Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis

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OBJECTIVE
To assess the effectiveness and safety of dual agent antiplatelet therapy combining clopidogrel and aspirin to prevent recurrent thrombotic and bleeding events compared with aspirin alone in patients with acute minor ischaemic stroke or transient ischaemic attack (TIA).

DESIGN
Systematic review and meta-analysis of randomised, placebo controlled trials.

DATA SOURCES
Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Library, ClinicalTrials.gov, WHO website, PsycINFO, and grey literature up to 4 July 2018.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES AND METHODS
Two reviewers independently screened potentially eligible studies according to predefined selection criteria and assessed the risk of bias using a modified version of the Cochrane risk of bias tool. A third team member reviewed all final decisions, and the team resolved disagreements through discussion. When reports omitted data that were considered important, clarification and additional information was sought from the authors. The analysis was conducted in RevMan 5.3 and MAGICapp based on GRADE methodology.

RESULTS
Three eligible trials involving 10 447 participants were identified. Compared with aspirin alone, dual antiplatelet therapy with clopidogrel and aspirin that was started within 24 hours of symptom onset reduced the risk of non-fatal recurrent stroke (relative risk 0.70, 95% confidence interval 0.61 to 0.80, I²=0%, absolute risk reduction 1.9%, high quality evidence), without apparent impact on all cause mortality (1.27, 0.73 to 2.23, I²=0%, moderate quality evidence) but with a likely increase in moderate or severe extracranial bleeding (1.71, 0.92 to 3.20, I²=32%, absolute risk increase 0.2%, moderate quality evidence). Most stroke events, and the separation in incidence curves between dual and single therapy arms, occurred within 10 days of randomisation; any benefit after 21 days is extremely unlikely.

CONCLUSIONS
Dual antiplatelet therapy with clopidogrel and aspirin given within 24 hours after high risk TIA or minor ischaemic stroke reduces subsequent stroke by about 20 in 1000 population, with a possible increase in moderate to severe bleeding of 2 per 1000 population. Discontinuation of dual antiplatelet therapy within 21 days, and possibly as early as 10 days, of initiation is likely to maximise benefit and minimise harms.

Introduction
Minor ischaemic strokes or transient ischaemic attacks (TIAs) put patients at risk of subsequent cardiovascular events, including devastating major strokes.1 2 Clinical trials and meta-analyses have shown that patients who experience minor ischaemic strokes or TIAs benefit from antiplatelet therapy.3 Consequently, current guidelines for the management of acute ischaemic stroke and TIA recommend antiplatelet therapy—typically providing strong recommendations for use of a single agent, most commonly aspirin.4 7 One guideline provides a weak recommendation for clopidogrel and aspirin therapy, initiated within 24 hours of a patient presenting with minor stroke or TIA, and continuing for 21 days.8

Several trials have tested the effectiveness and safety of clopidogrel and aspirin versus aspirin alone to prevent recurrent events in patients experiencing non-cardioembolic ischaemic stroke or TIA in both the acute phase9 10  and the chronic phase.11-13 The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial reported that adding clopidogrel to aspirin starting within 24 hours of a minor stroke or TIA and continuing for 21 days reduced stroke risk without increasing the risk of moderate or severe haemorrhage at three and 12 months.9 14

Despite findings from the CHANCE trial, many guideline recommendations persisted in recommending
single rather than dual agent clopidogrel and aspirin for the initial treatment of minor ischaemic stroke or TIA.\textsuperscript{4,15,16} Rationales provided by guideline authors for not recommending routine dual antiplatelet therapy in patients with minor stroke or TIA included the possibility that the aetiological case-mix of stroke in Chinese patients could differ from populations in other regions (Europe and North America), particularly in the higher frequency of intracranial atherosclerosis, and that secondary prevention strategies in China might differ in important ways from Western settings.\textsuperscript{17-19} Thus, guideline developers commented on the need to await findings from ongoing randomised controlled trials in more diverse populations.

