Clopidogrel plus aspirin versus aspirin alone for the treatment of acute minor ischemic stroke or high-risk TIA: A systematic review and meta-analysis

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Title page

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Clopidogrel plus aspirin versus aspirin alone for the treatment of acute minor ischemic stroke or high-risk TIA: A systematic review and meta-analysis

Abstract

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 ischemic stroke or TIA.

Design : Systematic review and meta-analysis of randomized, placebo-controlled trials;

Data sources : MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane library, Clinicaltrials.gov, WHO website, PsycINFO, and grey literature up to 4 July 2018

Review methods : Two reviewers independently screened all potentially eligible studies according to pre-defined 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 if there was disagreement, the team resolved issues through discussion. When reports omitted data that we considered important, we received clarification and additional information 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 proved eligible. Compared with aspirin alone, dual therapy with clopidogrel and aspirin commenced within 24 hours of symptom onset reduced non-fatal recurrent stroke (RR 0.70; 95% CI 0.61 to 0.80, I^2=0%, absolute risk reduction 1.9%, high quality evidence), without apparent impact on all-cause mortality (RR 1.27; 95% CI 0.73 to 2.23, I^2=0%, moderate quality evidence), but with a likely increase in moderate or severe extracranial bleeding (RR 1.71, 95% CI 0.92 – 3.2, I^2=32%, absolute risk increase 2 per 1,000, moderate quality evidence). Most stroke events, and the separation in incidence curves between dual and single therapy arms, occurred within 10 days of randomization; 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 approximately 20 in 1,000 with a possible increase in moderate to severe bleeding of 2 per 1,000. Discontinuation of dual therapy within 21 days, and possibly as early as 10 days, of initiation is likely to

maximize benefit and minimize harms.

SUMMARY BOXES

Section 1: What is already known on this topic

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.

Section 2: What this study adds

Pooled data from 3 trials including over 10,000 patients established an important benefit of dual therapy begun within 24 hours of presentation in reducing absolute recurrent stroke incidence by approximately 2%. Serious extracranial bleeding in this setting is uncommon, and any increase with dual therapy is likely to be very small.

Discontinuation of dual therapy within 21 days, and possibly within 10 days, of initiation is likely

to maximize benefits and minimize harms.

Background

Minor ischemic strokes or transient ischemic attacks (TIAs) put patients at risk of subsequent cardiovascular events, including devastating major strokes [1] [2]. Clinical trials and meta-analyses have demonstrated that patients who suffer minor ischemic strokes or TIAs benefit from antiplatelet therapy [3]. Consequently, current guidelines for the management of acute ischemic 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 suffering non-cardioembolic ischemic stroke or TIA in both the acute [9] [10] and 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 90 days reduced stroke risk without increasing the risk of moderate or severe hemorrhage at 3 and 12 months [9] [14].

Despite findings from the CHANCE trial, many guideline recommendations persisted in recommending single rather than dual agent clopidogrel/aspirin for the initial treatment of minor ischemic stroke or TIA [4 15 16]. Rationales provided by guideline authors for not recommending routine dual antiplatelet therapy (DAPT) in patients with minor stroke or TIA included the possibility that the etiological case-mix of stroke in Chinese patients may 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 may differ in important ways from Western settings [17-19]. Thus, guideline developers commented on the need to await findings from ongoing RCTs in more diverse populations.

Recently, the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) study [20], a randomized, blinded, placebo-controlled trial, reported on the effectiveness and safety of clopidogrel and aspirin administration versus aspirin. Though 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 therefore performed an updated systematic review and meta-analysis of all randomized, 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 single agent. This systematic review is part of the *BMJ* Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation program (www.magicproject.org) and *The BMJ* [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 multi-layered electronic format in *The BMJ* and MAGICapp.

Methods

Guideline panel and patient involvement

According to the BMJ Rapid Recommendations process, a multi-professional guideline panel that included three patients who had experienced an ischemic 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

We included studies meeting the following criteria: (1) Randomized, placebo-controlled trials; (2) Patients with a diagnosis of an acute minor ischaemic stroke or high-risk TIA (3) treatment onset within 3 days; (4) Interventions: dual antiplatelet therapy with clopidogrel and aspirin versus aspirin or clopidogrel alone. (5) Reporting 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 the following studies: (1) those in which more than 20% of patients experienced cardioembolic ischemic stroke or TIA that failed to report data specific to the subgroup with non-cardioembolic stroke; (2) cross-over studies; (3) studies published only in abstract form.

