Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke

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Network meta-analysis can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable. We used network meta-analysis to compare commonly used antiplatelet regimens in the prevention of serious vascular events after transient ischaemic attack (TIA) or stroke. We performed direct meta-analyses of randomized, controlled trials evaluating antiplatelet agents after TIA or stroke. We chose the endpoint stroke, myocardial infarction, and vascular death. Network meta-analysis was then used to estimate the relative efficacy of the various antiplatelet regimens. Twenty-four trials involving 42688 TIA or stroke patients who suffered 6830 serious vascular events were included. In the network meta-analysis, all antiplatelet regimens (aspirin, aspirin plus dipyridamole, thienopyridines, and combination of aspirin and thienopyridines) were significantly more effective than placebo. The combination of aspirin and dipyridamole was more effective than thienopyridines (OR, 0.84; 95% CI, 0.73–0.97) and more effective than aspirin (OR, 0.78; 95% CI, 0.70–0.87). Our analysis suggests that the most powerful antiplatelet regimen in the prevention of serious vascular events after TIA or stroke is the combination of aspirin and dipyridamole. Network meta-analysis could be used to synthesize accumulating evidence from clinical trials in a broad range of vascular disorders.

Keywords
Meta-analysis • Cerebrovascular disorders • Antiplatelet agents

Introduction

Statistical techniques have been developed to establish the relative efficacies of different treatment strategies even when these treatments have not been directly compared.1,2 The so-called ‘network meta-analysis’ has been used to compare the efficacy of different antihypertensive classes and to identify which antihypertensive class was most closely associated with diabetes or which treatment strategy prevented stroke in patients with atrial fibrillation.3–6 In a study on acute myocardial infarction, such a combination of direct and indirect comparison methods provided similar results to the results of a direct comparison.3

Different antiplatelet regimens have been tested in the secondary prevention after transient ischaemic attack (TIA) and ischaemic stroke. Direct comparisons have been performed of antiplatelet therapies with placebo and between some antiplatelet agents. However, randomized data comparing the relative effect of some antiplatelet regimens are currently lacking (e.g. aspirin and dipyridamole vs. thienopyridines alone or in combination with aspirin) or unethical in the case of placebo controlled trials. The number of direct comparisons increases rapidly when several treatment options are available.7 Indirect comparisons are often implicitly made in meta-analyses or in guidelines when multiple treatment options exist.

To illustrate the power of network meta-analysis, we used a combination of direct and indirect comparisons to estimate the relative odds of developing incident vascular events during long-term treatment with commonly used antiplatelet agents after TIA or ischaemic stroke. We were specifically interested whether the combination of aspirin and dipyridamole would be superior to thienopyridines. Both treatments are recommended after TIA or ischaemic stroke, but direct comparisons are currently lacking. The results from the Prevention Regimen For Effectively avoiding Second Strokes (PROFESS) trial, which compares aspirin...
Methods

Systematic review and data extraction
Two investigators searched the reference lists from published systematic reviews on antiplatelet agents in secondary prevention after stroke or TIA and updated these meta-analyses with additional trials through a PubMed search (1966–March 2007) and the Cochrane Register of Controlled Clinical Trials. In PubMed, the clinical trial filter with the option ‘Sensitive’ was chosen. The search terms were ‘cerebrovascular accident’, ‘platelet aggregation inhibitors’, ‘aspirin’, ‘dipyridamole’, ‘ticlopidin’, or ‘clopidogrel’. Additionally, the Stroke Trial Registry at www.strokecenter.org was searched. We included published long-term (>3 months) prevention trials that randomized patients after transient ischaemic attack or stroke to aspirin (ASA) vs. placebo (PLACEBO), thienopyridines (ticlopidin or clopidogrel, THIENO) vs. PLACEBO, aspirin and dipyridamole (ASA+DP) vs. placebo, ASA vs. THIENO, ASA vs. ASA+DP, combination of THIENO+ASA vs. ASA, combination of THIENO+ASA vs. THIENO. We excluded randomized studies of short duration (<3 months) or that only assessed surrogate outcomes. We also excluded randomized studies comparing aspirin with oral anticoagulants and aspirin with triflusal, studies with clostazol, studies with dipyridamole alone, and studies with glycoprotein IIb/IIa inhibitors as these treatments are not widely recommended after TIA or stroke or not available worldwide. We assumed a class effect for the thienopyridines to increase the number of trials available. From the trials one author (V.T.) extracted the composite endpoint non-fatal stroke, non-fatal myocardial infarction, and vascular death used in the Antiplatelet Trialists’ Collaboration (APTC) as this was available from most studies and used in systematic reviews from the APTC and the Cochrane collaboration. Data from the intention to treat analysis were used.

