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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Comparative effects of different antiplatelet strategies in carriers of CYP2C19 loss-of-function alleles: a network meta-analysis

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Background Carriers of cytochrome 2C19 (*CYP2C19*) loss-of-function (LoF) alleles treated with clopidogrel have impaired drug metabolism, resulting in reduced active metabolite levels, high platelet reactivity (HPR), and an increased risk of thrombotic events. Several alternative antiplatelet therapies have been proposed to overcome HPR in these patients, but their comparative effects remain poorly explored.

Methods Randomized controlled trials (RCTs) comparing different oral antiplatelet therapies in carriers of *CYP2C19* LoF alleles undergoing percutaneous coronary interventions (PCI) were included. A frequentist network meta-analysis was conducted to estimate mean difference (MD) or odds ratios and 95% confidence intervals (CI). The primary outcome was platelet reactivity assessed by VerifyNow and reported as $P2Y_{12}$ reaction unit (PRU). The secondary outcome was the rate of HPR. Standard dose of clopidogrel (75 mg daily) was used as a reference treatment.

Results A total of 12 RCTs testing 6 alternative strategies (i.e. clopidogrel 150 mg, prasugrel 3.75 mg, 5 mg, and 10 mg, ticagrelor 90 mg bid, and adjunctive cilostazol 100 mg bid) were included in the network. Compared with standard-dose clopidogrel, the greatest reduction in PRU was observed with prasugrel 10 mg (MD −127.91; 95% CI −141.04; −114.78) and ticagrelor 90 mg bid (MD −124.91; 95% CI −161.78; −88.04), followed by prasugrel 5 mg (MD −76.33; 95% CI −98.01; −54.65) and prasugrel 3.75 mg (MD −73.00; 95% CI −100.28; −45.72). Among other strategies, adjunctive cilostazol (MD −42.64; 95% CI −64.72; −20.57) and high-dose clopidogrel (MD −32.11; 95% CI −51.33; −12.90) were associated with a modest reduction in PRU compared with standard-dose clopidogrel.

Conclusion Among carriers of *CYP2C19* LoF alleles undergoing PCI, standard-dose prasugrel or ticagrelor are most effective in reducing platelet reactivity, while double-dose clopidogrel and additional cilostazol showed modest effects. Reduced-dose of prasugrel may represent a balanced strategy to overcome HPR without a significant increase in bleeding. The clinical implications of these pharmacodynamic findings warrant further investigation.

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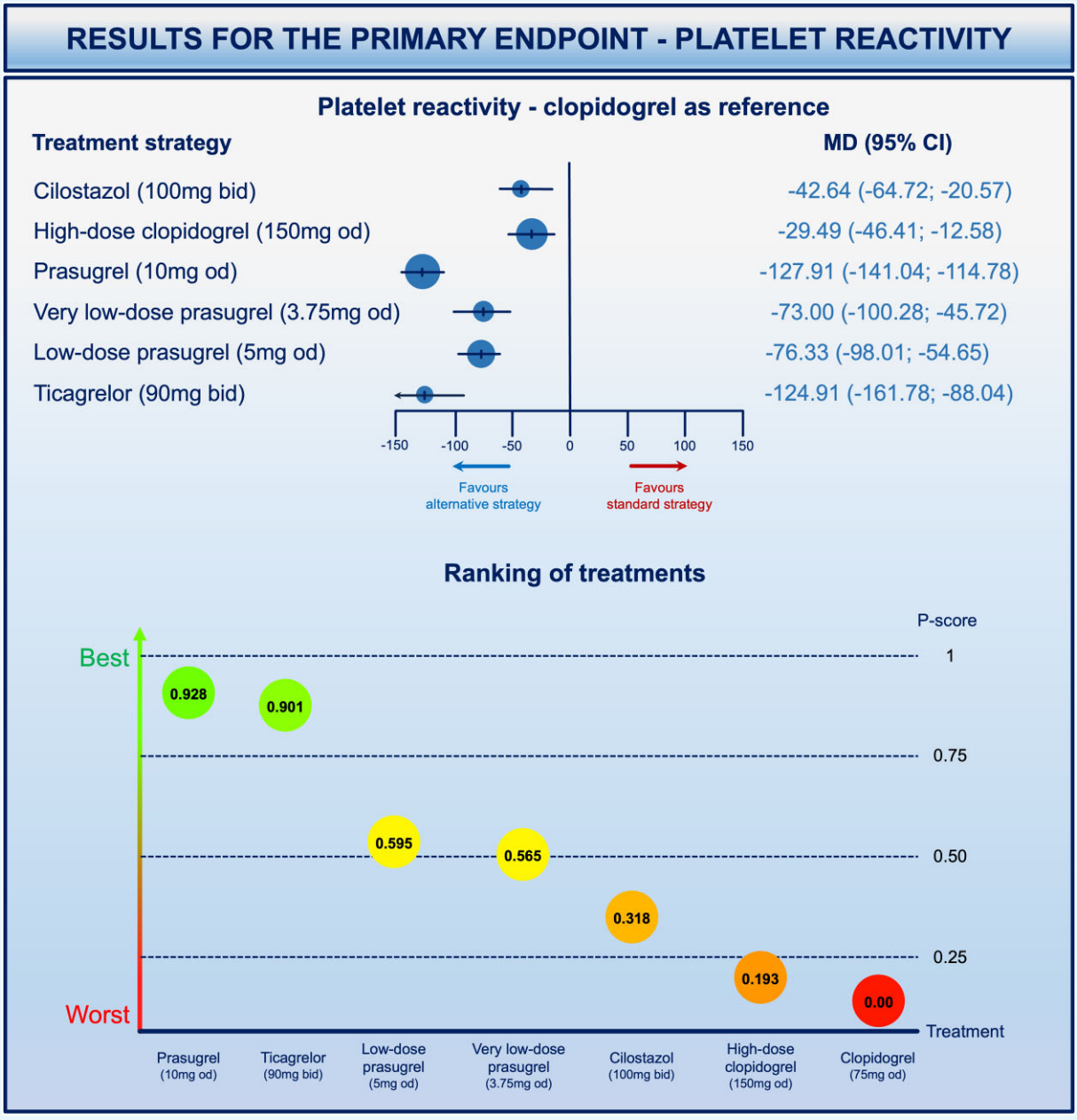
Graphical Abstract



Keywords CYP2C19 • Antiplatelet therapy • Clopidogrel resistance • Genotype • Prasugrel • Ticagrelor • Guided-therapy

Abbreviations

DAPT dual antiplatelet therapy
CYP Cytochrome P450
HPR high platelet reactivity
LoF loss-of-function
PCI percutaneous coronary intervention
PFT platelet function test
PD pharmacodynamic

