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**Brief Communication**

# Dual Antiplatelet Therapy in Minor Stroke/Transient Ischemic Attack – An Updated Network Meta-Analysis

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**ABSTRACT:** We previously analyzed five trials on ticagrelor/aspirin versus clopidogrel/aspirin in patients with minor stroke/ TIA in a network meta-analysis. We updated our search and identified 311 new citations with one study for inclusion: CHANCE2 enrolled patients with CYP2C19 loss-of-function alleles and randomized them to ticagrelor/aspirin or clopidogrel/aspirin. Pooling of CHANCE2 with the original studies could not be completed due to violation of NMA assumptions, due to significant inconsistency. This suggests patients with CYP2C19 loss-of-function alleles represent a subpopulation that is inherently different from the general stroke population in their antiplatelet response. Results from CHANCE-2 may not be generalizable without genotype testing.

**RÉSUMÉ : Le traitement des petits accidents vasculaires cérébraux et des accidents ischémiques transitoires par la bithérapie : mise à jour d'une méta-analyse en réseau.** L'équipe de recherche s'est déjà penchée, dans le cadre d'une méta-analyse en réseau (MAR), sur cinq essais de traitement par le ticagrélor et l'aspirine ou par le clopidogrel et l'aspirine chez des patients ayant subi un petit accident vasculaire cérébral ou un accident ischémique transitoire. Elle a ensuite procédé à une mise à jour de la recherche et a relevé 311 nouvelles citations et retenu une étude, soit CHANCE2, à laquelle ont participé des patients porteurs d'allèles de perte de fonction du CYP2C19 qui ont reçu au hasard soit l'association de ticagrélor et d'aspirine, soit l'association de clopidogrel et d'aspirine. Toutefois, la mise en commun de CHANCE2 avec les études originales n'a pu être achevée pour non-respect des hypothèses émises dans la MAR, en raison d'importantes incohérences. Les résultats portent donc à croire que les patients porteurs d'allèles de perte de fonction du CYP2C19 forment un sous-groupe particulier de malades qui réagit d'une manière fondamentalement différente de la population générale au traitement des AVC par les antiagrégants plaquettaires. Aussi se peut-il que les résultats de l'essai CHANCE2 ne soient pas généralisables sans test génotypique.

**Keywords:** stroke; transient ischemic attack (TIA); antiplatelet therapy; ticagrelor; clopidogrel; aspirin

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Patients with minor ischemic stroke or transient ischemic attack (TIA) are at high risk for recurrent stroke. We previously published a systematic review and network meta-analysis comparing ticagrelor and aspirin versus clopidogrel and aspirin in this population and found them similar in terms of both efficacy and safety profiles.[1] However, new evidence has been published on this topic – specifically, the CHANCE2 trial enrolled Chinese patients with minor ischemic stroke/TIA who were carriers of CYP2C19 loss-of-function alleles and found that the risk of stroke at 90 days was modestly lower with ticagrelor and aspirin than with clopidogrel and aspirin.[2] Thus, the objective of this study is to perform an updated systematic review and network meta-analysis incorporating newly published evidence on this topic.

The completed review has been prepared in consultation with the PRISMA Extension Statement for Network Meta-Analysis.[3] The study protocol for the original NMA was previously published and similar methodology was followed for the current study.[4]

We included randomized controlled trials that enrolled adult participants with minor ischemic stroke (with a National Institute of Health Stroke Severity Scale (NIHSS) of $\leq$5) or TIA (ABCD$^2$ score of $\geq$4) that started DAPT within 72 hours of presentation. The intervention and comparator had to be amongst the following, in any dose or formulation: ticagrelor+aspirin vs aspirin, clopidogrel+aspirin vs aspirin, or ticagrelor+aspirin vs clopidogrel+aspirin. Studies had to report outcomes for at least up to 30 days for inclusion. Additional criteria regarding our inclusion criteria can be found in the original study protocol.[4]

Our original search encompassed Medline, EMBASE, and Cochrane Registry of Clinical Trials from inception until February 2021. Our updated search strategy extended the search to December 2021. Additionally, we searched the abstracts database from both the World Stroke Congress and International Stroke Conference for potentially relevant abstracts over the last 20 years.

Two reviewers (DR, SD) independently completed Level 1 (title, abstract) and Level 2 (full-text) screening for articles using Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). Discrepancies were settled by discussion with a third reviewer (RL). Findings from the screening process were

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summarized using a flow diagram (Fig. 1).[5] Risk of bias of individual studies was assessed using the Cochrane Risk of Bias tool for randomized trials, version 2 (RoB2).[6] Raters independently implemented the tool and any disagreement in the rating was resolved by discussion.