Statistical analysis
Since multiple treatments are considered, the comparisons between treatments can be visualized in a network (Figure 1A), distinguishing between direct and indirect comparisons. For each of the direct comparisons between treatments, where information from more than one trial was available, we first performed a traditional fixed effect meta-analysis yielding the Mantel-Haenszel odds ratio. In one trial with zero events in both groups, the event rate has been artificially inflated by adding 0.5. Heterogeneity between trials was quantified with the I² and H measure, both of them being functions of Cochran’s heterogeneity statistic and its degrees of freedom. Estimates for indirect comparisons (comparison of conditions for which no trials are available) are obtained by modelling the log-odds ratios from all trials simultaneously, which also yields estimates for the direct comparisons. An analysis under homogeneity then corresponds to a regression model for the log-odds ratios for each treatment comparison with treatment as a factor (having five levels) and non-constant error variance which is assumed to be known and given by the estimated within-trial asymptotic variances of the log-odds ratios. Heterogeneity of the treatment effects can be captured by extending this model with a random trial effect, its variance reflecting the between-trial variance. Note that if only two treatments would be compared, the models under homogeneity and under heterogeneity correspond to the Mantel-Haenszel and DerSimonian and Laird approach, respectively. Within-trial and between-trial variances are not the only sources of uncertainty when indirect comparisons are involved. An additional source of variability is induced by the fact that multiple estimates can be obtained for a specific indirect comparison, resulting from various possible paths in the network. This additional level of uncertainty is denoted by Lumley as incoherence of the network.

Analyses were performed in the statistical package SAS (version 9.1), using the procedure PROC MIXED to perform the network analysis under homogeneity and heterogeneity. To estimate the incoherence of the network the lime function in the package R was used. To verify the robustness of the conclusions derived from the network analysis on the log-odds ratios, two additional approaches...
were followed. For both approaches, the unit of analysis is the information on treatment arm-level instead of the comparison of two arms (the odds ratio). In the first approach, a model similar to the model for the log-odds ratio is constructed for the log-odds. As such, the analysed dataset contains 51 observations. In the second approach, a binomial model is used for the arm-specific number of events. Details for both approaches can be obtained from the authors. The general purpose of these additional approaches is to verify the conclusions obtained from the classical analysis on the log-odds ratio, i.e., the conclusions with respect to the treatment differences and their variability.

Results

Included trials

A total of 16 trials were identified through the report of the APTC, one additional trial was selected from a cumulative analysis on the combination of aspirin and dipyridamol.14,17 No additional trial was found in the systematic review on thienopyridine derivatives, but data on the cerebrovascular subgroup from Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial were extracted from this meta-analysis.12,14 Twelve additional trials were identified through a Pubmed search or the Cochrane database of Controlled Clinical trials.14,22–33 Seven trials were excluded. Four trials randomized between different antiplatelet agents, but reported only surrogate outcomes.24,27,29,30 We excluded these trials because various open label controls were used or because the method of randomization was unclear.32–34

From the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance trial (CHARISMA) we used the unpublished, but presented results from the TIA or stroke subgroup and performed a separate analysis using the published endpoint rates of the ‘CAPRIE’ like subgroup, which included patients not only with stroke, but also with myocardial infarction and peripheral vascular disease.35–37

This left 24 randomized trials in our analysis (Table 1). Four were three-arm trials. The two doses of aspirin in the UK TIA trial were combined and considered a unique trial arm.38 There were 42 688 patients in whom 6830 (16.0%) vascular events occurred in 51 study arms (14 placebo, 19 ASA, eight THIENO, seven ASA+DP, and three ASA + THIENO).

Direct comparisons

Of the 10 possible pairwise comparisons between the five conditions, seven have been studied directly in one or more trials. Table 2 and Figure 1B show the odds ratios for each of these direct comparisons. There was moderate heterogeneity between the four trials of thienopyridines vs. aspirin (I² = 56%, P = 0.08). Owing to the presence of only a single trial, heterogeneity could not be evaluated for the comparison of thienopyridines and aspirin compared with aspirin. In all other trials, there was no observed heterogeneity (data not shown).

Combination of direct and indirect comparisons

Similar to the results obtained from the direct comparisons, evidence was lacking for the presence of variability beyond the sampling variability (the within-trial variance), i.e., parameters referring to heterogeneity and network incoherence were estimated to be 0. As such, the results from the final network analysis coincide with the results from a network analysis under homogeneity. The
same conclusion was obtained when using the alternative statistical approaches (analysis on log-odds and analysis on arm-specific event rates).