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the cornerstone of treatment in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).[1] Clopidogrel is the most commonly used $P2Y_{12}$ receptor inhibitor, but exhibits distinctive pharmacologic features leading to broad interindividual variability in its effects.[2] In fact, clopidogrel is a pro-drug that requires a two-step hepatic conversion into its active

metabolite by several cytochrome P450 (CYP) isoenzymes.[3] Of these, the CYP2C19 isoforms are particularly important because they take part in both biotransformation oxidative processes required to generate clopidogrel's active metabolite.[3,4] However, the genes that encode for the CYP2C19 enzymes are highly polymorphic, with some resulting in reduced [i.e. loss-of-function (LoF)] and others increased [i.e. gain-of-function (GoF)] clopidogrel metabolism.[5] While the clinical implications of GoF alleles among clopidogrel treated patients remain controversial, it is well established that carriers of one (intermediate metabolizers, IMs) or two (poor metabolizers, PMs) LoF alleles exhibit reduced levels of clopidogrel active metabolite resulting in high platelet reactivity (HPR) and enhanced risk of thrombotic complications.[5–8] Notably, carriers of LoF alleles are as frequent as 20–60% of treated patients, varying according to ancestry, underscoring its relevance in clinical practice.[8]

The association between *CYP2C19* LoF alleles and increased rates of thrombotic events among clopidogrel-treated patients has led the Food and Drug Administration as well as other drug governing authorities to issue a cautionary advisory recommending the use of alternative $P2Y_{12}$ inhibiting therapies in PMs.[9,10] Similarly, the 2019 expert consensus statement on platelet function test (PFT) and genetic testing for patients undergoing PCI and the 2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline and other expert consensus suggests the use of alternative $P2Y_{12}$ inhibitors among carriers of *CYP2C19* LoF alleles, particularly PMs.[8,11–13] Although the use of ticagrelor or prasugrel is recommended in PM, a number of alternative antiplatelet treatment regimens have been proposed to reduce platelet reactivity and minimize the rate of HPR, but comprehensive studies exploring the comparative effects of different alternative strategies are lacking.[14–22] Since levels of platelet reactivity are closely associated with adverse outcomes, pharmacodynamic studies comparing the effects of different alternative strategies on platelet function among *CYP2C19* LoF carriers may provide important clinical information.[7,23] On this background, we conducted a network meta-analysis to comprehensively assess the comparative effects of different alternative antiplatelet regimens among individuals carrying *CYP2C19* LoF alleles, consolidating results from randomized controlled trials (RCTs).

Methods

The study protocol adhered to the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for network meta-analyses (PRISMA-NMA) of RCTs (Supplementary material online, *Table S1*) and Cochrane Collaboration.[24,25] The study protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO ID: CRD42024509513). As the present research was a meta-analysis of published studies, the requirement to obtain approval from an ethics committee was waived.

Eligibility criteria

Studies were considered for inclusion in the network meta-analysis when the following criteria were satisfied: (i) patients were carriers of *CYP2C19* LoF alleles (e.g. *CYP2C19**2, *CYP2C19**3) diagnosed with atherosclerotic cardiovascular disease and undergoing PCI; (ii) random allocation to at least two different antiplatelet strategies; (iii) pharmacodynamic (PD) assessment (i.e. platelet reactivity) with at least one PFT.

Search, data extraction, and qualitative assessment

A systematic digital search using MEDLINE with PubMed interface, Cochrane Library, and Web of Science databases was carried out from database inception to 17 January 2024. Major scientific websites as well as abstracts and presentations from major cardiovascular meetings were also screened. The electronic search process was integrated by exploration of the reference lists of each eligible study (i.e. backward and forward snowballing). The full research strategy is reported in Supplementary material online, *Table S2*. Literature search terms were reviewed by an experienced medical librarian. No language restrictions or filters were applied.

Following the execution of search queries, two reviewers (R.L., G.O.) independently screened titles and abstracts to identify studies that met the inclusion criteria. Duplicate entries identified across various electronic databases were removed. The remaining reports underwent independent full-text screening by the same reviewers to confirm compliance with the eligibility criteria. Disagreements were solved by consensus under the supervision of the lead investigator (M.G.). Data pertaining to the outcomes of interest, as well as the primary clinical and procedural characteristics, design features, and endpoints definitions were extracted at study level and incorporated into dedicated electronic spreadsheets. Before running the statistical analyses, the reviewers collegially assessed the quality of each trial by using the Cochrane's Risk of Bias (RoB) 2 tool.

Inconsistency was evaluated by means of net heat plots, and node-splitting analysis. Finally, the impact of small-study effects and publication bias was estimated by visual inspection of comparison-adjusted funnel plots, and formally assessed by means of Egger's regression test.

Study endpoints

The pre-specified primary endpoint was the level of platelet reactivity between treatment arms as assessed by the VerifyNow $P2Y_{12}$ assay and measured as $P2Y_{12}$ reaction unit (PRU). The secondary endpoint was trial-defined rates of HPR. PD assessments obtained while on maintenance dose therapy were chosen over those following a loading dose. All study outcomes were extracted at the longest available follow-up.

Statistical analysis

A frequentist network meta-analysis was conducted to estimate the posterior mean effect, reported as odds ratio (OR) or mean difference (MD), as appropriate, and the 95% confidence interval (CI), for all the outcomes of interest. An estimated effect was considered significant when the upper or lower CI did not include the unity (i.e. null value). The analysis was conducted using the adjusted random effects weight, calculating the pooled effect size using the inverse variance method.

The network of evidence was visually and numerically assessed in terms of weights, comparisons, and individual trial influence for each outcome. Consistency between direct and indirect comparisons was examined by node splitting and visual inspection of net-heat plots. Results were displayed using forest plots illustrating the relative contribution of individual trials. The standard dose of clopidogrel (75 mg daily) was used as a reference treatment. Antiplatelet strategies were ranked according to *P*-scores, ranging between 0 (poor performance) and 1 (good performance). Between-study heterogeneity (i.e. statistical heterogeneity) was assessed according to the Cochran's Q test, Higgins and Thompson's I^2 statistics (with an I^2 value >50% being considered the result of severe heterogeneity); the heterogeneity variance τ^2 and standard deviation τ. Statistical analysis was conducted using R version 3.6 (R Foundation for Statistical Computing, Vienna) by using the packages 'netmeta' and 'gemtc'.

Pre-specified sensitivity analyses were conducted to explore the possible impact of clinical presentation [i.e. ACS vs. chronic coronary syndrome (CCS)] or ethnicity (i.e. East Asian vs. non-East Asian patients) on each endpoint.