Search methods

We identified a 2013 meta-analysis addressing early dual versus mono antiplatelet therapy for acute ischemic stroke or TIA [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.

We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials

(CENTRAL), Cochrane library, Clinicaltrials.gov, WHO website and PsycINFO, and grey literature (http://www.opengrey.eu/). The search strategy included the following keywords:

1. antiplatelet therapy
2. aspirin, acetylsalicylic acid, ASA
3. clopidogrel, Plavix, Iscover, thienopyridines, ADP receptor inhibitors
4. stroke, cerebral ischemia, cerebral infarction, transient ischemic attack, TIA
5. randomized controlled trial

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

Data collection

Two reviewers independently screened all potentially eligible studies at the title and abstract and full-text levels. A third team member reviewed all final decisions and if there was disagreement the team resolved issues through discussion. This process also applied to risk of bias ratings and extraction of key variables (e.g. 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 the following data independently using a pre-designed 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 time frame 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 randomized trials [23-26]. We assessed the following items.

- Generation for random sequence;
- Concealment for allocation sequence;
- Blind of participants
- Blinding of health care providers;
- Blinding of data collectors
- Blinding of outcome assessors and/or adjudicators;

- Incomplete outcome data (missing / lost to follow-up) (we judged low risk of bias if the rate of missing data was lower than 10%);
- Other potential source of bias (i.e., early trial discontinuation)

We rated 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 when there were differences across outcomes.

Statistical Analysis

Our primary analyses were based on the numbers of events that occurred 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 (CI). We assessed heterogeneity between studies using the chi-squared test for heterogeneity and the I^2 statistic.

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

We found that authors used different terms to categorize the following events: symptomatic intracerebral hemorrhage, symptomatic subdural hemorrhage, and symptomatic subarachnoid hemorrhage. 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 ischemic stroke, are equivalent in their importance, and that non-fatal hemorrhagic and ischemic 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 their outcomes allowing us to abstract all outcomes in this way. For instance, studies reported all-cause mortality and all ischemic stroke (including fatal and non-fatal) in effect double-counting ischemic stroke mortality that contributes to both all-cause mortality and ischemic stroke. The limitation necessitated contact with authors to obtain the data necessary for our analytic approach.

To address the issue of the timing of discontinuation of clopidogrel, the guideline panellists, by visual inspection of the incidence curves of the individual studies, hypothesized that most of the difference between DAPT and ASA in stroke occurs up to day 10, a smaller difference between days 11 and 21, and that there is no difference between the DAPT and ASA after day

21. They therefore constructed the intervention and comparator for the second PICO question as clopidogrel for 10 to 21 days versus clopidogrel for 22 to 90 days. They also hypothesized that the relative increase in bleeding risk would be similar between the intervention and comparator groups across the entire time frame.

Using the stroke and major bleed probabilities plotted within the Kaplan Meier curves of the two large eligible trials[9 27], we utilized the DigitizeIt software (DigitizeIt, 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 randomized to DAPT were prescribed DAPT for only 21 days, we used data only up to day 21.

We then calculated the individual time-to-event patient data[28]. We compared the original Kaplan Meier curves with the reconstructed Kaplan-Meier curves visually to ensure accuracy of the simulated individual patient time-to-event data, as well as the calculated hazard ratios and their CIs. We constructed curves for both the entire period and for the randomization to day 10, 11 to 21, and 22 to 90 periods.

We generated odds ratios for each period by conducting logistic regressions to test the effect of DAPT vs. ASA (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 time periods. We did not offer a hazard ratio for the entire 90 days because the hazard clearly changed over time.

To calculate absolute effects, we utilized the simulated individual patient data to compare the risk difference for DAPT vs ASA up to day 10, from day 11 to 21, and from 22 to 90 days.

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 [29]. This analysis attributed events in control patients lost to follow-up in the same ratio as those followed (e.g. if there is a 5% event rate in control patients followed, we imputed a 5% event rate in control patients lost). For the intervention group, we imputed 3 times the rate of events in those lost to follow-up as those followed (e.g. if there is a 5% event rate in intervention patients followed, we imputed a 15% event rate in intervention patients lost). We then combined patients who were followed and lost for each study 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 7 days after randomization, we used the 7-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 vs. 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 [30]. We rated quality of evidence as very low, low, moderate, or high by assessing imprecision, inconsistency, indirectness, publication bias, and the overall risk of bias, per 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 regarding 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 analytic approach.

