA (ABCD^2 score ≥4)[5] within 12 hours of the time last known free of new ischemic symptoms were randomly assigned 1:1 to either clopidogrel (loading dose of 600 mg on day 1, followed by 75 mg/d for 90 days) or matching placebo that was indistinguishable by appearance and taste. All patients were treated with aspirin 50 to 325 mg/d for 90 days. Treatment group was assigned centrally with a web-based randomization system, stratified by study site. The trial is registered at ClinicalTrials.gov (NCT00991029). The protocol was approved by the institutional review boards of all participating sites. The trial was approved by institutional review boards and ethics committees according to local and national regulatory requirements; all patients provided written informed consent before enrollment.

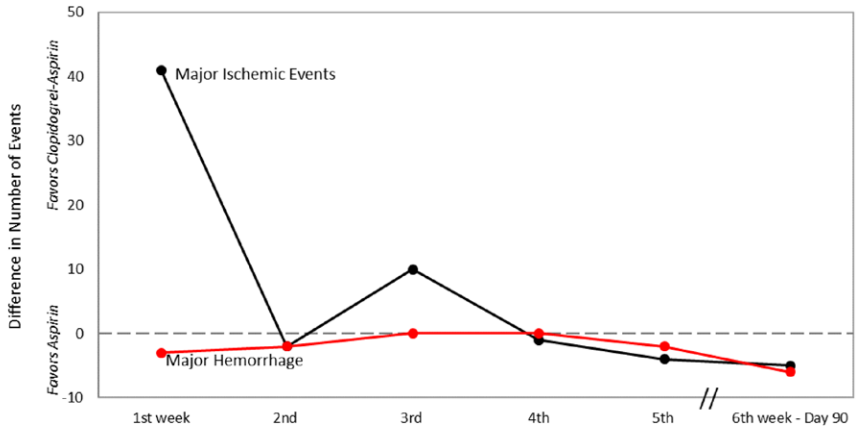
Outcomes

The primary efficacy outcome was major ischemic events: a composite of ischemic stroke, myocardial infarction, or death from an ischemic vascular event. The primary safety outcome was major hemorrhage, which was defined as symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of ≥2 units of red blood cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death attributable to hemorrhage.[11,12] Ischemic and hemorrhagic events were adjudicated by a central committee.

Statistical Methods

All analyses were performed using the intention-to-treat analysis sample in which patients were analyzed according to the randomized treatment assignment regardless of the type and amount of study drug actually received. The absolute number of events was estimated using the life-table method for the following time periods: 1st week, 2nd week, 3rd week, 4th week, 5th week, and 6th week to 90 days. The effective sample size for each time period was calculated as the sample size at the start of the time interval minus one-half the number of subjects censored in the time interval. The absolute difference in proportions (aspirin alone minus clopidogrel-aspirin) was calculated for each time period. The hazard rate was evaluated at the midpoint of the 7-day intervals using the life-table method.

As reported in the primary article, the proportional hazard assumption of the treatment effect did not hold for the primary efficacy outcome.[5] Because the efficacy and risk of clopidogrel-aspirin changed over time, we modeled the major



Number of Events by week (% of effective sample size)

		Total Events	1st week	2nd week	3rd week	4th week	5th week	6th week - Day 90
Major Ischemic Events	Aspirin (n=2449)	160	111 (4.60%)	14 (0.63%)	12 (0.55%)	4 (0.19%)	1 (0.05%)	18 (1.02%
	Clopidogrel-aspirin (n=2432)	121	70 (2.93%)	16 (0.71%)	2 (0.09%)	5 (0.23%)	5 (0.23%)	23 (1.26%
	Difference	39	41 (1.67%)	-2 (-0.08%)	10 (0.46%)	-1 (-0.04%)	-4 (-0.18%)	-5 (-0.25%
	Effective Sample Size		4805	4475	4366	4345	4332	3587
Major Hemorrhage	Aspirin	10	4 (0.17%)	0 (0.00%)	1 (0.04%)	1 (0.04%)	1 (0.04%)	3 (0.16%)
	Clopidogrel-aspirin	23	7 (0.29%)	2 (0.09%)	1 (0.04%)	1 (0.04%)	3 (0.13%)	9 (0.48%)
	Difference	-13	-3 (-0.13%)	-2 (-0.09%)	0 (0%)	0 (0%)	-2 (-0.1%)	-6 (-0.32%
	Effective Sample Size		4800	4632	4547	4534	4525	3742