We appraised the clinical and methodologic characteristics of the included studies to judge the appropriateness of the transitivity assumption. Due to the limited number of studies in the treatment network and based on previous adequate model fit in the original NMA, fixed effects (FE) models were used for all primary analyses. For the current study, we conducted FE pairwise meta-analyses of the available data to inspect for statistical heterogeneity of treatment effects using $I^2$ values. We performed all NMAs using BUGSnet 1.0.4 and JAGS packages in RStudio 1.4.1106, evaluated under a Bayesian framework with Markov Chain Monte Carlo simulation. Model fit was assessed by comparing the posterior total residual deviance with the number of unconstrained data points.[7] The selection between models was based on deviance information criteria (DIC), with smaller values indicative of a greater fit and a difference greater than five points suggesting an important difference, thus violating NMA assumptions.[8] We evaluated consistency of direct and indirect evidence by fitting an unrelated means model and comparing DIC and residuals with those from the corresponding consistency model. Convergence was visually inspected using trace plots.

The primary outcome was recurrent stroke or death at 90 days. Effect measures were reported using hazard ratios with 95% credible intervals (95% CrI) using arm-based analyses from intention-to-treat aggregate data in the original manuscripts.

Our original search identified 4014 unique citations, from which five RCTs were included and analyzed. We previously analyzed data from 22,098 individuals: 10,722 received aspirin, 5517 received clopidogrel + aspirin, and 5859 received ticagrelor + aspirin. With the updated search, we identified 311 new citations since February 2021, with only one study fitting our inclusion criteria (Fig. 1, Table 1).[2]

Our original NMA enrolled patients with similar ages, stroke severity scores, and timing from symptom onset to medication initiation; approximately half of our original NMA population was of White ethnicity (45%).[1] While the CHANCE and PRINCE trials did not report the proportions of ethnicities enrolled in their original studies, since the trials were conducted exclusively in China, the enrolled populations are likely made up of almost entirely Chinese patients, meaning approximately 43% of our original NMA population was of Chinese ethnicity.[9,10] An even higher proportion of Chinese representation may be possible given the poor reporting of ethnicities in acute clinical trials. Contrastingly, CHANCE2 enrolled a population with similar ages (median of 65 in both arms), stroke severity scores, and time to treatment, but the ethnicity of this population was almost exclusively Chinese (98.0%). Furthermore, all patients screened for inclusion received point-of-care genotyping for three single-nucleotide polymorphisms – *CYP2C19**2 (681G→A, rs4244285), *CYP2C19**3 (636G→A, rs4986893), and *CYP2C19**17 (−806C→T, rs12248560). Only patients with at least one loss-of-function allele (*2 or *3) were classified as loss-of-function carriers and enrolled in CHANCE2. CYP2C19 status was not consistently reported across the five studies included in the original NMA: only one study performed genotyping and reported the percentage of loss-of-function carriers – in the PRINCE trial, 374/650 (57.5%) were classified as CYP2C19 loss-of-function carriers.[10] This represents 1.7% of the total original NMA population; 1.3% of the population did not carry a loss-of-function allele, and the remaining 97.0% were unknown. A higher prevalence of the loss-of-function allele is well-known in the Han Chinese population, and while our original NMA population enrolled a high percentage of Chinese patients, this still represented less than half of the total analyzed population. It is possible that the clinical heterogeneity

