Supplementary Material

# Supplementary Data

Search strategy - Pubmed

(((((((((((("Pharmacogenomic Testing"[Mesh]) OR (Pharmacogenomic Testings OR Pharmacogenomic Screening OR Pharmacogenomic Screenings OR Pharmacogenetic Screening OR Pharmacogenetic Screenings OR Pharmacogenetic Testing OR Pharmacogenetic Testings OR Pharmacogenomic Analysis OR Pharmacogenomic Analyses OR Pharmacogenetic Study OR Pharmacogenetic Studies OR Studies, Pharmacogenetic OR Pharmacogenetic Analysis OR Pharmacogenetic Analyses OR Pharmacogenomic Study OR Pharmacogenomic Studies))) OR ("Precision Medicine"[Mesh] OR Medicine, Precision OR Personalized Medicine OR Medicine, Personalized OR Individualized Medicine OR Medicine, Individualized OR P Health OR P-Health OR P-Healths)) OR ("Genetic Testing"[Mesh] OR • Testing, Genetic OR Testing, Genetic Predisposition OR Predisposition Testing, Genetic OR Predictive Testing, Genetic OR Genetic Predictive Testing OR Testing, Genetic Predictive OR Predictive Genetic Testing OR Genetic Testing, Predictive OR Testing, Predictive Genetic OR Genetic Predisposition Testing OR Genetic Screening OR Genetic Screenings OR Screening, Genetic OR Screenings, Genetic (("Genotype"[Mesh]) OR "Polymorphism, Genetic"[Mesh])))))) AND (((((systematic review[ti] OR systematic literature review[ti] OR systematic scoping review[ti] OR systematic narrative review[ti] OR systematic qualitative review[ti] OR systematic evidence review[ti] OR systematic quantitative review[ti] OR systematic meta-review[ti] OR systematic critical review[ti] OR systematic mixed studies review[ti] OR systematic mapping review[ti] OR systematic cochrane review[ti] OR systematic search and review[ti] OR systematic integrative review[ti]) NOT comment[pt] NOT (protocol[ti] OR protocols[ti])) NOT MEDLINE [subset]) OR (Cochrane Database Syst Rev[ta] AND review[pt]) OR systematic review[pt])) AND review[pt]) OR systematic review[pt])) AND (("Clopidogrel"[Mesh]) OR "Warfarin"[Mesh])