Recently, the Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke (POINT) study,\textsuperscript{20} a randomised, blinded, placebo controlled trial, reported on the effectiveness and safety of clopidogrel and aspirin use versus aspirin alone. Although both POINT and CHANCE included patients with minor ischaemic stroke or TIA, the population in POINT was more ethnically and geographically diverse. The 28% reduction in hazard of stroke reported by the POINT authors mandates a new review to inform the optimal management of these patients.

We performed an updated systematic review and meta-analysis of randomised, placebo controlled trials that enrolled patients with non-cardioembolic minor ischaemic stroke or high risk TIA within three days of presentation and addressed the effectiveness and safety of dual antiplatelet therapy with clopidogrel and aspirin versus either agent alone. This systematic review is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www.magicproject.org) and The BMJ.\textsuperscript{21} The aim of the project is to respond to new potentially practice changing evidence and provide trustworthy practice guidelines in a timely manner. This systematic review informs a parallel clinical practice guideline to be published in a multilayered electronic format in The BMJ and MAGICapp.

**Methods**

**Guideline panel and patient involvement**

According to the BMJ Rapid Recommendations process, a multiprofessional guideline panel that included three patients who had experienced an ischaemic stroke provided oversight to the systematic review and identified populations and outcomes of interest. All outcomes identified by the panel, and in particular, by the patients, were included in the review.

**Eligibility criteria**

To be eligible the studies had to be randomised, placebo controlled trials and include patients with a diagnosis of an acute minor ischaemic stroke or high risk TIA, treatment onset within three days, and intervention of dual antiplatelet therapy with clopidogrel and aspirin versus aspirin or clopidogrel alone. The trials also had to report on at least one of the following outcomes up to 90 days: all cause and stroke specific mortality, non-fatal ischaemic or haemorrhagic stroke, extracranial haemorrhage (mild, moderate, or severe), TIA, myocardial infarction, functional status, and quality of life.

We excluded studies in which more than 20% of patients experienced cardioembolic ischaemic stroke or TIA that failed to report data specific to the subgroup with non-cardioembolic stroke; crossover studies; and studies published only in abstract form.

**Search methods**

We identified a 2013 meta-analysis addressing early dual versus single antiplatelet therapy for acute ischaemic stroke or TIA\textsuperscript{22} and judged that the search, up to November 2012, was comprehensive. We evaluated all 14 studies included in that review for eligibility, and then conducted a comprehensive search for other relevant studies from January 2012 to July 2018.

Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane library, ClinicalTrials.gov, WHO website, PsycINFO, and grey literature (www.opengrey.eu/) were searched. The search strategy included the keywords “antiplatelet therapy”, “aspirin”, “acetylsalicylic acid”, “ASA”; “clopidogrel”, “Plavix”, “Iscover”, “thienopyridines”, “ADP receptor inhibitors”, “stroke”, “cerebral ischemia”, “cerebral infarction”, “transient ischaemic attack”, “TIA”, and “randomised controlled trial”.

To identify trials that may not have been published in full or were missed through the electronic search, investigators manually searched all references from the included studies and relevant previous systematic reviews. Appendix 1 presents the full search.

**Data collection**

Two reviewers independently screened the title and abstract and full text levels of potentially eligible studies. A third team member reviewed all final decisions, and the team resolved disagreements through discussion. This process also applied to risk of bias ratings and extraction of key variables (eg, numbers of events). When reports omitted data that we considered important, we contacted authors for clarification and additional information.

**Data extraction and management**

Two reviewers independently extracted several data using a predesigned data extraction form: characteristics of enrolled patient population, description of intervention and control, and description and event rate of patient important outcomes. To determine the timeframe of any apparent benefit, we reviewed incidence curves presented in the primary studies.

**Assessment of risk of bias**

To address risk of bias we used a modified version of the Cochrane risk of bias tool for randomised trials.\textsuperscript{23-26} We assessed the generation for random sequence;
concealment for allocation sequence; blinding of participants, healthcare providers, data collectors, and outcome assessors or adjudicators, or both; incomplete outcome data (missing or lost to follow-up) (we judged low risk of bias if the rate of missing data was lower than 10%); and other potential sources of bias (ie, early trial discontinuation).