Study Identification

Figure 1 summarizes our search for eligible studies. Of the 14 studies in the 2013 systematic review [22], 2 proved eligible for our review [9 10]. Our search of electronic databases retrieved 2524 records of which 507 proved to be duplicates. We excluded 2017 records based on title and abstract and assessed 20 full-text articles, of which 2 proved eligible [9 20]. After 1 duplicate publication was removed, 3 studies proved eligible for this review [9 10 20].

Characteristics of included studies

Table 1 presents characteristics of the three eligible trials involving 10,447 participants. One study used a factorial design including a comparison between simvastatin and placebo [10]; the other two studies each included two treatment arms [9 20]. All studies enrolled patients with acute minor ischemic stroke or high-risk TIA within 12 or 24 hours after symptom onset, compared dual antiplatelet therapy to aspirin, and followed patients for 90 days. Sample size varied from 396 to 5,170; the two largest trials [9 20] contributed 10,051 patients. One trial was conducted in Asia[9 31 32], one in North America[10], and one in multiple countries[20]. Patients with an indication for oral anticoagulant therapy (e.g. atrial fibrillation) were excluded from POINT and CHANCE trial. The mean or median age ranged from 62 to 69.8 years, and the proportion of males from 52.8% to 66.2%. All eligible studies reported recurrent stroke events (ischemic or hemorrhagic) and bleeding events.

Risk of bias

Figure 2 summarizes our risk of bias assessment. All judgements concluded low risk of bias (including Incomplete outcome data - loss to follow up ranged from 0.7% [9] to 6.6% [20]) but one trial [20] was discontinued due an increase in major hemorrhage which very likely results in an overestimate of the impact of dual therapy on this outcome.

Outcomes

Non-fatal recurrent stroke

Three studies including 10,301 patients [9 10 20] reported the incidence of any non-fatal recurrent stroke. Pooled analysis showed that dual therapy reduced non-fatal recurrent stroke (RR 0.70; 95% CI 0.61 to 0.80, I^2=0%, absolute reduction 1.9%, high quality evidence) (Table 2, Appendix 2, Figure 1). The sensitivity analysis considering the missing data changed this result very little (RR 0.72, 95% CI 0.63 – 0.82) (Appendix 2, Figure 2).

Non-fatal recurrent stroke combines results from three studies including 10,301 patients [9 10 20] that reported the incidence of non-fatal ischemic stroke (RR 0.69; 95% CI 0.60 to 0.79, I^2=0%, absolute reduction 2.0%, high quality evidence) (Appendix 2, Figures 3 and 4) and three

studies including 10,301 patients that reported symptomatic non-fatal intracranial hemorrhage (RR 1.27; 95% CI 0.55 to 2.89 I^2= 0%, moderate quality evidence) (Appendix 2, Figure 5). Ischemic stroke dominated all stroke events because it proved far more common than hemorrhagic stroke (total of 786 ischemic strokes, 23 hemorrhagic strokes).

Incidence curves from the CHANCE and POINT studies were very consistent in demonstrating that most strokes occurred within 10 days of randomization. Moreover, visual inspection suggested that the entire separation between dual and single arms had occurred by 10 days; curves appeared parallel thereafter.

All-cause mortality

Two studies including 9,690 patients [9 20] reported all-cause mortality. Pooled analysis showed little apparent effect on all-cause mortality with confidence intervals that included both appreciable decrease and increase (RR 1.27; 95% CI 0.73 to 2.23, I^2=0%, moderate quality evidence) (Table 2, Appendix 2, Figure 6).

Major or moderate non-fatal extracranial hemorrhage

Studies differed in their definition of major bleeding (appendix 3). Three studies reported in 4

articles [9 10 20 33] including 10, 075 patients reported on major (POINT) or severe or moderate (CHANCE and FASTER) extracranial hemorrhage (we combined severe and moderate bleeding categories into major bleeding for these 2 trials). Pooled analysis showed that dual therapy is likely to increase major extracranial hemorrhage (RR 1.71; 95% CI 0.92 to 3.20, I^2=32%, absolute increase 0.2%, moderate quality evidence) (Table 2, Appendix 2, Figure 7).

Other outcomes

Two studies presented in 3 reports [9 20 34] including 9,690 patients reported functional outcomes measure by modified Rankin Scale (mRS) defining disability as an mRS of 2 or more with an mRS of 6 representing death. We derived non-fatal functional disability data by subtracting total mortality from proportion with mRS 2-6. Pooled analysis suggested a small impact of dual therapy on disability (RR 0.90; 95% CI 0.81 to 1.01, I^2=7%, moderate quality evidence (Table 2, Appendix 2, Figure 8).