# Supplementary Tables

**Table S1.** General characteristics and strategies of the included systematic reviews.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Objectives | Participant details | Setting and context | Number of databases sourced and searched | Date range of database search | Number of studies and types of studies included in each review | Instrument used to appraise quality of the primary studies |
| **Clopidogrel – *CYP2C19* (SRs with MA)** | | | | | | | |
| Alakbarzade et al., 2020 [1] | to assess the prevalence of HCPR in patients with IS/TIA, their outcome, and genetic basis of treatment response variability in IS/TIA patients | not specified | IS/TIA patients on Clopidogrel; HCPR at any time point after IS/TIA onset evaluated with any type of platelet function test, any type of study design with or without reported clinical outcomes/genotyping data | 4 | from its inception to Mar 2019 | 21; observational studies | not performed |
| Bauer et al., 2011 [2] | to evaluate the accumulated information from genetic association studies investigating the impact of variants of the *CYP2C19* genotype on the clinical efficacy of clopidogrel | ≥ 16 years old, any ethnicity | association of reduced or increased function genetic variants of *CYP2C19* with the occurrence of clinical outcomes in patients with established CAD who were treated with clopidogrel | 4 | 1966 to Dec 2010; 1974 to Dec 2010; 1980 to Dec 2010 | 14; observational studies | NOS |
| Holmes et al., 2011 [3] | to appraise evidence of the association of the *CYP2C19* genotype and clopidogrel response | not specified | associations of clopidogrel therapy with responsiveness (platelet response or clinical outcomes) in relation to the *CYP2C19* genotype | 5 | from its inception to Oct 2011 | 32; observational studies, RCT | not performed |
| Huang et al., 2017 [4] | to compare the cardiovascular and cerebrovascular outcomes in clopidogrel‑treated CCVD patients between *CYP2C19* \*17 carriers and noncarriers | not specified | CCVD patients who received clopidogrel treatment; compared outcomes between *CYP2C19* \*17 carriers and noncarriers | 3 | from its inception to Feb 2016 | 13; observational studies | NOS |
| Hulot et al., 2010 [5] | to perform a quantitative review of the relationship between the reduced-function *CYP2C19* \*2 allele, the use of PPIs and MACE, and mortality in patients with long-term exposure to clopidogrel | not specified | contribution of the *CYP2C19* \*2 LOF genetic variant, and of the use of PPIs, to the occurrence of cardiovascular outcomes in patients with established CAD who were treated with clopidogrel | 6 | 1966 to Oct 2009; 1980 to Oct 2009 | 23; observational studies | NOS |
| Jang et al., 2012 [6] | to determine the association of the LOF *CYP2C19* polymorphism and cardiovascular risk in patients with CAD who use clopidogrel | not specified | patients with CAD who were treated with clopidogrel; evaluation of the *CYP2C19* polymorphism and adverse clinical outcomes | 10 | 2001 to Sep 2011 | 16; observational studies, RCT | not performed |
| Jin et al., 2011 [7] | to derive a more precise estimation of the relationship between the *CYP2C19* \*2 polymorphism and atherothrombotic events, as a possible mechanism of nonresponsiveness to clopidogrel | not specified | patients with CAD undergoing PCI, receiving clopidogrel; evaluation of the *CYP2C19* polymorphism and clinical outcomes | 2 | Dec 2009 | 8; observational studies | not performed |
| Mega et al., 2010 [8] | to define the risk of MACE among carriers of one (∼26% prevalence in whites) and carriers of two (∼2% prevalence in whites) reduced-function *CYP2C19* variants in patients treated with clopidogrel | not specified | clopidogrel was initiated in predominantly invasively-managed patients in a manner consistent with the guideline recommendations | 3 | Jan 2000 to Aug 2010 | 9; observational studies | not performed |
| Niu et al., 2015 [9] | to perform a more comprehensive investigation, which not only takes ethnic factor into consideration, but also adjusts the time factor and predicts the *CYP2C19* metabolic phenotype according to the *CYP2C19* genotype | not specified | patients with CAD were treated with clopidogrel; reduced-function *CYP2C19* alleles were tested | 3 | from its inception to Aug 2013 | 36; observational studies | NOS |
| Pan et al., 2017 [10] | to assess the association between genetic polymorphisms, especially the *CYP2C19* genotype, and the occurrence of stroke and bleeding in clopidogrel-treated patients with IS/TIA | not specified | association of genetic polymorphisms with responsiveness to clopidogrel therapy in patients with IS/TIA | 7 | from its inception to Jun 2016 | 15; observational studies | NOS |