We rated the overall risk of bias for each study as the highest risk of bias for any criterion. We evaluated risk of bias on an outcome-by-outcome basis and noted any differences across outcomes.

Statistical analysis
Our primary analyses were based on the numbers of events in each intervention and control group. We used DerSimonian and Laird random effects models in RevMan 5.3 to conduct the meta-analyses. Study weights were generated using the inverse of the variance.

We present results as relative risks and associated 95% confidence intervals. The $\chi^2$ test for heterogeneity and the I$^2$ statistic were used to assess heterogeneity between studies.

As the POINT study enrolled a diverse, multinational population who underwent contemporary stroke management, we applied the relative risks to the baseline risks from this trial to calculate absolute effects (eg, 6.4% risk for recurrent stroke).

As authors used different terms to categorise symptomatic intracerebral haemorrhage, symptomatic subdural haemorrhage, and symptomatic subarachnoid haemorrhage, we consider the functional consequences of these events sufficiently similar to include in a composite variable of symptomatic intracranial haemorrhage. Considering that death from intracranial or extracranial bleeding, or from ischaemic stroke, are equally important, and that non-fatal haemorrhagic and ischaemic stroke have a similar distribution of functional outcomes, we considered our key outcomes all cause mortality, non-fatal stroke, and non-fatal serious bleeding.

Studies did not report outcomes exactly as we defined them; for instance, studies reported all cause mortality and all ischaemic stroke (including fatal and non-fatal), so in effect double counting ischaemic stroke mortality that contributes to both all cause mortality and ischaemic stroke. The limitation necessitated contact with authors to obtain the appropriate data for our analytical approach.

To address timing of discontinuation of clopidogrel, the guideline panellists visually inspected the incidence curves of the individual studies and hypothesised that most of the difference between dual antiplatelet therapy and aspirin in stroke occurs up to day 10, then a smaller difference between days 11 and 21, and no difference after day 21. They therefore constructed the intervention and comparator for the second PICO (population, intervention, comparison, outcome) question as clopidogrel for 10 to 21 days versus clopidogrel for 22 to 90 days. They also hypothesised that the relative increase in bleeding risk would be similar between the intervention and comparator groups across the entire timeframe.

Using the stroke and major bleed probabilities plotted within the Kaplan-Meier curves of the two large eligible trials, we utilised the Digitizelt software (Digitizelt, Braunschweig, Germany) to obtain the incidence probabilities for both stroke and bleeding. For the POINT trial we used the entire 90 days of follow-up; for the CHANCE trial, because participants randomised to dual antiplatelet therapy were prescribed the treatment for only 21 days, we used data only up to day 21.

We then calculated the individual time-to-event patient data. We visually compared the original Kaplan-Meier curves with the reconstructed Kaplan-Meier curves to ensure accuracy of the simulated individual patient time-to-event data, as well as the calculated hazard ratios and their confidence intervals. We constructed curves both for the entire period and for the randomisation to day 10, 11 to 21, and 22 to 90 periods.

For each period we generated odds ratios by conducting logistic regressions to test the effect of dual antiplatelet therapy versus aspirin (independent variable) on stroke and bleeding (dependent variables) for days 0 to 10, 11 to 21, and 22 to 90. We also generated pooled Kaplan-Meier curves for each of these periods. Because the hazard changed over time we did not present a hazard ratio for the entire 90 days.

To calculate absolute effects, we utilised the simulated individual patient data to compare the risk difference for dual antiplatelet therapy versus aspirin up to day 10, days 11 to 21, and days 22 to 90.