Results

Studies selection, network of evidence, and baseline characteristics

After screening, a total of 12 RCTs were included in the network meta-analysis (*Figure 1*).[14,26–36] The network of evidence for

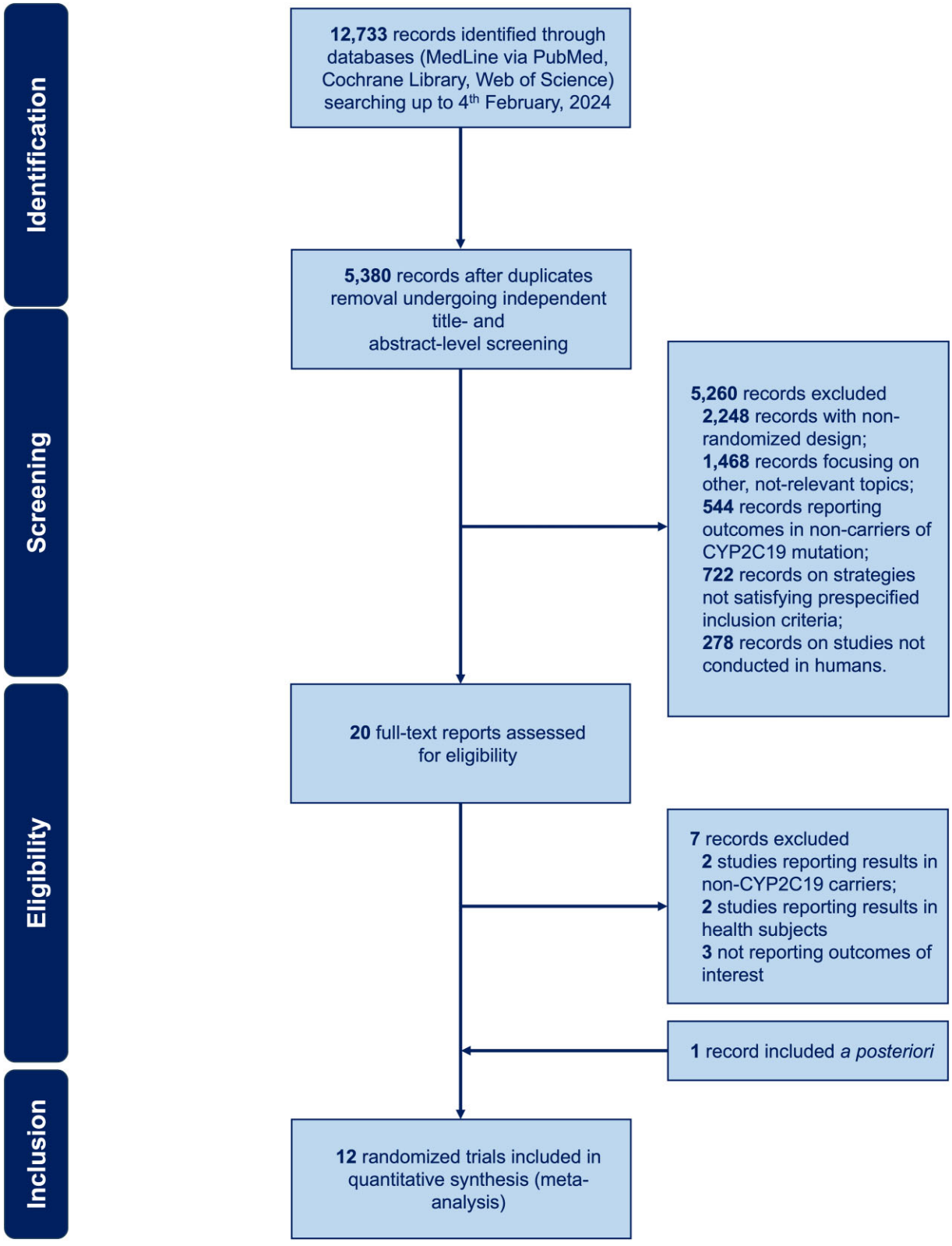


Figure 1 Systematic review flow-chart. The figure illustrates the level at which each study was excluded during the review process. CYP, Cytochrome P450.

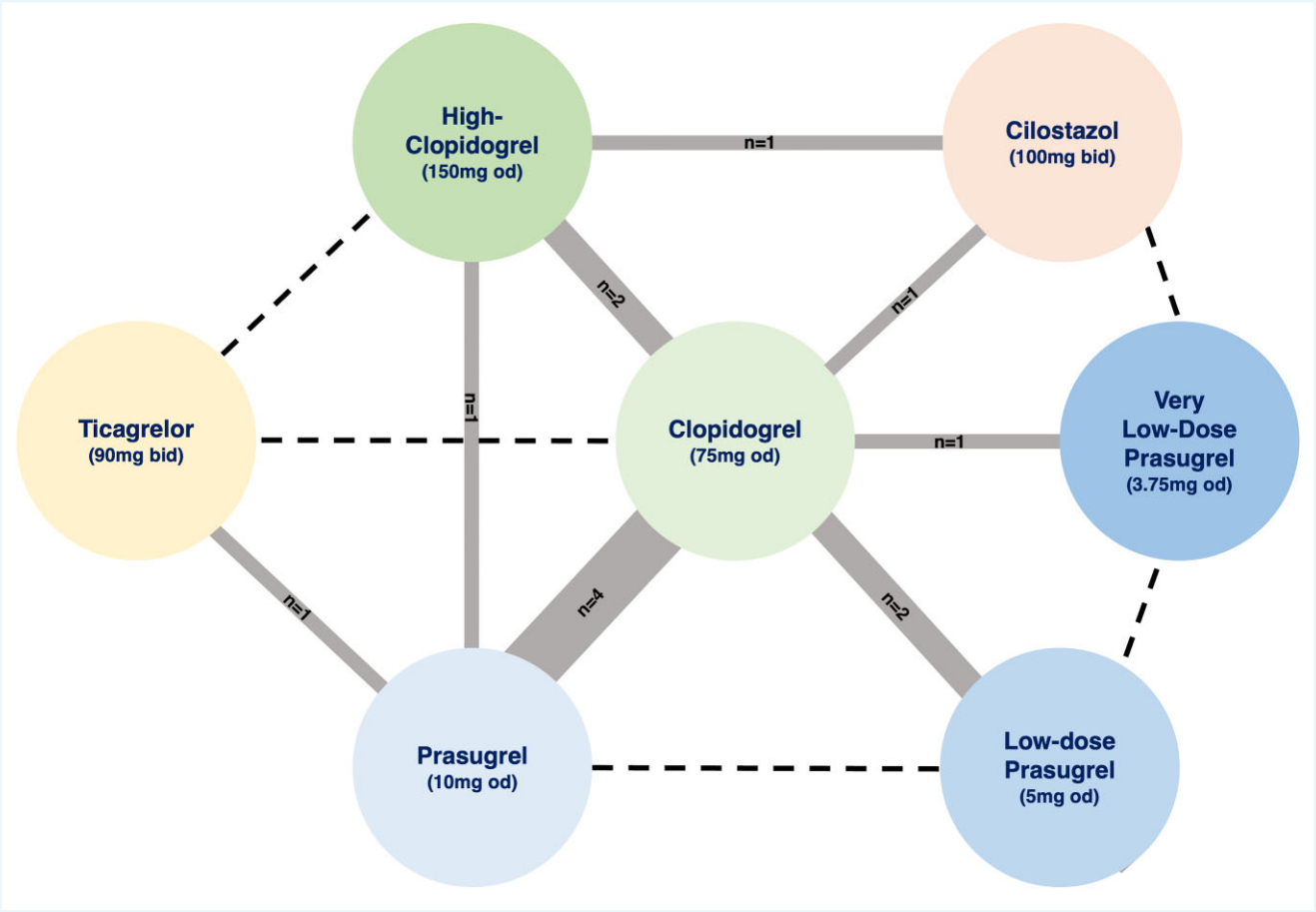


Figure 2 Network of the evidence. Direct comparisons are depicted as thick lines and indirect comparisons as dotted lines. Numbers indicate how many randomized controlled trials were included for each comparison.