Table 2 and Figure 1C show the results of the combination of indirect and direct comparisons. In general, the results obtained with the direct comparisons are also retrieved in the network analysis. The only discrepancy in conclusions pertains to the comparison of Thieno vs. Placebo, for which comparable estimates of the common odds ratio were obtained, but only the network analysis yielded a significant result. This finding is not surprising, since the direct comparison only involved two trials, hereby leading to a much larger confidence interval. Of real interest are the indirect comparisons provided by the network analysis. First, there is no evidence for a difference between aspirin combined with thienopyridines and aspirin combined with dipyridamole (OR = 1.12; 95% CI, 0.95–1.33). Secondly, with the combination of thienopyridines and aspirin (which has never been compared with placebo), an odds reduction of 25.3% (95% CI, 12.4–36.2%) is estimated. Finally, the combination of aspirin and dipyridamole yields an odds reduction of 15.7% (95% CI, 3.2–26.6%) when compared with thienopyridines.

**Sensitivity analyses**

Similar superiority of aspirin and dipyridamole over thienopyridines derivatives was obtained from the analysis on the arm-specific log-odds (OR, 0.85; 95% CI, 0.74–0.97) and event rates (OR, 0.80; 95% CI, 0.69–0.90).

Also, since the randomization method was unclear in one trial, we repeated the meta-analysis on the log-odds ratio excluding this trial. This analysis yielded a very similar result (OR, 0.84; 95% CI, 0.73–0.96).

In a final sensitivity analysis, the ‘CAPRIE-like’ subgroup of the CHARISMA study was used. This analysis confirmed the obtained result for the combination of aspirin and dipyridamole with thienopyridines (OR, 0.85; 95% CI, 0.74–0.97).

**Discussion**

Direct comparisons of a treatment with placebo or with an active control are the gold standard for determining the treatment efficacy. However, direct comparisons are not always feasible or ethical. Our analysis provides an estimate of the relative treatment efficacy of several antiplatelet regimens based on the performance of the antiplatelets in other trials. This approach is correct provided two assumptions are met: the included trials are internally valid (and therefore do not give a biased estimate of the effect found within each trial) and the relative effects of a particular treatment do not vary substantially across different trials and across the case mix of patients included in different studies, i.e. the external validity is high. This homogeneity assumption is often made in any meta-analysis, where trials with different individual features are often combined. Biological agents often work more or less similarly in different populations, but inverse effects where drugs are detrimental in one subgroup of patients and beneficial in another subgroup of patients are rare. To our knowledge, no subgroup has been reliably identified in patients with TIA or stroke where the efficacy of antiplatelet agents is clearly reduced or amplified. In the meta-analyses included in our study, treatment effects were usually very similar, as indicated by a very low between-trial heterogeneity. Only in the analysis of thienopyridines vs. aspirin, a moderate degree of heterogeneity was found. Even in this comparison, no trial showed clear opposite effects.

Some authors caution against the use of indirect comparisons, even when adjusted methods that compare relative efficacies are used. One author found that, in the field of HIV trials, estimates calculated from adjusted indirect comparisons overestimated the effects found in direct comparisons. He suggested several possible sources of bias related to indirect comparisons to explain the difference. Indirect comparisons require many more patients to be performed compared with direct comparisons, and subsequent direct comparisons, if of higher quality, will often show a less dramatic effect. Differences in follow-up or endpoint definitions or the thoroughness with which the endpoints are sought may differ between the trials included for the indirect comparison and the subsequent direct comparison. Finally, the most important source of bias was the differences in prognostic factors between the patients enrolled in direct comparison trials vs. indirect comparison trials.

Proponents of indirect comparisons are less pessimistic. In a review of 44 meta-analyses, the estimates derived from adjusted indirect comparisons were compared with the efficacy estimates

<table>
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<th>Placebo</th>
<th>ASA</th>
<th>Thieno</th>
<th>ASA + DP</th>
<th>Thieno + ASA</th>
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<td>0.93 (0.85–1.02)</td>
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<td>0.97 (0.84–1.10)</td>
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<tr>
<td>0.67 (0.60–0.75)</td>
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<tr>
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<td>0.95 (0.84–1.07)</td>
<td>1.12 (0.95–1.33)</td>
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Comparison of results of direct comparisons (upper diagonal part) and the results from a network meta-analysis combining both direct and indirect comparisons (lower diagonal part). Each cell gives an odds ratio (and 95% confidence interval); in the lower diagonal part, this OR compares the row condition with the column condition, and in the upper diagonal part, the OR compares the column condition with the row condition.
derived from head-to-head comparisons. Only in three out of 44 analyses the estimates between direct and adjusted indirect comparisons were significantly different. There was a moderate agreement between the estimates derived from the two types of comparisons. More often, significant effects from direct comparisons became non-significant in indirect comparisons because confidence intervals were wider with the indirect comparison. In a systematic overview of different methods of indirect comparisons, it was concluded that the use of indirect comparisons may be justified when direct evidence from good-quality RCTs is lacking. These analyses pertained to indirect comparisons of two competing interventions, both of which were compared to placebo or another third intervention. Other limitations might come in play when more than two competing interventions are assessed as in our analysis.