Missing data
When studies reported missing data (loss to follow-up), we conducted a complete case analysis as our primary analysis. We also investigated the robustness of any outcome in which the confidence interval excluded no effect, by conducting a plausible worst case sensitivity analysis. This analysis attributed events in control patients lost to follow-up in the same ratio as those followed (eg, if there was a 5% event rate in control patients followed, we imputed a 5% event rate in control patients lost). For the intervention group, we imputed three times the rate of events in those lost to follow-up as those followed (eg, if there was a 5% event rate in intervention patients followed, we imputed a 5% event rate in intervention patients lost). For each study we then combined patients who were followed and those who were lost and pooled the new results across studies to determine the extent to which results are robust to these assumptions. Because most strokes occurred in the first seven days after randomisation, we used the seven day loss to follow-up reported in POINT rather than the 90 day loss to follow-up.

If at least three studies were available for each subgroup, we planned a subgroup analysis of studies judged at high risk of bias versus low risk of bias.
Quality of evidence
We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess quality of evidence and presented the data using MAGICapp.20 We rated quality of evidence as very low, low, moderate, or high by assessing precision, inconsistency, indirectness, publication bias, and the overall risk of bias, for each outcome. We developed summary of finding tables using MAGICapp and included the reasons for rating down the quality of the evidence.

Results
We requested information on the distribution of fatal and non-fatal outcomes from the principal investigators of two studies,9 20 both of whom provided the information necessary for our analytical approach.

Study identification
Figure 1 summarises our search for eligible studies. Of the 14 studies in the 2013 systematic review,22 two were eligible for our review.9 10 Our search of electronic databases retrieved 2524 records, of which 507 were duplicates. We excluded 2017 records based on title and abstract and assessed 20 full text articles, of which two were eligible.9 20 After removal of one duplicate study, three studies were eligible for review.9 10 20

Characteristics of included studies
Table 1 presents the characteristics of the three eligible trials involving 10 447 participants. One study used a factorial design including a comparison between simvastatin and placebo10; the other two studies each included two treatment arms.9 20 All studies enrolled patients with acute minor ischaemic stroke or high risk TIA within 12 or 24 hours after symptom onset, compared dual antiplatelet therapy with aspirin, and followed patients for 90 days. Sample size varied from 396 to 5170; the two largest trials9 20 contributed 10 051 patients. One trial was conducted in Asia,9 one in North America,20 and one in multiple countries.20 Patients with an indication for oral anticoagulant therapy (eg, atrial fibrillation) were excluded from the POINT and CHANCE trials. The mean or median age ranged from 62 to 69.8 years, and the proportion of men from 52.8% to 66.2%. All eligible studies reported recurrent stroke events (ischaemic or haemorrhagic) and bleeding events.

Risk of bias
Figure 2 summarises our risk of bias assessment. All judgments concluded low risk of bias (including incomplete outcome data—loss to follow-up ranged from 0.7% to 6.6%20), but one trial20 was discontinued owing to an increase in major haemorrhage, which likely results in an overestimate of the impact of dual antiplatelet therapy on this outcome.

Outcomes
Non-fatal recurrent stroke
Three studies including 10 301 patients9 10 20 reported the incidence of any non-fatal recurrent stroke. Pooled analysis showed that dual antiplatelet therapy started within 24 hours of symptom onset reduced the risk of non-fatal recurrent stroke (relative risk 0.70, 95% confidence interval 0.61 to 0.80, I²=0%, absolute risk reduction 2.0%, high quality evidence) (table 2, fig 2). This result was minimally changed in the sensitivity analysis that considered missing data (0.72, 0.63 to 0.82) (appendix 2, fig 2).

Non-fatal recurrent stroke combines results from three studies including 10 301 patients9 10 20 that reported the incidence of non-fatal ischaemic stroke (0.69, 0.60 to 0.79, I²=0%, absolute reduction 2.0%, high quality evidence) (appendix 2, figs 3 and 4) and three studies including 10 301 patients that reported symptomatic non-fatal intracranial haemorrhage (1.27, 0.55 to 2.89, I²=0%, moderate quality evidence) (appendix 2, fig 5). Ischaemic stroke dominated all stroke events and was more common than haemorrhagic stroke (total of 786 ischaemic strokes, 23 haemorrhagic strokes).