each outcome is illustrated in *Figure 2*. Seven antiplatelet strategies were compared: standard-dose (i.e. 75 mg od) clopidogrel (reference strategy), high-dose clopidogrel (150 mg od), adjunctive cilostazol (100 mg bid), standard-dose ticagrelor (90 mg bid), standard-dose prasugrel (10 mg od), low-dose prasugrel (5 mg od), and very-low-dose prasugrel (3.75 mg od).[29] Two loops were closed, made by the comparisons of standard-dose clopidogrel, high-dose clopidogrel, and standard-dose prasugrel for the first loop, and standard-dose clopidogrel, high-dose clopidogrel, and cilostazol for the second loop. For these strategies, both direct and indirect evidence were available. All other comparisons were made by indirect comparisons.

Table 1 summarizes the key clinical characteristics of the included trials. The number of included patients from randomized trials reporting data on carriers of *CYP2C19* LoF ranged from 24 to 485. Women were under-represented, with a percentage ranging between 9.2 and 32.8%. Four studies were conducted exclusively in East Asia, and among those three out of four focused exclusively on patients with ACS.[30–32] The proportion of PM or IM was not reported in 6 out of the 12 included trials, but only represented a minority in the overall population in the other 6 RCTs, ranging from 5 to 20%. Three studies were conducted exclusively in patients with CCS.[14,29,35,37] Importantly, all studies assessed platelet reactivity reported as PRU using VerifyNow-P2Y12 Assay. A detailed description of the assays used for genotyping and PFT across trials is reported in Supplementary material online, *Table S3*. HPR definitions across trials are reported in Supplementary material online, *Table S4*.

The overall and individual risk for bias of included trials is shown in Supplementary material online, *Figure S1*. Some concerns arose in six studies,[26,29,30,32,34] three of them due to RoB arising from the randomization process,[30,32] and three of them due to missing outcome data.[26,29,34] Although Egger's regression test suggested absence of publication bias, the inspection of the funnel plot for visual asymmetry revealed slight asymmetry for both platelet reactivity and HPR (Supplementary material online, *Figure S2*).

Network meta-analysis

Compared with standard-dose clopidogrel, the primary endpoint of PRU was reduced with all alternative antiplatelet strategies, except for adjunctive cilostazol. Specifically, the reduction was greatest with standard-dose prasugrel (MD −127.91; 95% CI −141.04; −114.78) and standard-dose ticagrelor (MD −124.91; 95% CI −161.78; −88.04), followed by low-dose prasugrel (MD −76.33; 95% CI −98.01; −54.65), and very-low dose prasugrel (MD −73.00; 95% CI −100.28; −45.72) (*Figure 3*). High-dose clopidogrel and adjunctive cilostazol were associated with a modest reduction of PRU compared with standard-dose clopidogrel (MD −29.49; 95% CI −46.41; −12.58 and −42.64; 95% CI −64.72.; −20.57, respectively) (*Figure 3*).

The node split analysis for the comparisons reporting both direct and indirect evidence (standard-dose prasugrel, standard-dose clopidogrel, and high-dose clopidogrel) for the primary endpoint, did not reveal inconsistency, with results of the network mostly laying on

Table 1 Key characteristics of randomized trials included in the systematic review and meta-analysis

Study, Year	LoF carriers	Percentage of poor metabolizers *n* (%)	Age	Female (%)	Race (%)	Genotype	Diabetes (%)	Scenario (%)	Interventional Group	Control Group
Varenhorst et al. (2009)[35]	52	NA	63.8	9.2	§ Caucasian: 100%	Multiple, Heterozygous	19.4%	§ CCS: 100%	Prasugrel 60 mg LD/10 mg MD	Clopidogrel 600 mg LD/75 mg MD
Alexopoulos et al. (2011)[26]	21	NA	65.0	11.0	NA	Multiple, Heterozygous	36.0%	§ ACS: 70.3%	Clopidogrel 150 mg/Prasugrel 10mg	Prasugrel 10 mg/ Clopidogrel 150 mg
Kim In-Suk et al. (2011)[31]	77	19 (15)	61.4	24.7	§ Asian: 100%	Multiple, Heterozygous	28.6%	§ ACS: 100%	Adjunctive cilostazol 100mg	Clopidogrel 150 mg
Mega et al. (2011)[14]	86	5 (5.81)	60.2	25.2	§ White: 88.0% § Asian: 2.4% § Black: 9.0%	Heterozygous or Homozygous	35.4%	§ CCS: 100%	Clopidogrel 150 mg	Clopidogrel 75 mg
Park et al. (2011)[36]	283	52 (10.7)	63.4	30.1	§ Asians: 100%	Multiple, Heterozygous	36.7	§ Referred for PCI:100%	Adjunctive Cilostazol 200 mg LD/100 mg MD	Clopidogrel 600 mg LD/75mg
Roberts et al. (2012)[33]	46	7 (15.2)	60.2	22	NA	Multiple, Heterozygous	22.5%	§ ACS: 37.4% § CCS: 62.6%	Clopidogrel 600 mg LD/Prasugrel 10 mg MD	Clopidogrel 600 mg LD/75 mg MD
Braun et al. (2013)[27]	49	NA	61.6	18.9	§ Caucasian: 90.3%	Multiple, Heterozygous	25.7%	NA	Prasugrel 60 mg LD/10 mg MD	Clopidogrel 75 mg MD
Gurbel et al. (2014)[29]	41	NA	65.5	32.8	§ Caucasian: 93.9%	Multiple, Heterozygous	NA	§ CCS: 100%	Prasugrel 10 mg MD Prasugrel 5 mg MD	Clopidogrel 75 mg MD Clopidogrel 75 mg MD
Rossi et al. (2014)[34]	50	NA	63.3	29.2	NA	Heterozygous or Homozygous	42.1%	NA	Clopidogrel 150mg	Clopidogrel 75 mg
Ogawa et al. (2016)[32]	485	154 (19.9)	64.3	18.9	§ Asian: 100%	Heterozygous or Homozygous	35.7%	§ ACS: 100%	Prasugrel 20 mg LD/3.75 mg MD	Clopidogrel 300 mg LD/75 mg MD
Franchi et al. (2020)[28]	65	8 (12)	59.0	21.5	§ White: 67.7%	Multiple, Heterozygous	37.0%	§ ACS: 54.9% § CCS: 45.1%	Prasugrel 60 mg LD/10 mg MD	Ticagrelor 180 mg LD/90 mg MD
Jin et al. (2020)[30]	70	NA	63.0	29.6	§ Asian: 100%	Multiple, Heterozygous	31.7%	§ ACS: 100%	Prasugrel 30 mg LD/5 mg MD	Clopidogrel 600 mg LD/75 mg MD

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; *n*, number; NA, not available; LD, loading dose; MD, maintenance dose; LoF, loss of function.