One study presented in 3 reports [9 34 35] and including 5,131 patients, reported quality of life measure by EuroQol-5 Dimension (EQ-5D) defining poor quality of life as EQ-5D index score of 0.5 or less and high-risk TIA. The study also found that the proportion of poor quality of life was slightly lower in patients receiving dual therapy than those receiving aspirin alone (RR 0.81; 95% CI 0.66 to 1.01), moderate quality evidence (Table 2).

Two studies including 9,916 patients reported on recurrent TIA. Pooled analysis suggested little impact of dual therapy on TIA with wide confidence intervals (RR 0.90; 95% CI 0.71 to 1.14, I^2=0%, moderate quality evidence) (Table 2, Appendix 2, Figure 9).

Three studies including 10,075 patients [9 10 20] reported mild bleeding. Pooled analysis showed that dual therapy increased the risk of mild/minor extracranial bleeding (RR 2.22; 95% CI 1.60 to 3.08, I^2=18%, absolute increase 0.7% high quality evidence) (Table 2, Appendix 2, Figures 10 and 11).

Myocardial infarction

Two studies including 9,690 patients [9 20] reported on myocardial infarction. Pooled analysis provided very wide, essentially non-informative, confidence intervals (RR 1.45; 95% CI 0.62 to 3.38, I^2=0%, low quality evidence) (Appendix 2, Figure 12).

Recurrent stroke (Fatal and Non-fatal)

Three studies including 10,301 patients [9 10 20] reported all recurrent stroke (fatal or non-fatal). Pooled analysis showed that dual therapy reduced all recurrent stroke (RR 0.71; 95% CI 0.63

to 0.82, I^2=0%) (Appendix 2, Figures 13 and 14).

The sensitivity analysis considering the missing data among these studies did not appreciably change the results in any case.

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). Further, 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%); 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 DAPT or ASA. Figure 3A demonstrates that the stroke

rates in the DAPT and aspirin groups diverge rapidly after day 1. They continue to diverge until day 10. Subsequent to day 10, they continue essentially in parallel, with very little or no incremental benefit with DAPT. Figure 1, Appendix 4, illustrates this further through separate Kaplan-Meier curves up to day 10, 11 to 21, and 22 -90, These demonstrate that that almost all, if not all of the benefit of DAPT in reducing stroke occurs in the first 10 days, (2% absolute stroke reduction, odds ratio 0.64, 95% CI 0.55 to 0.76).; there is certainly no appreciable additional benefit in days 22 to 90 (OR 1.47, 95% CI 0.84 to 2.56).

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

Discussion

Principal findings

Our review summarizes high quality evidence that, in patients with minor ischemic stroke or high-risk TIA, administration of clopidogrel and aspirin commenced within 24 hours of the event reduces subsequent stroke over a 30 to 90-day period (relative risk reduction 30%, absolute

risk reduction 1.9%, Table 2) without apparent impact on all-cause mortality (Table 2). Although dual antiplatelet therapy may increase hemorrhagic stroke, recurrent ischemic stroke is much more common (786 Vs. 23 events), resulting in clear net benefit on recurrent stroke.

Dual antiplatelet therapy likely increases moderate or serious extracranial bleeding, but again these events are much less common than recurrent ischemic stroke (best estimate of increase in bleeding 0.2%) (Table 2). Results provide high quality evidence of an increase in minor bleeding with dual 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 therapy on TIA, myocardial infarction, or functional status is limited or absent.

Most of the benefit in terms of strokes prevented with DAPT occurs within the first 10 days after stroke; evidence strongly suggest no important reduction – and likely no reduction at all - after 21 days (Figure 3, Table 3). On the other hand, DAPT consistently increases the risk of bleeding for the duration that the patients remained on DAPT (Figure 3, Table 3).

Strengths and limitations

Strengths of this review include a comprehensive search for randomized, placebo-controlled trials; explicit eligibility criteria with a focus on populations most likely to benefit from dual

therapy; assessment of risk of bias; provision of important data not included in the 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 ischemic stroke, and the clinicians responsible their care.

Our study suffers from 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 (300mg vs. 600mg) (Table 1). This may 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 populations with moderate to severe ischemic stroke.

Those who believe that, if one is going to use a single antiplatelet agent, it should be clopidogrel would be interested in a comparison of clopidogrel to DAPT with the addition of aspirin. We sought, and did not find, any trial addressing that question. It therefore remains unanswered.