| Sofi et al., 2011 [11] | to conduct a systematic review of all the published prospective cohort studies that have investigated the *CYP2C19* \*2 polymorphism in relation to adverse clinical outcome in CAD patients who were undergoing clopidogrel treatment | not specified | evaluation of CAD patients on antiplatelet treatment; evaluation of the *CYP2C19* \*2 polymorphism | 5 | 1966 to Jan 2010; 1980 to Jan 2010 | 7; observational studies | not performed |
| Sorich et al., 2014 [12] | to evaluate the evidence supporting the hypothesis that the effect size associated with the *CYP2C19* LOF allele carriers on the risk of MACE differs between use of clopidogrel for PCI compared with other indications and between white and Asian populations | white and Asian populations | participants who used clopidogrel, were genotyped for *CYP2C19* LOF alleles (minimally \*2) and reported follow-up for MACE | 4 | from its inception to Nov 2014 | 24; observational studies | not performed |
| Xi et al., 2019 [13] | to evaluate the impact of *CYP2C19* on clinical outcomes after PCI in Asians receiving clopidogrel therapy | Asian patients | with coronary heart disease receiving clopidogrel; analyzed genotype data for the *CYP2C19* LOF polymorphisms | 3 | from its inception to Jan 2017 | 20; observational studies | NOS |
| Zabalza et al., 2012 [14] | to analyse the association between *CYP2C19* loss- and gain-of-function variants and cardiovascular outcomes and major bleeding in patients with CAD treated with clopidogrel; and to explore the potential causes of heterogeneity between studies | not specified | patients with CAD receiving clopidogrel treatment; analysed genotype data for the *CYP2C19* loss- or gain-of-function polymorphisms | 2 | from its inception to Oct 2010 | 13; observational studies | not performed |
| Zhang et al., 2015 [15] | to evaluate the antiplatelet effects of high-dose clopidogrel according to *CYP2C19* \*2 alleles in patients undergoing PCI | not specified | high-dose clopidogrel (600 mg or 900 mg loading dose and/or 150 mg/day maintenance dose); to report at least one of the outcome measures: HTPR and clinical outcomes; *CYP2C19* \*2 alleles should be genotyped | 3 | from its inception to Jun 2014 | 19; not specified | own checklist, not validated |
| Zheng et al., 2019 [16] | to evaluate whether genotype-guided antiplatelet therapy reduces the rates of cardiovascular events and bleeding events in patients with ACS compared with conventional treatment | not specified | patients with ACS with PCI or without PCI; studies comparing genotype-guided antiplatelet therapy with conventional treatment | 3 | from its inception to Sep 2018 | 5; observational studies, RCT | Jadad scale, NOS |
| **Clopidogrel – *CYP2C19* (SRs without MA)** | | | | | | | |
| Ali and Elewa, 2019 [17] | to estimate the prevalence of *CYP2C19* genetic variants in the MENA region, and to evaluate the effect of these variants, as well as the nongenetic factors on clopidogrel responsiveness | ≥ 16 years old from the MENA region | Patients with ACS who require PCI and/or CABG, and are starting or continuing clopidogrel; clopidogrel users for an indication other than a cardiac one, such as stroke secondary prevention, were also included | 6 | from its inception to Apr 2016 | 20; observational studies | NHLBI tool for observational cohort and cross-sectional studies |
| **Warfarin – *CYP2C9* and *VKORC1* (SRs with MA)** | | | | | | | |
| Goulding et al., 2015 [18] | to quantify the clinical effectiveness of genotype-guided prescription | not specified | use of genetic information such as SNP or CNV to guide drug prescription (e.g. dose, choice of drug) and measured clinical outcome or outcomes that determine the benefits of using the genetic information | 3 | Jan 1980 to Dec 2013 | 15; RCT | Cochrane risk-of-bias tool for randomized trials |
| Jorgensen et al., 2012 [19] | to enable fair and accurate interpretation of which variants affect which outcomes, in which patients, and to what extent | not specified | patients who are commencing/ established on warfarin and genotyped for *CYP2C9*/*VKORC1* variants, to investigate their effect on treatment response | 1 | Sep 2009 | 117; observational studies, RCT | Jorgensen and Williamson, 2008 [20] |
| Sanderson et al., 2005 [21] | to examine the strength and quality of existing evidence about *CYP2C9* gene variants and clinical outcomes in warfarin-treated patients | not specified | patients who are commencing/ established on warfarin who were tested for *CYP2C9* variants from anticoagulant clinics or their equivalent | 6 | 1980 to Jan 2003 | 11; observational studies | not performed |
| Shi et al., 2015 [22] | to evaluate whether pharmacogenetics-based dosing improves clinical outcomes compared to conventional dosing | ≥ 16 years old | patients with an indication for anticoagulation of warfarin | 6 | from its inception to Mar 2015 | 11; RCT | Cochrane risk-of-bias tool for randomized trials |