Incidence curves from the CHANCE and POINT studies were consistent in showing that most strokes occurred within 10 days of randomisation. Moreover, visual inspection suggested that the dual and single therapy arms had separated entirely by 10 days; the curves appeared parallel thereafter.

All cause mortality
Two studies including 9690 patients9 20 reported all cause mortality. Pooled analysis showed little apparent effect on all cause mortality, with confidence intervals that included both an appreciable decrease and an appreciable increase (1.27, 0.73 to 2.23, I²=0%, moderate quality evidence) (table 2, appendix 2, fig 6).

Fig 1 | Flowchart for eligibility assessment according to PRISMA guidelines
Table 1 | Characteristics of the three eligible trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Design</th>
<th>Proportion stroke/TIA</th>
<th>No of patients randomised (clopidogrel/no clopidogrel)</th>
<th>Treatment onset</th>
<th>Intervention with dosages</th>
<th>Control with dosages</th>
<th>Duration of treatment/ control follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy (2007), FASTER</td>
<td>North America (Factorial design: including a comparison between simvastatin and placebo)</td>
<td>Acute minor stroke (NIHSS score ≤3)/TIA (WHO definition: Proportion not reported)</td>
<td>52.8</td>
<td>396 (201/195)</td>
<td>&lt;24 hours, median: 8.2-9.1 hours</td>
<td>Loading dose 300 mg clopidogrel followed by 75 mg clopidogrel daily+81 mg aspirin daily for study duration. If patient naive to aspirin, loading dose 162 mg aspirin followed by 75 mg clopidogrel+81 mg aspirin daily for study duration.</td>
<td>81 mg aspirin daily, with loading dose of 162 mg aspirin if patient naive to aspirin before study enrolment</td>
<td>90/90</td>
</tr>
<tr>
<td>Wang (2013), CHANCE</td>
<td>China (Two treatment arms)</td>
<td>Acute minor stroke (NIHSS score ≤3)/ high risk TIA (ABCD2 score ≥4): 72.1%/7.9%</td>
<td>66.2</td>
<td>5170 (2584/2586)</td>
<td>&lt;24 hours, mean 13 hours</td>
<td>75-300 mg aspirin at discretion of physician, and loading dose 300 mg clopidogrel on day 1, followed by 75 mg clopidogrel+75 mg aspirin daily on days 2-21.</td>
<td>75-300 mg aspirin at discretion of physician on day 1. 75 mg aspirin daily on day 2-90</td>
<td>21/90</td>
</tr>
<tr>
<td>Johnston (2018), POINT</td>
<td>North America, Europe, Australia, and New Zealand (Two treatment arms)</td>
<td>Acute minor ischaemic stroke (NIHSS score ≤3)/ high risk TIA (ABCD2 score ≥4): 56.8%/43.2%</td>
<td>55.0</td>
<td>4881 (2432/2449)</td>
<td>&lt;12 hours, mean 7 hours</td>
<td>A loading dose of 600 mg clopidogrel on day 1, followed by 75 mg clopidogrel+50 to 325 mg aspirin daily from day 2 through 90. Recommended initial dose of 162 mg aspirin for 5 days, followed by 81 mg aspirin daily</td>
<td>50-325 mg aspirin daily day 2-90</td>
<td>90/90</td>
</tr>
</tbody>
</table>

*Mean (SD).
†Median (range).

Mortality
Recurrent stroke (fatal and non-fatal)
Two studies including 10,101 patients reported that dual antiplatelet therapy reduced the risk of recurrent stroke compared with aspirin alone (0.61, 0.46 to 0.80, I2=43%, moderate quality evidence) (appendix 2, fig 3, 4). The sensitivity analysis considering the missing data among these studies did not appreciably change the results in any case.