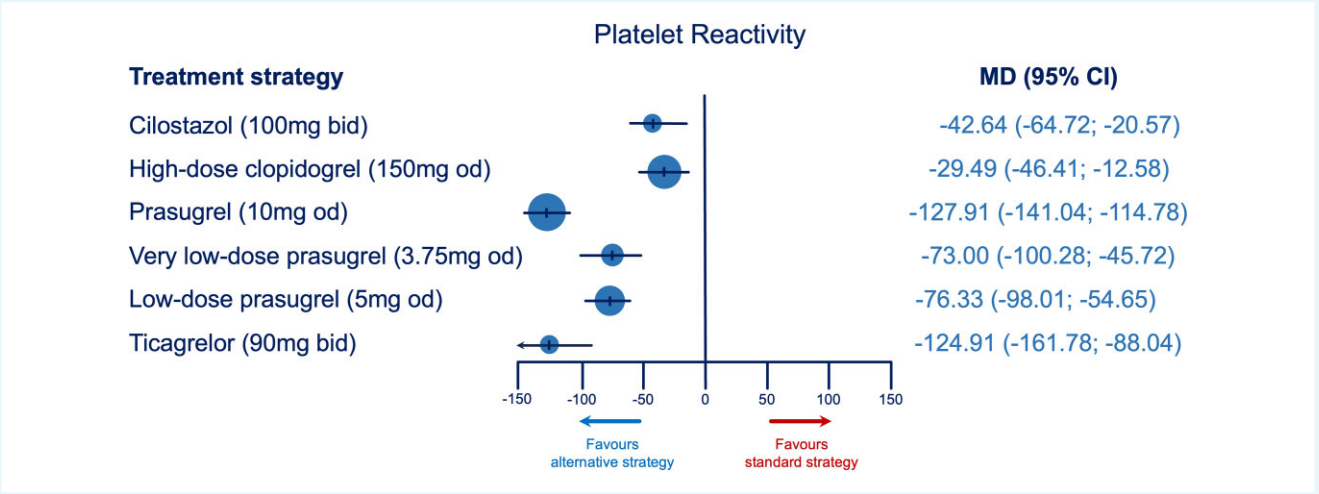


Figure 3 Forest plot for the primary endpoint (i.e. platelet reactivity). The figure illustrates treatment estimate among different antiplatelet strategies for the primary endpoint. Standard-dose (75 mg od) clopidogrel was used as reference strategy. The primary endpoint was the level of platelet reactivity between treatment arms as assessed by the VerifyNow $P2Y_{12}$ assay and reported as P2Y12 reaction unit (PRU). For each comparison, treatment estimates and respective 95% CI are illustrated by one circle and line, respectively, along with text highlighting the specific mean difference and 95% CI. BID, bis in die; CI, confidence interval; MD, mean difference; OD, once daily.

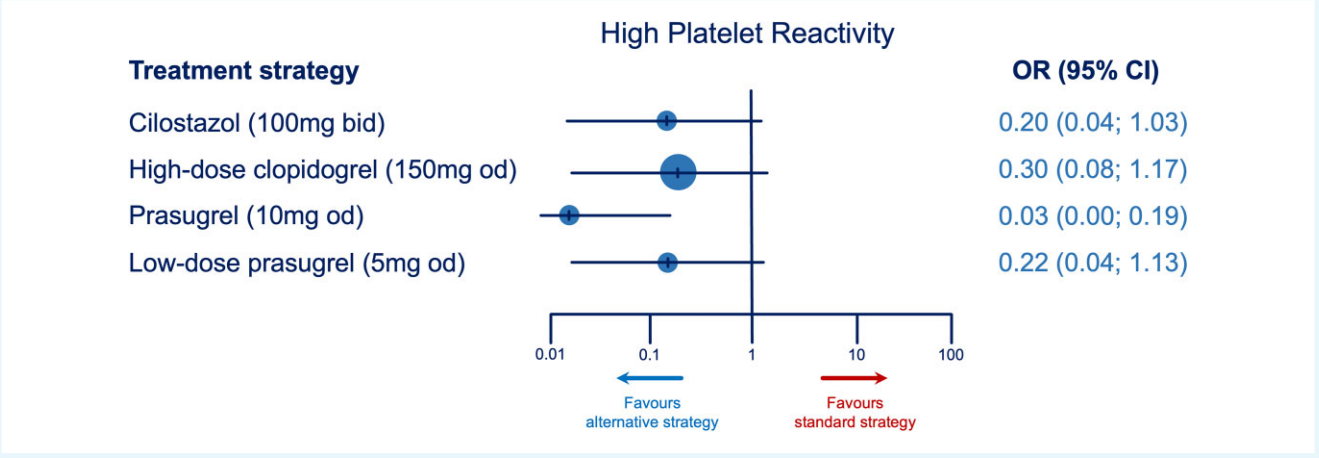


Figure 4 Forest plot for the secondary endpoint (i.e. high-platelet reactivity rates). The figure illustrates the treatment estimate among different antiplatelet strategies for the secondary endpoint of trial-defined high-platelet reactivity rates. Standard-dose (75 mg od) clopidogrel was used as reference strategy. For each comparison, treatment estimates and respective 95% CI are illustrated by one circle and line, respectively, along with text highlighting the specific odds ratio and 95% CI. BID, bis in die; CI, confidence interval; OD, once daily; OR, odds ratio.

direct comparisons (Supplementary material online, *Figure S3*). The net heat plot revealed the consistency between direct and indirect evidence (Supplementary material online, *Figure S4*),

The secondary outcome of HPR rates was not available for the treatment arms of standard-dose ticagrelor and very low-dose prasugrel. All the alternative antiplatelet strategies were associated with reduced HPR, but the reduction was statistically significant only with standard dose of prasugrel (OR 0.03; 95% CI 0.00; 0.19) (*Figure 4*).

Node split analysis for the comparisons reporting both direct and indirect evidence (standard-dose prasugrel, standard-dose clopidogrel, and high-dose clopidogrel for the first loop, and standard-dose clopidogrel, high-dose clopidogrel, and cilostazol for the second loop) did not reveal any inconsistency, with results of the network laying mostly on direct comparisons (Supplementary material online, *Figure S5*). Net heat plot revealed strong consistency between direct and indirect evidence (Supplementary material online, *Figure S6*).

Ranking of treatments

Ranking of treatments according to *P*-scores for primary and secondary outcomes is displayed in the central figure and in Supplementary material online, *Figures S7* and *S8*. With regard to the primary endpoint, standard-dose prasugrel ranked as the best treatment (*P*-score = 0.928), followed by ticagrelor (*P*-score = 0.901), and low-dose prasugrel (*P*-score = 0.595), very-low dose prasugrel (*P*-score = 0.5654), cilostazol (*P*-score = 0.318), high-dose clopidogrel

(*P*-score = 0.193). Rankograms for the secondary endpoint should be interpreted in light of the fact that rates of HPR were not available for the treatment arms of standard-dose ticagrelor and very low-dose prasugrel.