It is possible that different categories of ischemic 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 fail to document convincing evidence of different subgroup effects according to different types of stroke. What we can say with confidence is that all three studies enrolled populations heterogeneous with respect to etiology, excluding major cardioembolic causes with an indication for oral anticoagulant therapy, and across these heterogeneous population the net benefit of adding clopidogrel is clear.

Our review has important strengths relative to previous reviews [22 36-39]. We chose to focus on a specific population, used the GRADE approach to establish quality of evidence, chose an analytic 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 summarized in our review has important implications for the duration of dual therapy. The Chinese CHANCE trial continued dual therapy for 21 days; the other trials for 90 days. The incidence curves from both CHANCE and POINT are striking in that they demonstrate most stroke events occurred in the first seven days. Furthermore, separation of the treatment and control groups' incidence curves happen within the first 10 days, with incidence curves essentially parallel thereafter (Figure 3, Table 3).

The failure of dual therapy to provide benefit beyond the first three weeks after initiation is generally consistent with results from other studies examining the commencement of dual therapy substantially later than the first three days [12 13 40]. These include the Secondary Prevention of Small Subcortical Strokes (SPS3) study, a randomized multicenter trial involving 3020 patients that failed to find a benefit of dual 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 subsequent stroke by approximately 2% with few serious adverse consequences. Discontinuation of dual therapy as early as 10 days, and no later than 21 days, after initiation is likely to maximize its net benefit.

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Contributors statement:

GHG conceived the study idea; QH and MT designed the search strategy and screened studies for eligibility; QH, MT, MOD and GHG assessed study risk of bias and the quality of the body of evidence; 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. GHG is the guarantor.

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Transparency statement:

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.

Differences between protocol and review

Authors developed and submitted a protocol to PROSPERO before the initiation of the review process. We conducted the review, largely in accordance with the criteria and methods detailed in the original protocol though there were a few noteworthy modifications. We added additional patient-important outcomes to the original list of outcomes for data collection as mandated by the panel. These include quality of life and functional outcomes. Additionally, during the data extraction process authors found that the definition of certain outcomes varied between the three included studies and especially so for the outcome of bleeding. After extensive discussion about how to define and pool bleeding events, we decided to group intracranial cerebral bleeding + severe extracranial bleeding + moderate extracranial bleeding as moderate or major bleeding events (fatal and non-fatal separately). Similarly, we grouped asymptomatic + mild extracranial bleeding events as mild bleeding events and revised criteria for defining and pooling death events. We also assessed all stroke, ischemic stroke, and hemorrhagic stroke separated as fatal and non-fatal events to avoid double counting deaths. Methods-wise, there were no significant changes except for the decisions to only explore

subgroup differences between studies at high and low risk of bias if there were at least three studies available per subgroup, present absolute effects if there were statistically and/or clinically significant differences between the intervention and control groups, and use 7-day loss to follow-up data (as presented in POINT) versus the overall 90 day loss to follow up data because most events, and all the treatment efffect, occurred within the first 7 days. We also conducted initially unplanned analyses exploring the distribution of intervention effects over time. When data were not available nor presented in the desired formats, we contacted original study authors. Finally, for the sensitivity analyses, we originally proposed using five times the events in the intervention group as the events in the patients lost to follow up. We modified this to three times the events as, on reflection, we felt the five times event rate was an overly conservative adjustment.

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Appendix 1: Search strategies and results

Appendix 2: Forest plots and sensitivity analysis

Appendix 3: The definition of bleeding events and the stroke subtypes in the three included trials.