Mortality:
Recurrent stroke (fatal and non-fatal)
Two studies including 10,101 patients reported that dual antiplatelet therapy reduced the risk of recurrent stroke compared with aspirin alone (0.61, 0.46 to 0.80, I2=43%, moderate quality evidence) (appendix 2, fig 3, 4). The sensitivity analysis considering the missing data among these studies did not appreciably change the results in any case.

Other outcomes
Other outcomes:
Mortality:
Recurrent stroke (fatal and non-fatal)
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Although description of subtypes of stroke was not comprehensively detailed in all three studies, the presentation makes clear that each included a mix of small and large vessel disease (appendix 3). Furthermore, only CHANCE conducted a subgroup analysis addressing intracranial large vessel stenosis (versus those without intracranial large vessel stenosis), which failed to suggest any difference in effect between the two (appendix 3). In FASTER, the authors documented the distribution of stroke type as cardioembolic (6.6%), lacunar (28.8%), large artery (24.0%), unknown (36.7%), and other (1.3%) (appendix 3).

Effect by stroke subtypes
Although description of subtypes of stroke was not comprehensively detailed in all three studies, the presentation makes clear that each included a mix of small and large vessel disease (appendix 3). Furthermore, only CHANCE conducted a subgroup analysis addressing intracranial large vessel stenosis (versus those without intracranial large vessel stenosis), which failed to suggest any difference in effect between the two (appendix 3). In FASTER, the authors documented the distribution of stroke type as cardioembolic (6.6%), lacunar (28.8%), large artery (24.0%), unknown (36.7%), and other (1.3%) (appendix 3).

Timing of discontinuation of clopidogrel
Figure 3 shows the pooled Kaplan-Meier curves for ischaemic stroke and moderate or major bleeding for patients randomised to dual antiplatelet therapy or aspirin. The stroke rates in the dual antiplatelet therapy and aspirin groups diverge rapidly after day 1. They continue to diverge until day 10. Before day 10, they continue essentially in parallel, with little or no incremental benefit with dual antiplatelet therapy. Appendix 4, figure 1, illustrates this further through separate Kaplan-Meier curves up to days 10, 11 to 21, and 22 to 90. These show that almost all, if not all, of the benefit of dual antiplatelet therapy in reducing the risk of stroke occurs in the first 10 days (2% absolute stroke reduction, odds ratio 0.64, 95% confidence interval 0.55 to 0.76); there is no appreciable additional benefit in days 22 to 90 (1.47, 0.84 to 2.56).

In contrast, the Kaplan-Meier curve for bleeding (fig 3) shows divergence beginning from randomisation, with the curves continuing to separate to day 90. Thus, while the benefit is restricted to the first 21 days, and possibly the first 10 days, the harm continues to accrue thereafter with continued clopidogrel use.

Discussion
Our review summarises high quality evidence that in patients with minor ischaemic stroke or high risk transient ischaemic attack (TIA), clopidogrel and aspirin used within 24 hours of the event reduces the risk of subsequent stroke over a 30 to 90 day period (relative risk reduction 30%, absolute risk reduction 1.9%, table 2) without an apparent impact on all cause mortality (table 2). Although dual antiplatelet therapy may increase the risk of haemorrhagic stroke, recurrent ischaemic stroke is more common (786 vs 23 events), resulting in a clear net benefit on recurrent stroke.

Dual antiplatelet therapy likely increases moderate or serious extracranial bleeding, but these events were much less common than recurrent ischaemic stroke (best estimate of increase in bleeding 0.2%) (table 2). The results provide high quality evidence of an increase in minor bleeding with dual antiplatelet therapy, but the absolute effect is small (increase of 0.7%) and this outcome is far less important than a recurrent stroke. Results suggest that the impact of dual antiplatelet therapy on TIA, myocardial infarction, or functional status is limited or absent.

Most of the benefit in terms of strokes prevented with dual antiplatelet therapy occurs within the first 10 days after stroke; evidence strongly suggests no important reduction—and likely no reduction at all—after 21 days (fig 3, table 3). However, dual antiplatelet therapy consistently increases the risk of bleeding for the duration that patients receive treatment (fig 3, table 3).