ACS: acute coronary syndrome; CABG: coronary-artery bypass grafting; CAD: coronary artery disease; CCVD: cardiovascular and cerebrovascular disease; CNV: copy number variation; *CYP*: cytocrome p450; HCPR: high on-clopidogrel platelet reactivity; HTPR: high on-treatment platelet reactivity; IS/TIA: ischaemic stroke or transient ischaemic attack; LOF: loss of function; MA: meta-analysis; MACE: major adverse cardiovascular events; MENA: Middle East and North Africa; NHLBI: national heart, lung, and blood institute; NOS: Newcastle-Ottawa scale; PCI: percutaneous coronary intervention; PPI: proton pump inhibitors; RCT: randomized controlled trial; SR: systematic review; SNP: single nucleotide polymorphism; *VKORC1*: vitamin K epoxide reductase complex subunit 1.

**Table S2.** Methodological quality of included systematic reviews, according to AMSTAR-2.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Systematic review | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | 10 | 11 | | 12 | 13 | 14 | 15 | 16 | Quality |
| RCT | NRSI | RCT | NRSI |
| **Clopidogrel – CYP2C19 (SRs with MA)** | | | | | | | | | | | | | | | | | | | |
| Alakbarzade et al., 2020 | yes | no | no | yes | yes | no | no | yes | \_\_ | no | no | \_\_ | yes | no | no | yes | yes | yes | critically low |
| Bauer et al., 2011 | yes | no | yes | yes | yes | yes | yes | yes | \_\_ | yes | yes | \_\_ | yes | yes | yes | yes | yes | yes | high\* |
| Holmes et al., 2011 | yes | yes | no | p-y | no | no | yes | yes | p-y | p-y | yes | no# | no# | yes | yes | yes | yes | yes | critically low |
| Huang et al., 2017 | yes | no | no | p-y | no | yes | no | p-y | \_\_ | yes | no | \_\_ | yes | no | no | yes | no | yes | critically low |
| Hulot et al., 2010 | yes | no | yes | p-y | yes | yes | no | p-y | \_\_ | yes | no | \_\_ | yes | no | no | no | yes | no | critically low |
| Jang et al., 2012 | yes | no | yes | no | yes | yes | no | no | no | no | no | no# | no# | no | no | yes | yes | no | critically low |
| Jin et al., 2011 | yes | no | no | p-y | no | yes | no | yes | \_\_ | no | no | \_\_ | yes | no | no | yes | no | yes | critically low |
| Mega et al., 2010 | yes | no | yes | no | no | no | p-y | no | \_\_ | p-y | no | yes | yes | no | no | yes | no | yes | critically low |
| Niu et al., 2015 | yes | no | no | p-y | yes | no | no | no | \_\_ | yes | no | \_\_ | yes | no | no | no | yes | yes | critically low |
| Pan et al., 2017 | yes | no | no | yes | yes | yes | no | yes | \_\_ | yes | no | yes | yes | no | no | no | yes | yes | critically low |
| Sofi et al., 2011 | yes | no | no | p-y | yes | yes | no | yes | \_\_ | no | no | \_\_ | yes | no | no | yes | yes | yes | critically low |
| Sorich et al., 2014 | yes | no | yes | no | no | no | no | yes | \_\_ | no | yes | \_\_ | yes | no | no | yes | yes | yes | critically low |
| Xi et al., 2019 | yes | no | no | no | yes | yes | no | yes | \_\_ | yes | no | \_\_ | yes | no | no | yes | yes | yes | critically low |
| Zabalza et al., 2012 | yes | no | no | no | no | yes | yes | no | \_\_ | no | no | \_\_ | yes | yes | no | yes | yes | yes | critically low |
| Zhang et al., 2015 | yes | no | no | p-y | yes | yes | yes | no | no | no | no | no | no | no | yes | yes | yes | yes | critically low |
| Zheng et al., 2019 | yes | no | no | no | no | yes | no | yes | p-y | yes | no | yes | yes | no | no | no | yes | yes | critically low |
| **Clopidogrel – *CYP2C19* (SRs without MA)** | | | | | | | | | | | | | | | | | | | |
| Ali and Elewa, 2019 | yes | yes | no | p-y | yes | no | yes | yes | \_\_ | yes | no | n/a | n/a | n/a | no | no | n/a | yes | low |
| **Warfarin – *CYP2C9* and *VKORC1* (SRs with MA)** | | | | | | | | | | | | | | | | | | | |
| Goulding et al., 2015 | yes | no | yes | yes | yes | yes | no | yes | yes | \_\_ | no | yes | \_\_ | yes | yes | yes | no | yes | critically low |
| Jorgensen et al., 2012 | yes | yes | no | no | yes | yes | no | p-y | no | no | no | yes | no | no | no | no | no | yes | critically low |
| Sanderson et al., 2005 | yes | no | no | yes | no | yes | no | p-y | yes | no | no | yes | no | no | yes | yes | no | no | critically low |
| Shi et al., 2015 | yes | yes | no | yes | yes | yes | no | yes | yes | \_\_ | no | yes | \_\_ | yes | yes | yes | yes | yes | low |

\*Despite a lack of protocol, this is rated “high” because the SR was published in 2011, when this requirement was not mandatory yet. #meta-analysis includes RCT and observational studies without sensibility analysis. MA: meta-analysis; N/A: Not applicable because no meta-analysis conducted; NRSI: non-randomized studies of intervention; p-y: partial yes; RCT: randomized controlled trial; SR: systematic review.

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