Sensitivity analyses

The replication of analyses after the exclusion of studies selectively including patients with ACS (Supplementary material online, *Figure S9*) or CCS (Supplementary material online, *Figure S10*) showed consistent results with the main analysis. Similarly, the analysis run after the exclusion of studies selectively including Caucasian (Supplementary material online, *Figure S11*) or East Asian patients (Supplementary material online, *Figure S12*) showed results similar to the main analysis.

Discussion

The results of this network meta-analysis assessing the comparative effects of different alternative antiplatelet regimens by consolidating results from RCTs among individuals carrying *CYP2C19* LoF alleles can be summarized as follows: (i) all alternative antiplatelet strategies were associated with reduced platelet reactivity compared with standard-dose clopidogrel, the magnitude of which, however, varied widely across different strategies; (ii) standard-dose prasugrel or ticagrelor are associated with the greatest reduction in platelet reactivity, followed by reduced- and very low-dose of prasugrel, compared with standard-dose clopidogrel; (iii) double-dose clopidogrel and adjunctive cilostazol were associated with a modest reduction in platelet reactivity, compared with standard-dose clopidogrel; (iv) compared with standard-dose clopidogrel, there was a reduction in HPR with all treatments, that was statistically significant with standard-dose prasugrel.

Platelet function may be assessed by different assays, allowing for the identification of patients at HPR, low platelet reactivity (LPR), or optimal range of platelet reactivity (OPR).[8] Point-of-care assays have the advantage of providing rapid bedside results by non-expert personnel in a timely fashion compared with laboratory-based assays. Among these, the VerifyNow P2Y12 assay is one of the most commonly used.[8,38] HPR among clopidogrel-treated patients undergoing PCI has been consistently shown to be associated with increased major adverse cardiovascular events (MACE), including death and stent thrombosis, and that LPR is not associated with a further reduction of MACE, but increased bleeding, as compared with OPR patients.[7,23] This has represented the rationale for proposing a potential 'therapeutic window' of platelet inhibition in PCI patients.[8,39,40]

The understanding that the interindividual variability in clopidogrel response lies, at least in part, in the fact that 20–60% of treated patients are carriers of *CYP2C19* LoF alleles (e.g. *CYP2C19**2, *CYP2C19**3), the prevalence of which is largely influenced by ethnicity, being more common in East Asian than European and African ancestry populations.[4,8] The fact that heterozygote patients are IMs associated with reduced clopidogrel active metabolite, and homozygote patients are PMs associated with nearly no generation of clopidogrel active metabolite, has stimulated the interest in the use of genetic testing to identify patients non-responding to clopidogrel.[4] Indeed, genetic testing for *CYP2C19* LoF alleles have the key advantage that the genetic makeup of an individual remains unvaried over time and does not require the patient to be on treatment with clopidogrel.[4,8] Studies have shown that IM, and particularly PM phenotypes for *CYP2C19* LoF alleles, are associated with reduced levels of clopidogrel active metabolite, diminished platelet inhibition, and high rates of HPR resulting in increased rates MACE and stent thrombosis following PCI.[41] On this background, several drug governing authorities have issued a cautionary advisory recommending the use of alternative $P2Y_{12}$ inhibiting therapies in carriers of *CYP2C19* LoF alleles, particularly for PM, a recommendation also supported by expert consensus documents.[8–11]

On this background, several studies have explored the clinical impact of using alternative oral antiplatelet therapies among carriers of *CYP2C19* LoF alleles treated with clopidogrel.[14–22] Early strategies tested in RCTs first included increased dose of clopidogrel (i.e. 150 mg od) or adjunctive cilostazol on top of DAPT.[14–20] Subsequent studies have tested the use of newer generation $P2Y_{12}$ inhibitors (i.e. prasugrel or ticagrelor).[21,22] Although the results of these studies were not univocal due to a number of pitfalls in their design, the overall clinical evidence suggest that the use of prasugrel or ticagrelor as alternative therapy to clopidogrel could reduce MACE in *CYP2C19* LoF carriers but with increased bleeding without any additional reduction in ischaemic events in patients responding to clopidogrel.[41] Importantly, the use of PFT and genetic testing has been associated with improved outcomes compared with standard antiplatelet therapy in both ACS and CCS patients undergoing PCI.[42,43]

The clinical impact of alternative antiplatelet therapy in *CYP2C19* LoF allele carriers stems from their pharmacologic characteristics. Indeed, ticagrelor does not require hepatic activation by the CYP2C19 enzyme, while the role of this enzyme in the conversion of prasugrel into its active metabolite is limited.[32] Moreover, cilostazol is a selective phosphodiesterase-3 inhibitor that inhibits platelet aggregation by increasing cyclic adenosine monophosphate in platelets and is not affected by the CYP2C19 enzyme.[44] However, the comparative effects of these alternative antiplatelet agents among *CYP2C19* LoF carriers has never been tested. Because platelet reactivity assessed by PFT is closely associated with adverse clinical outcomes, we performed a network meta-analysis of RCTs comparing different alternative antiplatelet agents among *CYP2C19* LoF carriers and reporting measures deriving from PFT.[7] We found that all strategies were associated with reduced rates of HPR, but that the reduction in platelet reactivity varied widely across the different alternative regimens, being maximum with standard dose of the newer generation $P2Y_{12}$ inhibitors (prasugrel 10 mg od or ticagrelor 90 mg bid), and progressively decreasing with the reduction of its dose (i.e. prasugrel 5 and 3.75 mg). There is no data with reduced dose of ticagrelor (e.g. 60 mg bid). Notably, double-dose clopidogrel and additional cilostazol had a modest reduction in platelet reactivity, compared with standard-dose clopidogrel. These findings are consistent with previous studies, but add important insights on how reduced doses of prasugrel may perform in *CYP2C19* LoF carriers compared with other doses and other alternative strategies. In fact, a dose reduction of prasugrel after a short course of standard DAPT represents one of the possible de-escalation strategies after ACS/PCI, although the clinical evidence in support of this strategy is scarce and comparative effects of different de-escalation antiplatelet strategies are lacking.[45–48]

Moreover, our results support previous findings suggesting that adjunctive cilostazol on top of DAPT could enhance the inhibition of $P2Y_{12}$ signalling, reducing platelet reactivity and improving outcomes in patients undergoing PCI.[49] However, it should be acknowledged that VerifyNow is a test primary designed to assess the effects of $P2Y_{12}$ inhibitors, and therefore it is inevitably less sensitive to assess the antiplatelet effects of cilostazol.

Given the importance of OPR in optimizing the balance between ischaemic and bleeding risks in ACS/PCI patients, our findings suggest that a reduced-dose of prasugrel may provide an adequate balance between efficacy, by reducing the rates of HPR in carriers of *CYP2C19* LoF, and safety, by reducing the rates of patients expected to be at LPR compared to other alternative strategies (i.e. standard-dose ticagrelor

or prasugrel).[39] These findings are hypothesis generating and should be confirmed in dedicated clinical studies.