Figure 1. Time course of the absolute treatment difference.
Differences between clopidogrel-aspirin and aspirin groups are shown for major ischemic events (black) and major hemorrhage (red) by week after randomization. Greater benefits with clopidogrel-aspirin (fewer ischemic events and fewer hemorrhages) are shown as positive numbers.

ischemic events with a binary treatment group indicator Z_1 and a time-dependent indicator function in which $Z_2(t) = (Z_1$ if $t > T$ and 0 if $t \leq T)$, where t is time in days and T is the cut point of the relative risk. To determine the optimal cut point for the piecewise proportional hazard model, we fit a model with a cut point at every day from 7 to 45 days, and the optimal cut point was the day in which the partial log-likelihood was maximized.[13]

A post hoc, exploratory analysis was conducted to estimate the treatment effect modeling a range of potential initiation times beyond 12 hours from symptom onset. All events through the optimal duration of treatment (21 days) were included in the analysis. By assuming that there was no accumulated benefit of antiplatelet effect, the treatment effect was modeled as follows: For each patient, the time from index event (TIA or minor stroke) onset to major ischemic events or censoring was derived. Beginning at 12 hours after onset, for every 6-hour period up to 168 hours (1 week), events and censoring time were left-truncated if the event or censoring occurred before the given time period by removing the participant from the numerator (event count) and the denominator (number at risk set) before calculating the proportion for each group. The absolute difference in proportions of events was calculated for each treatment group along the 95% (Wald) confidence intervals. The same approach was used to model major hemorrhage.

RESULTS

A total of 4881 patients (2449 in the aspirin group and 2432 in the clopidogrel-aspirin group) were enrolled into the POINT trial between May 2010 and December 2017. The trial was stopped early by the Data Management and Safety Committee because of early concerns about safety and also evidence of efficacy. All enrolled patients are included in this analysis. In the aspirin group, 160 (6.5%) major ischemic events occurred within 90 days, with most events occurring in the first week (Figure 1). In the clopidogrel-aspirin group, 121 (5.0%) major ischemic events occurred within 90 days, with most events also occurring in the first week. Major ischemic events were less frequent in patients randomly assigned to daily clopidogrel-aspirin versus aspirin in the first 3 weeks after enrollment but not in subsequent weeks (Figure 1).

The hazard rate of major ischemic events was high within the first several weeks, but then markedly decreased (Figure 2). In contrast, the hazard rate of major hemorrhage was low but constant over time for both treatment groups. By day 28, the rate for ischemic events no longer decreased and was constant for both treatment groups. With the use of a model-based

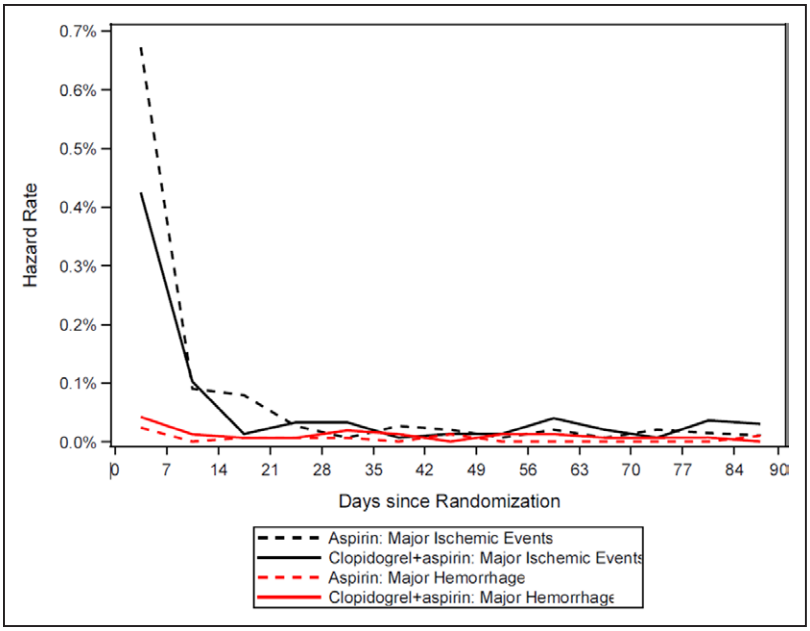


Figure 2. Hazard rates by week after randomization.
Results for major ischemic events (black) and major hemorrhage (red) are stratified by treatment group (clopidogrel-aspirin, solid; aspirin, dashed).

approach, the optimal cut point of relative risk for major ischemic events was 21 days (Table).