Strengths and limitations of this study
Strengths of this review include a comprehensive search for randomised, placebo controlled trials; explicit eligibility criteria with a focus on populations most likely to benefit from dual antiplatelet therapy; assessment of risk of bias; provision of important data not included in there published reports provided by the authors of the two large studies; use of the GRADE approach to determine our certainty in the evidence; and an innovative approach to creating a single incidence curve that informs the optimal duration for continuing clopidogrel from the two large studies. The consistent results across studies, and the clear benefit of dual antiplatelet therapy on recurrent stroke without evidence of important adverse effects, is likely to provide clear guidance for patients with high risk TIA and minor ischaemic stroke and for the clinicians responsible for their care.
Table 2  GRADE summary of findings for clopidogrel plus aspirin versus aspirin alone for the treatment of acute minor ischaemic stroke or high risk transient ischaemic attack (TIA)  

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin alone</th>
<th>Clopidogrel and aspirin</th>
<th>Difference (95% CI)</th>
<th>GRADE quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.2 (95% CI 0.00 to 0.40)</td>
<td>Moderate</td>
</tr>
<tr>
<td>All non-fatal recurrent stroke</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 1.9 (95% CI 1.22 to 2.58)</td>
<td>Moderate</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.2 (95% CI 0.00 to 0.40)</td>
<td>Moderate</td>
</tr>
<tr>
<td>All non-fatal recurrent stroke</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 1.9 (95% CI 1.22 to 2.58)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Functional disability measured by modified Rankin Scale score 2 (mRS 2)</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.4 (95% CI 0.2 to 0.6)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor quality of life measured by EQ-5D index score of ≤0.5</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.3 (95% CI 0.1 to 0.5)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Recurrent TIA</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.0 (95% CI 0.0 to 0.0)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mid or minor extracranial bleeding events</td>
<td>Moderate due to serious imprecision</td>
<td>Moderate due to serious imprecision</td>
<td>Difference 0.0 (95% CI 0.0 to 0.0)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Our study has some limitations. The loading dose and treatment onset time differed among the three studies: CHANCE and FASTER used a smaller loading dose of clopidogrel compared with POINT (300 mg v 600 mg) (table 1). This could leave clinicians with uncertainty as to which loading dose to choose. Our review does not address other populations of potential interest, including those who have experienced low risk TIA and those with moderate to severe ischaemic stroke.

No trial compared clopidogrel with dual antiplatelet therapy and the addition of aspirin. It is possible that different categories of ischaemic stroke subtypes—small vessel disease, large vessel stenosis, and cryptogenic—will respond differently to the addition of aspirin, and the net benefit of adding clopidogrel will therefore differ. The three trials did not address this issue in detail—to the extent they did, they failed to document convincing evidence of different subgroup effects according to different types of stroke. All three studies, however, enrolled populations heterogeneous for aetiology and excluded major cardioembolic causes with an indication for oral anticoagulant therapy, and the net benefit of adding clopidogrel across these heterogeneous population is clear.

Our review has important strengths compared with previous reviews.22 34-37 We focused on a specific population, used the GRADE approach to establish quality of evidence, chose an analytical strategy that clearly separated mortal and morbid events, obtained data from authors that allowed implementation of this plan, and conducted an innovative analysis that documented the duration of intervention effects. Most importantly, we included the recent POINT study conducted in heterogeneous Western populations with its striking replication of the previous Chinese CHANCE study.

Meaning of the study

The evidence summarised in our review has important implications for the duration of dual antiplatelet therapy. The CHANCE trial continued dual antiplatelet therapy for 21 days; the other trials for 90 days. The incidence curves from both CHANCE and POINT are striking in that they show that most stroke events occurred in the first seven days. Furthermore, separation of the incidence curves in the treatment and control groups happened within the first 10 days, with the curves thereafter essentially parallel (fig 3, table 3).