Some modelling assumptions are inherent in network meta-analysis. Consider as an example the treatment heterogeneity parameter (between-trial variance) which is assumed in the current analysis to be common to all treatments. A substantial increase in the number of trials is needed to use a model which relaxes this assumption. As such, it is unknown how large the impact is of this assumption on the obtained results. Our study included a few multi-arm studies. In the analyses on the log-odds ratios, this complication is ignored. However, both the analysis on the log-odds and the random-effects binomial model are not suffering from this simplification.

Network meta-analysis complements traditional meta-analyses and systematic reviews. Faced with multiple treatment options, these analyses provide the clinician, the guideline developer, or health care authorities with some hierarchy of effect when different competing interventions are considered or when direct evidence is lacking. Within the field of vascular medicine, areas where network meta-analysis can be applied are frequent, given that multiple treatment strategies are often available and novel compounds are explored in randomized trials. The results can be embedded within a cost-effectiveness analysis. Similar to other meta-analyses, gaps in research and areas of uncertainty can be identified. Moreover, adequate sample sizes can be determined in order to plan head-to-head comparisons.

Our results suggest a superiority of ASA + DP over thienopyridines derivatives. The results from the Prevention Regimen For Effectively avoiding Second Strokes (PROFESS) trial, which compares aspirin and extended release dipyridamole with clopidogrel, will provide an opportunity to determine whether the estimate derived from this indirect comparison is valid. In PROFESS, the sample size is calculated based on a 13% relative risk reduction in the primary endpoint stroke. This is clearly in line with the estimated 16% odds reduction in stroke, myocardial infarction, and vascular death seen in our indirect comparison.

There are some limitations to the present analysis. The APTC endpoint has been criticized for its lower power in the context of stroke trials. The external validity of some of the included trials has been questioned. This analysis does not incorporate all the risks such as major bleeding associated with antiplatelet agents. The risks of treatment have to be weighted against the benefits of these treatment regimens. Finally, we used subgroups of large scale randomized trials that also included patients with multiple risk factors, peripheral artery disease, and coronary artery disease. We feel that it is reasonable to use the subgroups from these trials because it increases the comparability of the trial populations by restricting the analysis to TIA or stroke patients or patients in secondary prevention.

In conclusion, this meta-analysis, which combines both direct and indirect evidence sources, provides a league table of multiple different treatment options after TIA or stroke. The results are valid under the provision that the internal validity and external validity of the evidence from the included trials is high. The technique should be applied more broadly in the field of vascular disorders.

**Conflict of interest:** V.T. reports having received lecture fees from Boehringer Ingelheim and Pfizer, and travel support from Boehringer Ingelheim and Pfizer.

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**References**


Twelve-month-old girl with myocardial ischaemia

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A 12-month-old girl was admitted to Kanagawa Children’s Medical Center because of the diagnosis of anomalous origin of the right coronary artery from the main pulmonary artery (ARCAPA). The electrocardiogram (ECG) recorded non-significant findings at rest but the ST depression from V1 to V3 at her crying.

On the coronary angiography, it looked like a single coronary artery from the left coronary sinus; however, this artery was dilated and meandering and linked the RCA whose flow was retro-perfusion, that is, continuous flow poured into proximal of the main pulmonary trunk beside the aortic root, namely, the original site of RCA (Figure). The operation confirmed the budding and meandering conus branch of the RCA on the right ventricular outflow tract and linked the RCA originated from the main pulmonary trunk to the left anterior descending artery. Re-implantation was performed using cardiopulmonary bypass, and the anomalous artery was anastomosed with the ascending sorta that was hinged with a J-shaped incision. The postoperative course was excellent. When last seen, 20 months after the operation, she was well with no evidence of myocardial ischaemia.

ARCAPA is rare. To the best of our knowledge, it had been reported that there were only three cases of isolated ARCAPA reported under 2 years of age. The reason is many of these cases were reported not lethal or asymptomatic, in contrast to the origin of the left coronary artery from the pulmonary artery. However, it has some reported sudden death ARCAPA cases revealed by autopsy. In our case, ECG demonstrated myocardial ischaemia at the time of her crying.

Figure. Angiography: pre-operative. Left coronary arteriography showing the flow of anomalous origin of the right coronary artery from the main pulmonary artery to the main pulmonary trunk. Collateral artery linked from the left anterior descending artery to the right coronary artery poured into the main pulmonary trunk. White arrow shows collateral artery and the conus branch of the right coronary artery.

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