Within the first 21 days, major ischemic events occurred in 137 patients (5.6%) in the aspirin group and in 88 patients (3.6%) in the clopidogrel-aspirin group (absolute risk difference of 1.98%; 95% CI, 0.80%–3.15%), in comparison to an absolute risk difference of 1.56% (95% CI, 0.25%–2.86%), for 90-day treatment. Within the first 21 days, major hemorrhage occurred in 5 patients (0.2%) in the aspirin group and in 10 patients (0.4%) in the clopidogrel-aspirin group with a nonsignificant absolute risk difference of –0.21% (95% CI, –0.52% to 0.10%), whereas, for 90-day treatment, the difference was –0.54% (95% CI, –1.00% to –0.08%).

In analyses of treatment effect that modeled time to initiation of treatment beyond 12 hours, the absolute risk of ischemic events at 21 days remained lower in the clopidogrel-aspirin group even when it was initiated days after symptom onset (Figure 3). The benefit of clopidogrel-aspirin was greatest when initiated within 12 hours of symptom onset, but remained consistently beneficial even when started 72 hours after onset. The absolute risk of hemorrhage was smaller and not significant at all modeled time points for the initiation of treatment (Figure 3). In a sensitivity analysis that assumed that the risk of hemorrhage was the same regardless of when treatment was initiated, a 0.7% absolute benefit in reduction of ischemic events with initiation at 72 hours was balanced with a 0.5% absolute increase in major hemorrhage.

DISCUSSION

Treatment with clopidogrel-aspirin started within 12 hours after minor ischemic stroke or high-risk TIA and continued for 90 days reduces major ischemic events at the cost of a small increase in major hemorrhage.[5] The overall rate of major ischemic events is highest during the first week then markedly decreases, whereas the incidence of major hemorrhage remains low and relatively constant. The POINT trial was stopped early by recommendation of its Data Safety and Monitoring Committee because of early efficacy and also safety, with the knowledge that a shorter duration of treatment could improve the benefit-risk ratio. This secondary analysis suggests that the benefit of clopidogrel-aspirin in reducing major ischemic events occurs predominantly within the first 21 days with no substantial benefit afterward. Although clopidogrel-aspirin increased major hemorrhage risk, the absolute risk of major hemorrhage with clopidogrel-aspirin was smaller than the benefit in reduction of ischemic events, and remained relatively constant over 90 days. Thus, limiting clopidogrel-aspirin use to 21 days rather than 90 days would be expected to proportionally reduce the risk of major hemorrhage.

With 21 days of treatment, the absolute number of major ischemic events prevented by clopidogrel-aspirin far exceeded the absolute number of major hemorrhage

Table. Hazard Ratios for Efficacy and Safety Events by Time Period (N=4881)

Events	Hazard Ratio (95% CI)	*P* Value
Major ischemic events*		
0–21 days	0.65 (0.50–0.85)	0.0015
22–90 days	1.38 (0.81–2.35)	0.24
Major hemorrhage†		
0–90 days	2.32 (1.10–4.87)	0.02

*Piecewise Cox model for efficacy with change point at 21 days.
†Cox proportional hazard model for safety (proportional hazard assumption holds).