Appendix 4: Adequate duration of therapy with dual antiplatelet therapy

Table 1: Characteristics of the three eligible trials

Author (Year), Trial	Country/ies	Proportion stroke/TIA	Sex (% male)	Age in years (mean or median/SD or range)	No. of patients randomized (Clopidogrel/no clopidogrel)	Treatment onset time	Intervention with dosages	Control with dosages	Duration of treatment/ control follow-up
Kennedy (2007), FASTER	North America	Acute minor stroke (NIHSS score ≤ 3) / TIA (WHO definition): Proportion not reported	52.8%	Mean: 68.1 (13.1)	396 (201/195)	within 24 hours; median: 8.2-9.1 hours	Loading dose of 300 mg clopidogrel followed by 75 mg clopidogrel daily + 81 mg aspirin daily for study duration. If patient naive to aspirin, loading dose of 162 mg aspirin followed by 75 mg clopidogrel + 81 mg aspirin daily for study duration.	81 mg aspirin daily, with a loading dose of 162 mg aspirin if patient was naive to aspirin before study enrollment	90 days/90 days
Wang (2013), CHANCE	China	Acute minor stroke (NIHSS score ≤3) / high-risk TIA (ABCD2 score ≥ 4): 72.1%/27.9%	66.2%	Median, Interquartile range: Intervention: (63, 55-72) Control: (62, 54-71)	5170 (2584/2586)	within 24 hours; mean 13 hours	75 to 300 mg aspirin at the discretion of physician and a loading dose of 300 mg of clopidogrel on day 1, followed by a dose of 75 mg clopidogrel + 75 mg aspirin daily on days 2 through 21. From day 22 to day 90, 75 mg clopidogrel alone.	75 to 300 mg aspirin at the discretion of physician on day 1. 75 mg aspirin daily on day 2 through 90	21 days/90 days
Johnston (2018) POINT	North America, Europe, Australia, and New Zealand	Acute minor ischemic Stroke (NIHSS score ≤ 3)/ high-risk TIA (ABCD2 score ≥ 4): 56.8%/43.2%	55.0%	Median, Interquartile range: Intervention: (65, 37-96) Control: (65, 56-74)	4881 (2432/2449)	Within 12 hours; mean 7 hours	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 an initial dose of 162 mg aspirin for 5 days, followed by 81mg aspirin daily.	50-325 mg aspirin daily from day 2 to 90. Recommended an initial dose of 162 mg aspirin for 5 days, followed by 81mg aspirin daily.	90 days/90 days

Table 2: GRADE summary of findings for Clopidogrel plus aspirin versus aspirin alone for the treatment of acute minor ischemic stroke or high-risk TIA

Population: Patients with minor ischemic strokes or high-risk TIA

Intervention: Clopidogrel and aspirin

Comparator: Aspirin alone

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Aspirin alone	Clopidogrel and aspirin	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
All non-fatal recurrent stroke	Relative risk: 0.7 (CI 95% 0.61 - 0.8) Based on data from 10301 patients in 3 studies[1] Follow up 90 days	**63** per 1000	**44** per 1000 Difference: **19 fewer per 1000** (CI 95% 25 fewer - 13 fewer)	**High**	Dual antiplatelet therapy has a small but important benefit in reducing recurrent strokes
All-cause mortality	Relative risk: 1.27 (CI 95% 0.73 - 2.23) Based on data from 9690 patients in 2 studies[2] Follow up 90 days	**2** per 1000	**4** per 1000 Difference: **1 more per 1000** (CI 95% 1 fewer - 6 more)	**Moderate** Due to serious imprecision[3]	Dual antiplatelet therapy probably has little or no impact on all-cause mortality
Moderate or major extracranial hemorrhage defined by individual study (non-fatal)	Relative risk: 1.71 (CI 95% 0.92 - 3.2) Based on data from 10075 patients in 3 studies[1] Follow up 90 days	**3** per 1000	**5** per 1000 Difference: **2 more per 1000** (CI 95% 0 fewer - 7 more)	**Moderate** Due to serious risk of bias and imprecision.[3,5]	Dual antiplatelet therapy probably results in a very small, possibly important increase in moderate or major extracranial bleeding.
Functional disability measure by modified Rankin Scale (mRS: 2-5) (Non-fatal)	Relative risk: 0.90 (CI 95% 0.81 - 1.01) Based on data from 9690 patients in 2 studies[2] Follow up 90 days	**142** per 1000	**128** per 1000 Difference: **14 fewer per 1000** (CI 95% 27 fewer - 1 more)	**Moderate** Due to serious imprecision[3]	Dual antiplatelet therapy possibly has a small but important benefit on patient function.
Poor quality of life measured by EQ-5D index score of 0.5 or less	Relative risk: 0.81 (CI 95% 0.66 - 1.01) Based on data from 5131 patients in 1 studies[4]	**68** per 1000	**55** per 1000 Difference: **13 fewer per 1000** (CI 95% 23 fewer - 1 more)	**Moderate** Due to serious imprecision[3]	Dual antiplatelet therapy probably has a s mall important benefit on quality of life.
Recurrent TIA	Relative risk: 0.9 (CI 95% 0.71 - 1.14)	**40** per 1000	**36** per 1000	**Moderate** Due to serious imprecision[3]	Dual antiplatelet therapy probably has little or no

	Based on data from 9916 patients in 2 studies[2] Follow up 90 days	Difference: **4 fewer per 1000** (CI 95% 12 fewer - 6 more) Difference: **2 more per 1000** (CI 95% 0 fewer - 7 more)		impact on recurrent TIA.
Mild/minor extracranial bleeding events	Relative risk: 2.22 (CI 95% 1.60 - 3.08) Based on data from 10075 patients in 3 studies[1]	**6** per 1000 **13** per 1000 Difference: **7 more per 1000** (CI 95% 4 more - 12 more)	**High**	Dual antiplatelet therapy results in a small and possibly important increase in mild extracranial bleeding.