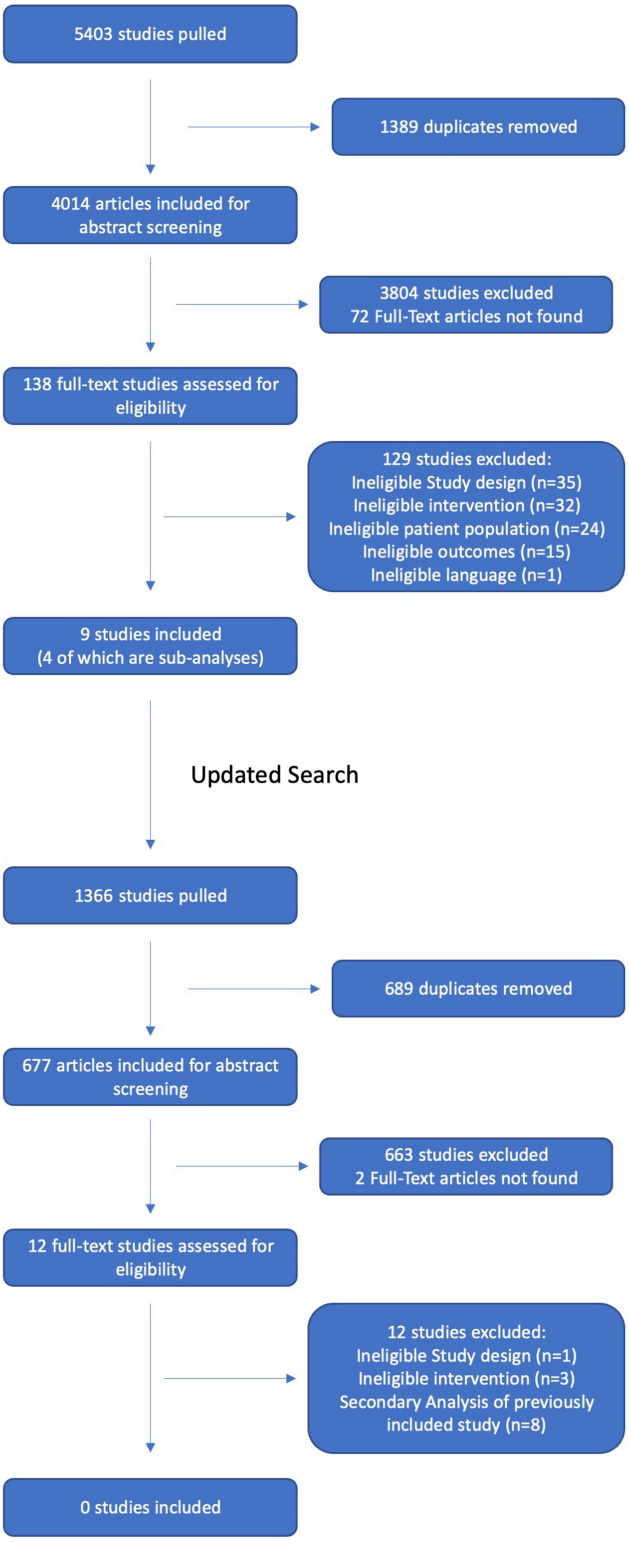


**Figure 1:** PRISMA flow diagram.

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**Table 1:** Study and patient characteristics for included studies

| | CHANCE | FASTER | POINT | PRINCE | THALES | CHANCE2 |
|---|---|---|---|---|---|---|
| **Time from symptom onset to treatment** | 24h | 24h | 12h | 24h | 24h | 24h |
| **NIHSS** | 0–3 | 0–3 | 0–3 | 0–3 | 0–5 | 0–3 |
| **ABCD$^2$ score** | 4–7 | NA | 4–7 | 4–7 | 6–7 | 4–7 |
| **DAPT treatment duration** | 21 days | 90 days | 90 days | 21 days | 30 days | 21 days |
| **Country (Publication)** | China | Canada | United States | China | United States | China |
| **Clopidogrel loading dose** | 300mg | 300mg | 600mg | 300mg | . | 300mg |
| **Clopidogrel maintenance dose** | 75mg | 75mg | 75mg | 75mg | . | 75mg |
| **Ticagrelor loading dose** | . | . | . | 180mg | 180mg | 180mg |
| **Ticagrelor maintenance dose** | . | . | . | 90mg | 90mg | 90mg |
| **ASA loading dose** | 75–300mg | 162mg | 50–325mg | 100–300mg | 300–325mg | 75–300mg |
| **ASA maintenance dose** | 75mg | 81mg | 50–325mg | 100mg | 75–100 mg | 75mg |
| **Follow-up period (days)** | 90 | 90 | 90 ± 14 | 7–90 | 30–60 | 90 |
| **Mean/ Median* Age** | Cl+ASA: **63** ASA: **62** | Cl+ASA +Simvastatin: 67.1 −Simvastatin: 68.9 ASA: +Simvastatin: 66.6 −Simvastatin: 69.8 | Cl+ASA: **65** ASA: **65** | Tic+ASA: **62** Cl+ASA: **61** | Tic+ASA: 65.2 ASA: 65.1 | Tic+ASA: **65** Cl+ASA: **64.6** |
| **%Male** | 66.2 | 52.8 | 55.1 | 73.2 | 61.7 | 66.2 |
| **%White** | NA | 91.8 | 75.1 | NA | 53.8 | NA; 97.8% Han Chinese |