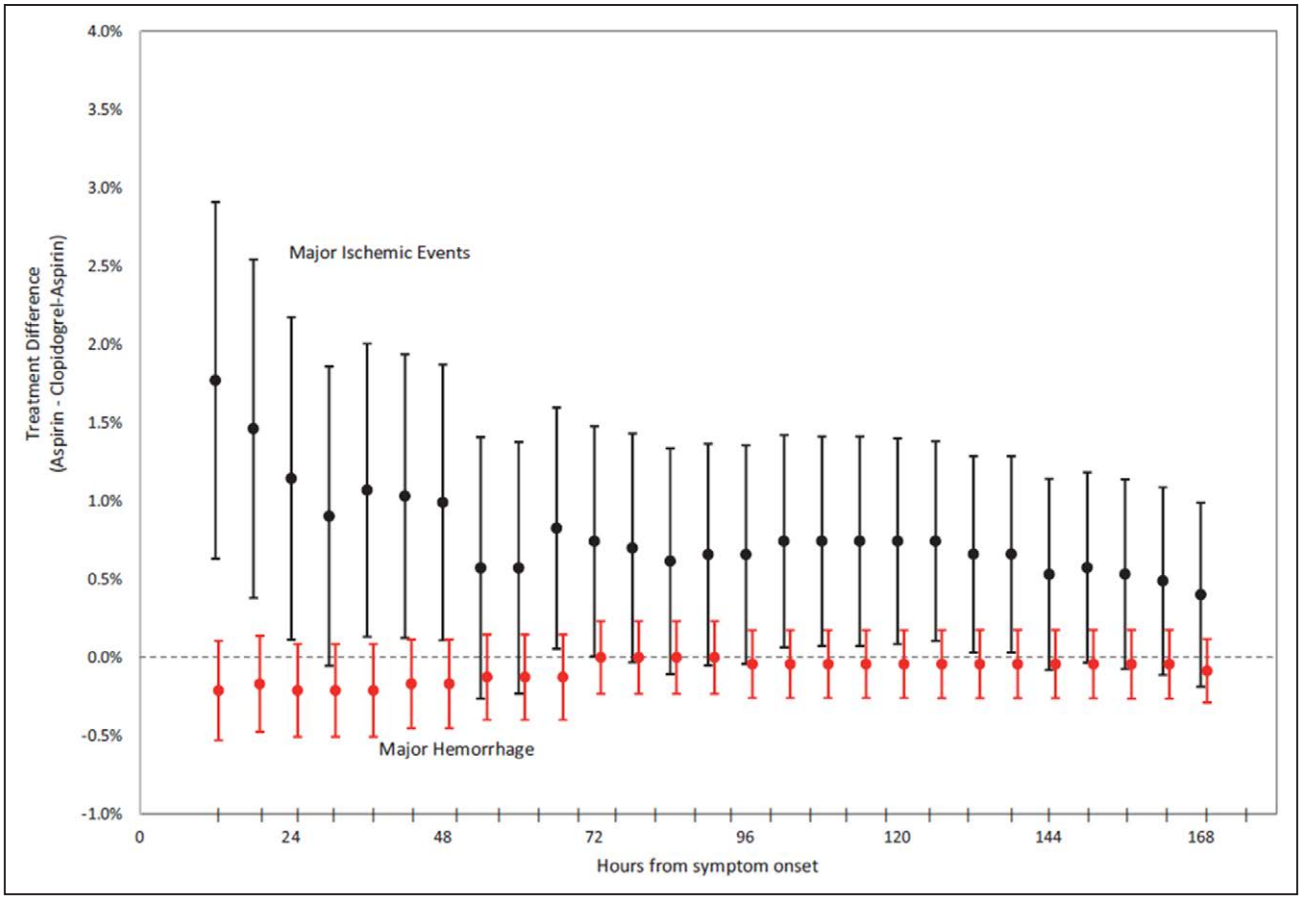


Figure 3. Impact of timing of the initiation of treatment.
The effect of timing of initiating clopidogrel-aspirin treatment on cumulative probability of events at 21 days was modeled. The absolute differences in proportions and 95% confidence intervals are shown for major ischemic events (black) and major hemorrhage (red) for patients modeled to start treatment at various times after symptom onset.

events caused. For every 1000 patients treated for 21 days with clopidogrel-aspirin, 20 major ischemic events would be prevented (95% CI, 8–32) and 2 major hemorrhages would be expected (95% CI, –5 to 1), which is more favorable than with 90-day treatment, during which 16 major ischemic events would be prevented (95% CI, 3–29) and 5 major hemorrhages produced (95% CI, –1 to 10).[5]

These results are consistent with those found in CHANCE, a similar trial that randomly assigned patients to 90-day treatment with aspirin or to clopidogrel-aspirin for 21 days followed by clopidogrel alone.[6] CHANCE also used clopidogrel 300 mg as a loading dose in comparison to a 600-mg loading dose in POINT. Over 90-day follow-up in CHANCE, the benefits of clopidogrel-aspirin were similar to those seen in POINT, whereas no increase in moderate-to-severe hemorrhage was reported. A time-course analysis from CHANCE suggested that the benefit of clopidogrel-aspirin was not apparent after the first 2 weeks, but stroke rates declined quickly and a treatment effect in the third week may not have been demonstrated because of limited power.[9] A 2-week treatment course in POINT would have reduced the impact of treatment, resulting in 4 fewer ischemic events prevented per 1000 people treated and the same number of major hemorrhages in comparison to 3-week treatment.