1. Systematic review with included studies: POINT 2018, FASTER 2007, CHANCE 2013 Baseline/comparator: POINT 2018
2. Systematic review with included studies: POINT 2018, CHANCE 2013 Baseline/comparator: POINT 2018
3. Imprecision: Serious. Wide confidence intervals;
4. Systematic review with included studies: CHANCE 2013 Baseline/comparator: Control arm of reference used for intervention.
5. Risk of bias: Serious. POINT was stopped earlier than scheduled, resulting in potential for overestimating benefits; Imprecision: confidence interval includes a small reduction in risk and a large relative increase.

Table 3. GRADE Evidence profile: after 21 days of therapy with clopidogrel and ASA, what is the impact of stopping clopidogrel vs. continuing clopidogrel for 90 days total?

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Stop clopidogrel, continue ASA	Continue clopidogrel & ASA	**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
Ischaemic stroke 22-90 days	Odds Ratio: 1.47 (CI 95% 0.84 - 2.56) Based on data from 4406 patients in 1 study Follow up 90 days	**10** per 1000	**14** per 1000 Difference: **4 more per 1000** (CI 95% 2 fewer - 11 more)	**Moderate** Due to indirectness[1]	A longer duration of DAPT probably does not result in an important reduction in ischaemic stroke.
Moderate or severe bleeding 22-90 days	Odds Ratio: 2.20 (CI 95% 0.83 - 5.78) Based on data from 4599 patients in 1 study Follow up 90 days	**3** per 1000	**6** per 1000 Difference: **3 more per 1000** (CI 95% 1 fewer - 7 more)	**High** The consistency of the effect of clopidogrel on bleeding throughout the 90 days led us to not to rate down for imprecision[2]	A longer duration of DAPT increases the risk of moderate or major bleeding by a small amount.

1. **Indirectness: Serious.** The patients were randomized 21 days prior to the 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 randomized to ASA had a stroke before day 21. Therefore, the patients who continued clopidogrel and ASA were probably at higher risk of having a stroke after day 21.
2. **Imprecision: Serious.** Confidence interval includes no difference.