**Table 2:** Fixed effects model measures for 90-day outcomes of hemorrhagic stroke and mortality. Effect measures are reported as hazard ratios (HR) with 95% credible intervals (CrI). Probabilities of treatments being the "best" treatment based on surface under the cumulative rank curve (SUCRA) plots are presented for comparison. Statistically significant results are outlined in **bold**

| | Estimates from NMA | | | |
|---|---|---|---|---|
| | Cl + ASA versus ASA | Tic + ASA versus ASA | Cl + ASA versus Tic + ASA | |
| Outcome measure | HR (95% CrI) | HR (95% CrI) | HR (95% CrI) | SUCRA (values nearest 1 denote preferred treatment) |
| Hemorrhagic stroke only | 1.15 (0.64–2.08) | 0.99 (0.46–2.12) | 1.16 (0.55–2.49) | Cl+ASA: 0.17 Tic+ASA: 0.44 ASA: 0.39 |
| Mortality | 1.06 (0.72–1.55) | **0.68 (0.46–0.99)** | **1.56 (1.02–2.40)** | Cl+ASA: 0.96 Tic+ASA: 0.017 ASA: 0.020 |

between the original NMA population and CHANCE2 was too great such that pooling of populations was not feasible, though this is speculative without knowing the true percentage of loss-of-function genetic carriers.

Three methodologic assumptions must be met before proceeding with pooling of results for NMA: homogeneity, similarity, and consistency. Assessment of homogeneity for pairwise meta-analysis of the treatment arms was previously outlined in Supplemental Materials eTable 2 of the original publication.[1] The $I_2$ value for the pairwise meta-analysis of clopidogrel and aspirin against aspirin alone was 0.65. representing moderate heterogeneity (1.38 [95%CI 1.20–1.59]). Study and patient characteristics were deemed to be clinically homogeneous with the exception of ethnicity and CYP2C19 status. We then examined the DIC values for RE and FE models to evaluate consistency (Supplemental Materials eTable 1). For the primary outcome, the DIC value for the FE consistency model was 30.88 compared to 22.68 for the inconsistency model (difference of 8.03). Given the difference of > 5 between models with a lower DIC value in the inconsistency model, pooling of results for NMA could not proceed due to violation of assumptions of consistency. Similar results were observed for the outcomes of ischemic stroke and functional disability. However, consistency violations were not met for 90-day outcomes of hemorrhagic stroke and mortality, and thus we proceeded with pooling for these secondary outcomes (Table 2). There was no statistically significant difference between the three treatment arms for hemorrhagic stroke, but the combination of ticagrelor and aspirin was associated with significantly lower hazard ratios of mortality compared to aspirin alone (HR 0.68; 95% CrI 0.46–0.99) and compared to aspirin and clopidogrel (HR 0.64; 95% CrI 0.42–0.98). However, these results should be interpreted with caution given the wide credible intervals with proximity to 1.

Our results suggest that patients with minor ischemic stroke/TIA who carry a CYP2C19 loss-of-function allele respond

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differently to antiplatelet therapies compared to the general stroke population. This was evidenced by statistical inconsistency during attempted pooling of data for an updated network meta-analysis. Other reasons the CHANCE2 trial may not be generalizable to the general population would include inherent differences in risk factors for stroke in Chinese patients. For example, Chinese patients are in general younger and have less prevalent vascular risk factors, but a higher prevalence of intracranial atherosclerotic disease compared to Caucasian stroke patients.[11,12] Geographical and societal factors may also contribute to differences in time from last seen well to presentation to seek medical attention – Jin et al found the median prehospital delay time in China is 15 hours, which is significantly longer than those reported by Western countries.[13] These differences may contribute to additional clinical heterogeneity that is unquantifiable and suggest that results from exclusive ethnic populations should be extrapolated with caution.

Clopidogrel is a prodrug that requires hepatic conversion into its active metabolite – a process that is influenced by CYP2C19 genetic polymorphisms.[2] In patients with these polymorphisms undergoing percutaneous coronary intervention, there has been conflicting evidence in terms of response to antiplatelet therapies, and thus the clinical significance of these loss-of-function alleles was unclear.[14] CHANCE2 is the only study to examine this population after stroke/TIA, and they found a reduced risk of stroke with ticagrelor, although the ticagrelor arm also had higher rates of discontinuation of treatment due to adverse events (particularly bleeding and dyspnea).[2] However, practitioners should be cautious before extrapolating the results of CHANCE2 to the general stroke population, as individual CYP2C19 status is often unknown. The clinical applicability of these results is limited by the availability of rapid CYP2C19 genotyping techniques, and the cost-effectiveness of genotype-guided strategies requires further investigation.

Patients with CYP2C19 loss-of-function alleles may represent a subpopulation that is inherently different from the general population in terms of their response to antiplatelet treatments, resulting in significant heterogeneity. Our results suggest the clinical trial results from this population may not be generalizable to the stroke population without genotype testing.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2023.287.

**Author contribution.** R.L. and G.Z. contributed equally as co-first authors.
Study concept and design: R.L., G.Z., D.R., S.D., and D.D.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: R.L. and G.Z.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: R.L., G.Z., S.D., and D.R.
Administrative, technical, or material support: R.L., G.Z., and D.D.
Study supervision: D.D.

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