Some uncertainty remains about whether clopidogrel-aspirin is worth the risk when treatment cannot be initiated within 12 hours of symptom onset. CHANCE enrolled patients up to 24 hours after symptom onset and observed a benefit of clopidogrel-aspirin similar to that found in POINT.[6] In the present analysis from POINT, the benefit of clopidogrel-aspirin persisted even if only events occurring after the first 72 hours (3 days) were considered in the analysis. Hemorrhage risk was lower and insignificant at all delayed initiation time points; however, in a sensitivity analysis that assumed hemorrhage risk was similar regardless of when treatment was initiated, the benefit of clopidogrel-aspirin was balanced with a similar risk of major hemorrhage. Although this suggests that treatment initiated days after a cerebral ischemic event may still be beneficial, this conclusion should be considered cautiously because it is based on findings from a post hoc secondary analysis of modeled results. Furthermore, it should not discourage

emergent treatment whenever possible. It is interesting to note that the TARDIS trial (Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke) of intensive versus single-antiplatelet therapy in patients with ischemic stroke or TIA failed to show a treatment effect overall, but did find an effect among those in whom treatment was initiated within 12 to 24 hours.[14]

Trials of clopidogrel-aspirin initiated well after a stroke or TIA, in the nonacute period, have not found a benefit of treatment. Three large-scale trials that enrolled patients months to years after their initial ischemic events did not demonstrate a reduction in ischemic events with clopidogrel-aspirin in comparison to single-antiplatelet agents, but observed a small but significant increased risk of major hemorrhage.[15–17] These trials do not support the use of clopidogrel with aspirin for secondary stroke prevention during the nonacute phase, which is consistent with the findings from POINT and CHANCE in which the benefit of clopidogrel-aspirin was largely realized in the first few days to weeks after symptom onset, whereas the risk of hemorrhage was more constant over time.

There are several limitations of this analysis. Although a limited analysis of treatment effect and major hemorrhage at time cut points was prespecified, this secondary analysis is exploratory and thus does not meet the standards of evidence of a primary clinical trial. Over a quarter of patients discontinued study medication before 90 days, which may have led to an underestimation of the benefits and risks of clopidogrel-aspirin in later time periods. The efficacy of clopidogrel may vary by genotypes that are represented variably in international populations.[18] The method used to define the optimal time cut point may overestimate the differences between treatment periods. The analysis assumes that there is no rebound effect on stopping clopidogrel-aspirin; however, there was no evidence of a rebound effect when clopidogrel-aspirin was stopped at 21 days in the CHANCE trial.[6] Finally, modeling potential treatment benefits when initiating treatment beyond 12 hours after onset may not reflect the impact of delayed treatment because it includes data only on those actually treated within 12 hours; clot organization, alterations in platelet reactivity over time, differences in patient characteristics for those arriving after greater delay, or an accumulating impact of antiplatelet agents could alter the treatment impact of clopidogrel-aspirin in ways not reflected in our model. Ideally, the effective window to initiate clopidogrel-aspirin after symptom onset and the optimal treatment duration would be evaluated directly in randomized trials, but the expense and ethics of such trials may make them infeasible.

This analysis suggests that the benefit of clopidogrel-aspirin occurs predominantly within the first 21 days after onset of acute cerebral ischemia, and outweighs the small, increased risk of major hemorrhage. It also raises the possibility that benefits may outweigh risks even for patients started on treatment >3 days after symptom onset. These findings may have implications for treatment guidelines for dual-antiplatelet therapy use in clinical practice, but, as secondary analyses, should be weighted accordingly and distinctly from the level of evidence provided by the primary trial results.

ARTICLE INFORMATION

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