Figures

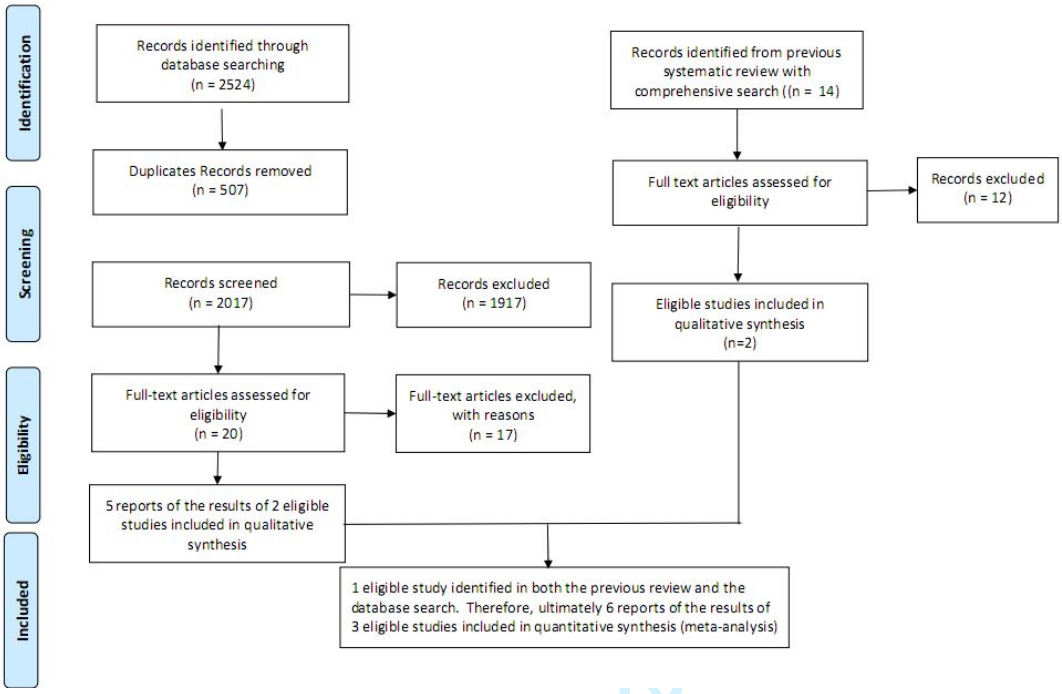

Figure 1: Flow chart for eligibility assessment according to PRISMA guidelines

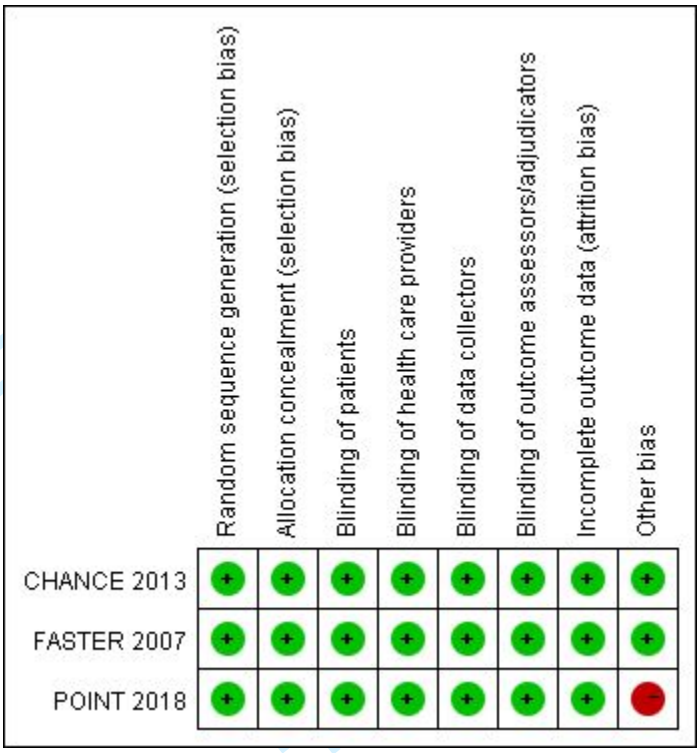

Figure 2: Risk of bias about each risk of bias item for each included study

Footnotes:

*Other risk of bias domain from POINT, 2018 designated as high risk of bias refers only to the outcome of extracranial bleeding because the investigators stopped the study early because of an increased in this outcome in the dual therapy arm with very few events.

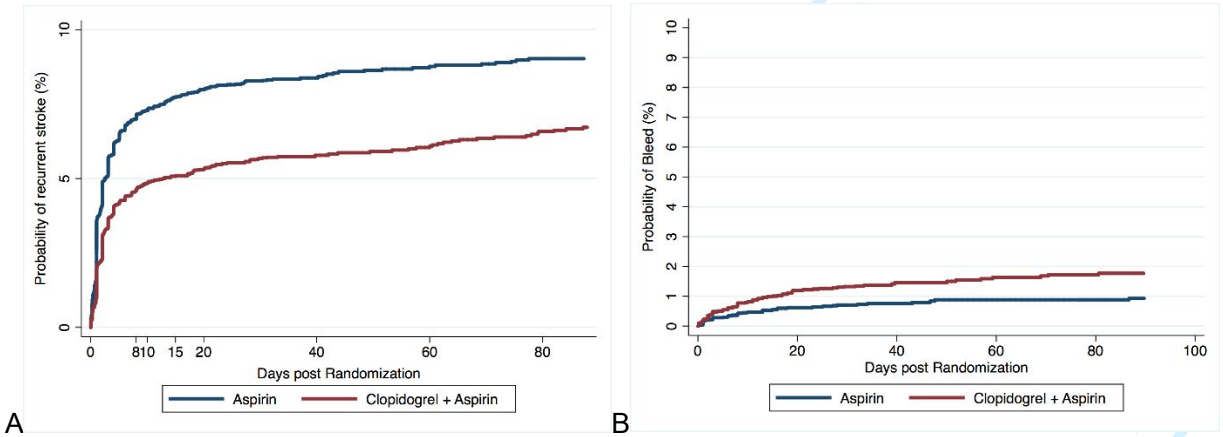

Figure 3. Pooled Kaplan-Meier time-to-event curves for stroke (A) and bleeding (B).