INPLASY

Impact of CYP2C19 genotype on clinical outcomes of non-Asian patients with stroke or transient ischemic attack undergoing clopidogrel therapy: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202370067

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 July 2023 and was last updated on 17 July 2023.

INTRODUCTION

Review question / Objective To quantitatively summarize the evidence on the association between CYP2C19 genotype and clinical outcomes of non-Asian patients with stroke or transient ischemic attack undergoing clopidogrel therapy.

Rationale Clopidogrel is a thienopyridine prodrug which requires hepatic biotransformation, mainly mediated by the CYP2C19 enzyme, to form an active metabolite that prevents platelet aggregation by selectively and irreversibly binding to the adenosine diphosphate (ADP) P2Y12 receptor. There is convincing evidence that reduced-function CYP2C19 allele carriers of Han-Chinese ancestry have an increased risk for further vascular events following transient ischemic attack (TIA) or ischemic stroke when treated with clopidogrel. However the evidence in other populations is not certain. The aim of the present study is to conduct a systematic review and meta-analysis to quantitatively estimate the impact of CYP2C19 genotype on clinical outcomes in non-Asian patients with stroke or TIA receiving clopidogrel.

Condition being studied Stroke or transient ischemic attack.

METHODS

Search strategy A comprehensive literature search (PubMed, Web of Knowledge and Cochrane Library databases) will be conducted to identify all potential eligible studies. The combination of the following key terms will be used: (clopidogrel OR Plavix) AND (stroke OR "cerebrovascular accident" OR "cerebrovascular disorder" OR "cerebral infarction" OR "transient ischemic attack" OR "TIA" OR "transient cerebral ischemia") AND CYP2C19. The retrieved studies will be read in their entirety to assess their appropriateness for inclusion in the meta-analysis. All references cited in the eligible studies will be

also reviewed to identify additional published works not initially retrieved. If two or more studies share part of the same patient population, the more complete or the one with the larger sample size will be included.

Participant or population Stroke or transient ischemic attack patients treated with clopidogrel monotherapy or clopidogrel plus aspirin.

Intervention Carriers of reduced-function CYP2C19 alleles.

Comparator Noncarriers of reduced-function CYP2C19 alleles.

Study designs to be included This systematic review will include case-control studies, cohort studies or randomized clinical trials.

Eligibility criteria 1. Patients with stroke or transient ischemic attack treated with clopidogrel monotherapy or clopidogrel plus aspirin in non-Asian countries.2. Sufficient data to estimate the rate of at least one of the following outcomes: stroke recurrence, composite vascular events and bleeding.3. Studies reporting comparison of clinical outcomes between carriers and non-carriers of loss-of-function CYP2C19 alleles.4. Studies will be excluded if they meet one or more of the following criteria:a) conducted exclusively in Asian population; b) studies including patients treated with clopidogrel for conditions other than TIA or stroke; c) studies with less than 10 eligible cases; d) article written in a language other than English.

Information sources PubMed, Web of Knowledge and Cochrane Library databases.

Main outcome(s) Primary outcome is recurrent stroke including ischemic stroke or hemorrhagic stroke.

Additional outcome(s) Secondary outcomes include composite clinical vascular events and bleeding.

Data management Two investigators (S.C. and S.T.) will independently review titles and abstracts, and select the articles. Potentially eligible studies will be then read in their entirety to assess their appropriateness for inclusion in the meta-analysis. For each study included in the meta-analysis, the following data will be extracted: the first author's last name, year of publication, study location, diagnosis of participants, total number of patients, mean age of patients, percentage of women, percentage of patients with diabetes mellitus, the investigated outcomes, mean follow-up, clopidogrel dose, CYP2C19 alleles analysed, number of events in both carriers and noncarriers of reduced-function CYP2C19 alleles for each investigated outcome. Any disagreements will be resolved through discussion and consensus.

Quality assessment / Risk of bias analysis Methodological study quality will be independently assessed by two authors (S.C. and S.T.) using the Newcastle–Ottawa scale (NOS) for case-control or cohort studies (https://www.ohri.ca//programs/clinical_epidemiology/oxford.Asp). Disagreements between reviewers were resolved by consensus.
Publication bias will be evaluated graphically by drawing funnel plots and statistically analysed by means of the Egger's test. In case of statistical evidence of funnel plot asymmetry (Egger's p-value <0.10), the "trim-and-fill" procedure will be used to determine the stability of the results.

Strategy of data synthesis Risk ratio (RR) estimates from each study will be combined using random-effects models (DerSimonian–Laird method) which incorporate the between-study heterogeneity and allow for a different effect in each study. Between-study heterogeneity will be estimated by using the chi-square–based Cochran's Q statistic. The I2 index will be also reported, which quantifies heterogeneity irrespective of the number of included studies.

Subgroup analysis For each outcome of interest, subgroup analyses will be conducted if relevant data are reported in at least three independent studies.

Sensitivity analysis Leave-one-out sensitive meta-analyses will be performed to assess the contribution of each study to the pooled estimate by excluding individual results one at a time and recalculating the pooled RR estimates for the remaining results.

Language restriction English.

Country(ies) involved Italy.

Keywords Ischemic stroke; transient ischemic attack; clopidogrel; CYP2C19.

Dissemination plans The findings will be disseminated via oral/poster presentations at conferences, seminars, workshops and peer-reviewed publications.

Contributions of each author

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