The failure of dual antiplatelet therapy to provide benefit beyond the first three weeks after treatment initiation is generally consistent with results from other studies examining the commencement of dual antiplatelet therapy substantially later than the first three days.12 13 38 These include the Secondary Prevention of Small Subcortical Strokes (SPS3) study, a randomised multicentre trial involving 3020 patients who failed to find a benefit of dual antiplatelet therapy but did show an increase in adverse events.12
Conclusion
Dual antiplatelet therapy with clopidogrel and aspirin given within 24 hours after high risk TIA or minor ischaemic stroke reduces the risk of subsequent stroke by about 2%, with few serious adverse consequences. Discontinuation of dual antiplatelet therapy as early as 10 days, and no later than 21 days, after initiation is likely to maximise its net benefit.

These data provide direct evidence on the effect of dual antiplatelet therapy with clopidogrel and aspirin for patients who have experienced high risk TIA or minor ischaemic stroke. The findings of this research paper raise questions about how the dual antiplatelet therapy should be used in clinical practice. In the linked article readers will find recommendations on the use of dual antiplatelet therapy with clopidogrel and aspirin for patients with high risk TIA or minor ischaemic stroke based on data from this paper. To do this a guideline panel has considered how direct this evidence is and using GRADE methodology has integrated this with for example the values and preferences of patients and resource implications. To read more about the guidelines please see the guideline article in this package.

Linked articles in this BMJ Rapid Recommendations cluster

- MAGICapp version: MAGICapp (www.magicapp.org/public/guideline/nyq1Yn) – Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

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Contributors: GHG conceived the study. QH and MT designed the search strategy and screened studies for eligibility. QH, FF, and RS wrote the first draft of the manuscript and conducted data analysis. MT, MOD, and GHG interpreted the data analysis and critically revised the manuscript. QH and GHG are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Table 3 | GRADE evidence profile: Dual antiplatelet with clopidogrel and aspirin for 10-21 days versus 22-90 days after transient ischaemic attack (TIA) or minor stroke

<table>
<thead>
<tr>
<th>Outcome; timeframe</th>
<th>Study results and measurements</th>
<th>Absolute effect estimates</th>
<th>Certainty in effect estimates (quality of evidence)</th>
<th>Plain text summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke; 90 days</td>
<td>Odds ratio 1.47 (95% CI 0.84 to 2.61), based on data from 4406 patients in one study. Follow-up 90 days</td>
<td>Stop clopidogrel: continue aspirin 10/1000, Continue clopidogrel and aspirin 14/1000</td>
<td>Difference: 4 more per 1000 (95% CI 2 fewer to 11 more, high)</td>
<td>Longer duration of dual antiplatelet therapy probably does not result in an important reduction in ischaemic stroke</td>
</tr>
<tr>
<td>Moderate or severe bleeding; 90 days</td>
<td>Odds ratio 2.20 (95% CI 0.83 to 5.78), based on data from 4599 patients in one study. Follow-up 90 days</td>
<td>Stop clopidogrel: continue aspirin 3/1000, Continue clopidogrel and aspirin 6/1000</td>
<td>Difference: 3 more per 1000 (95% CI 1 fewer to 7 more, high)</td>
<td>Longer duration of dual antiplatelet therapy increases risk of major bleeding by small amount</td>
</tr>
</tbody>
</table>

*Indirectness: serious. Patients were randomised 21 days before decision point of whether to stop clopidogrel or not, and patients who had a stroke within the first 21 days were not included in this analysis. More patients randomised to aspirin had a stroke before day 21. Therefore, patients who continued clopidogrel and aspirin were probably at higher risk of a stroke after day 21.
†Imprecision: serious. Confidence interval includes no difference.
submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The manuscript’s guarantors (GHG and QH) affirm that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

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Key points


Supplementary appendix 1: Search strategies and results
Supplementary appendix 2: Forest plots and sensitivity analysis
Supplementary appendix 3: Definition of bleeding events and stroke subtypes in the three included trials
Supplementary appendix 4: Adequate duration of therapy with dual antiplatelet therapy