Limitations

This analysis has several limitations. First, this is a study-level rather than a patient-level meta-analysis. Therefore, it was not possible to stratify the analysis according to IM vs PM. In fact, the proportion of IM or PM was not reported in 6 out of the 12 included trials, but only represented a minority in the population of the other 6 RCTs. Although the pre-specified sensitivity analysis according to ethnicity found consistent results after excluding East Asian patients—that are those characterized by the higher prevalence of PM—further studies specifically focusing on IM are needed to support the validity of our findings in these patients. Second, we focused on PD measures rather than clinical outcomes as our endpoints. This was due to the fact that RCTs reporting clinical outcomes in this setting are scarce and do not allow for the implementation of a network to compare different alternative antiplatelet strategies. Therefore, whether these findings could translate into similar clinical outcomes remains to be explored. Third, although we performed a sensitivity analysis according to ethnicity, it should be acknowledged that RCTs reporting outcomes of low-dose prasugrel were exclusively conducted in East Asians, thus limiting the generalizability of its findings to other ethnicities.[50] Forth, the secondary endpoint result of HPR should be interpreted with caution, given that trial-defined HPR definitions were used, the limited statistical power and the fact that this outcome was not available for all included regimens. Fifth, a limitation in several of the provided effect estimates is represented by the presence of 'open-loops', thus mainly relying on indirect comparisons. Nevertheless, the results obtained through the node-split analysis for the closed loops, showed consistency between direct, indirect, and network evidence for both the primary and secondary endpoints and provide an important focus on the reliability of standard-dose prasugrel when compared to standard- and high-dose clopidogrel. Sixth, the population included in our analysis encompassed both patients with ACS and CCS. Nevertheless, we conducted a pre-specified sensitivity analysis to explore the influence of clinical presentation among outcomes. Seventh, the timing in the evaluation of platelet reactivity differed across studies, but the optimal timing for PFT to be performed remains debated.[8]

Conclusions

Our findings show that all alternative antiplatelet strategies reduced platelet reactivity compared to standard-dose clopidogrel among carriers of *CYP2C19* LoF alleles, but the reduction varies widely across strategies. Standard-dose prasugrel or ticagrelor are associated with the greatest reduction in platelet reactivity, followed by low- and very low-dose of prasugrel. Double-dose clopidogrel and adjunctive cilostazol showed modest effects. Reduced-dose of prasugrel may represent a balanced strategy to overcome high-platelet reactivity without a significant increase in bleeding. The clinical implications of these pharmacodynamic findings warrant further investigation.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

This study did not combine individual patient data. However, trial-level data used across analyses are available upon reasonable request.

References

1. Angiolillo DA, Galli M, Collet J-P, Kastrati A, O'donoghue MO. Antiplatelet therapy after percutaneous coronary intervention. *EuroIntervention* 2022;**17**:e1371–e1e96.
2. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, Trabattoni D. Comparative efficacy and safety of oral $P2Y_{12}$. *Inhibit Acute Coronary Syndr* 2020;**142**:150–160.
3. Pereira NL, Rihal CS, So DYF, Rosenberg Y, Lennon RJ, Mathew V, Goodman SG, Weinshilboum RM, Wang L, Baudhuin LM, Lerman A, Hasan A, Iturriaga E, Fu Y-P, Geller N, Bailey K, Farkouh ME. Clopidogrel pharmacogenetics. *Circ Cardiovasc Interv*. 2019;**12**:e007811.
4. Galli M, Franchi F, Rollini F, Cavallari LH, Capodanno D, Crea F, Angiolillo DJ. Genetic testing in patients undergoing percutaneous coronary intervention: rationale, evidence and practical recommendations. *Expert Rev Clin Pharmacol*. 2021;**14**:963–978.
5. Mega JL, Simon T, Collet J-P, Anderson JL, Antman EM, Bliden K, Cannon CP, Danchin N, Giusti B, Gurbel P, Horne BD, Hulot J-S, Kastrati A, Montalescot G, Neumann F-J, Shen L, Sibbing D, Steg PG, Trenk D, Wiviott SD, Sabatine MS. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010;**304**:1821–1830.
6. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;**360**:363–375.
7. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, Ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J* 2015;**36**:1762–1771.
8. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, Collet J-P, Cuisset T, Franchi F, Gross L, Gurbel P, Jeong Y-H, Mehran R, Moliterno DJ, Neumann F-J, Pereira NL, Price MJ, Sabatine MS, So DYF, Stone GW, Storey RF, Tantry U, Trenk D, Valgimigli M, Waksman R, Angiolillo DJ. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y(12) receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;**12**:1521–1537.
9. Holmes DR, Jr., Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2010;**56**:321–341.
10. https://www.ema.europa.eu/en/medicines/human/EPAR/plavix. Accessed 20 February 2024.

11. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, Kisor DF, Limdi NA, Lee YM, Scott SA, Hulot J-S, Roden DM, Gaedigk A, Caudle KE, Klein TE, Johnson JA, Shuldiner AR. Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. *Clin Pharmacol Ther* 2022;**112**:959–967.
12. Marcucci R, Berteotti M, Gragnano F, Galli M, Cavallari I, Renda G, Capranzano P, Santilli F, Capodanno D, Angiolillo DJ, Cirillo P, Calabrò P, Patti G, De Caterina R. Monitoring antiplatelet therapy: where are we now? *J Cardiovasc Med (Hagerstown, Md)* 2023;**24**:e24–e35.
13. https://www.knmp.nl/dossiers/farmacogenetica/pharmacogenetics. Accessed 20 February 2024.
14. Mega JL, Hochholzer W, Frelinger AL, Kluk MJ, Angiolillo DJ, Kereiakes DJ, Isserman S, Rogers WJ, Ruff CT, Contant C, Pencina MJ, Scirica BM, Longtine JA, Michelson AD, Sabatine MS. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. *JAMA* 2011;**306**:2221–2228.
15. Ari H, Ozkan H, Karacinar A, Ari S, Koca V, Bozat T. The EFFect of hIgh-dose ClopIdogrel treatmENT in patients with clopidogrel resistance (the EFFICIENT trial). *Int J Cardiol* 2012;**157**:374–380.
16. Bonello L, Camoin-Jau L, Arques S, Boyer C, Panagides D, Wittenberg O, Simeoni M-C, Barragan P, Dignat-George F, Paganelli F. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 2008;**51**:1404–1411.
17. Wang X-D, Zhang D-F, Zhuang S-W, Lai Y. Modifying clopidogrel maintenance doses according to vasodilator-stimulated phosphoprotein phosphorylation index improves clinical outcome in patients with clopidogrel resistance. *Clin Cardiol* 2011;**34**:332–338.
18. Mayer K, Schulz S, Bernlochner I, Morath T, Braun S, Hausleiter J, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sibbing D. A comparative cohort study on personalised antiplatelet therapy in PCI-treated patients with high on-clopidogrel platelet reactivity. Results of the ISAR-HPR registry. *Thromb Haemostasis* 2014;**112**:342–351.
19. Tang Y-D, Wang W, Yang M, Zhang K, Chen J, Qiao S, Yan H, Wu Y, Huang X, Xu B, Gao R, Yang Y, Yuan X, Ji H, Zhou Z, Liu Z, Chen J, Yuan J, Liu H, Qian J, Hu F, Shao C, Zhao H, Hua Y, Lu J. Randomized comparisons of double-dose clopidogrel or adjunctive cilostazol versus standard dual antiplatelet in patients with high posttreatment platelet reactivity: results of the CREATIVE trial. *Circulation* 2018;**137**:2231–2245.
20. Price MJ. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;**305**:1097–1105.
21. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, Richardt G, Jakubowski JA, Neumann FJ. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. *J Am Coll Cardiol* 2012;**59**:2159–2164.
22. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae J-H, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu Y-P, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay J-F, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* 2020;**324**:761–771.
23. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann F-J, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Gurbel PA, Xu K, Parise H, Kirtane AJ, Brodie BR, Mehran R, Stuckey TD. Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): a prospective multicentre registry study. *Lancet (London, England)* 2013;**382**:614–623.
24. Hutton B, Moher D, Cameron C. The PRISMA extension statement. *Ann Intern Med* 2015;**163**:566–567.
25. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ (Clin Res Ed)* 2021;**372**:n160.
26. Alexopoulos D, Dimitropoulos G, Davlouros P, Xanthopoulou I, Kassimis G, Stavrou EF, Hahalis G, Athanassiadou A. Prasugrel overcomes high on-clopidogrel platelet reactivity post-stenting more effectively than high-dose (150-mg) clopidogrel: the importance of CYP2C19*2 genotyping. *JACC Cardiovasc Interv* 2011;**4**:403–410.
27. Braun OO, Angiolillo DJ, Ferreiro JL, Jakubowski JA, Winters KJ, Effron MB, Duvvuru S, Costigan TM, Sundseth SS, Walker JR, Saucedo JF. Enhanced active metabolite generation and platelet inhibition with prasugrel compared to clopidogrel regardless of genotype in thienopyridine metabolic pathways. *Thromb Haemost* 2013;**110**:1223–1231.
28. Franchi F, Rollini F, Rivas J, Rivas A, Agarwal M, Briceno M, Wali M, Nawaz A, Silva G, Shaikh Z, Maailiki N, Been L, Pineda AM, Suryadevara S, Soffer D, Zenni MM, Bass TA, Angiolillo DJ. Prasugrel versus ticagrelor in patients with CYP2C19 loss-of-function genotypes: results of a randomized pharmacodynamic study in a feasibility investigation of rapid genetic testing. *JACC Basic Transl Sci* 2020;**5**:419–428.
29. Gurbel PA, Bergmeijer TO, Tantry US, Ten Berg JM, Angiolillo DJ, James S, Lindahl TL, Svensson P, Jakubowski JA, Brown PB, Duvvuru S, Sundseth S. The effect of CYP2C19 gene polymorphisms on the pharmacokinetics and pharmacodynamics of prasugrel 5-mg, prasugrel 10-mg and clopidogrel 75-mg in patients with coronary artery disease. *Thromb Haemostasis* 2014;**112**:589–597.
30. Jin CD, Kim MH, Guo LZ, Jin E, Shin E-S, Ann SH, Cho Y-R, Park JS, Kim SJ, Lee MS. Pharmacodynamic study of prasugrel or clopidogrel in non-ST-elevation acute coronary syndrome with CYP2C19 genetic variants undergoing percutaneous coronary intervention (PRAISE-GENE trial). *Int J Cardiol* 2020;**305**:11–17.
31. Kim I-S, Jeong Y-H, Park Y, Park K-S, Yun S-E, Park J-R, Hwang S-J, Koh E-H, Kwak CH, Hwang J-Y, Kim S. Platelet inhibition by adjunctive cilostazol versus high maintenance-dose clopidogrel in patients with acute myocardial infarction according to cytochrome P450 2C19 genotype. *JACC Cardiovasc Interv* 2011;**4**:381–391.
32. Ogawa H, Isshiki T, Kimura T, Yokoi H, Nanto S, Takayama M, Kitagawa K, Nishikawa M, Miyazaki S, Ikeda Y, Nakamura M, Tanaka Y, Saito S. Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. *J Cardiol* 2016;**68**:29–36.
33. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, Dick A, Marquis J-F, O'brien E, Goncalves S, Druce I, Stewart A, Gollob MH, So DY. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet (London, England)* 2012;**379**:1705–1711.
34. Rossi JS, Cammarata M, Dharmavaram J, Weck K, Walko C, Gabriel D, Kuritzky J, Muldrew K, Stouffer GA. Clopidogrel dose adjustment after outpatient screening for CYP2C19 variant alleles: a pilot study. *Pharmacogenomics* 2014;**15**:915–923.
35. Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, Siegbahn A, Walker J, Wallentin L, Winters KJ, Close SL. Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur Heart J* 2009;**30**:1744–1752.
36. Park KW, Park JJ, Lee S-P, Oh I-Y, Suh J-W, Yang H-M, Lee H-Y, Kang H-J, Cho Y-S, Koo B-K, Youn T-J, Chae I-H, Choi D-J, Oh B-H, Park Y-B, Kim H-S. Cilostazol attenuates on-treatment platelet reactivity in patients with CYP2C19 loss of function alleles receiving dual antiplatelet therapy: a genetic substudy of the CILON-T randomised controlled trial. *Heart* 2011;**97**:641–647.
37. Gladding P, Webster M, Zeng I, Farrell H, Stewart J, Ruygrok P, Ormiston J, El-Jack S, Armstrong G, Kay P, Scott D, Gunes A, Dahl M-L. The antiplatelet effect of higher loading and maintenance dose regimens of clopidogrel: the PRINC (Plavix Response in Coronary Intervention) trial. *JACC Cardiovasc Interv* 2008;**1**:612–619.
38. Galli M, Franchi F, Rollini F, Angiolillo DJ. Role of platelet function and genetic testing in patients undergoing percutaneous coronary intervention. *Trends Cardiovasc Med* 2023;**33**:133–138.
39. Galli M, Ortega-Paz L, Franchi F, Rollini F, Angiolillo DJ. Precision medicine in interventional cardiology: implications for antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Pharmacogenomics* 2022;**23**:723–737.
40. Capodanno D, Angiolillo DJ. Personalised antiplatelet therapies for coronary artery disease: what the future holds. *Eur Heart J* 2023;**44**:3059–3072.
41. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, So D, Geller N, Goodman SG, Hasan A, Lerman A, Rosenberg Y, Bailey K, Murad MH, Farkouh ME. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y(12) inhibitor therapy: a meta-analysis. *JACC Cardiovasc Interv* 2021;**14**:739–750.
42. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'amario D, Porto I, Angiolillo DJ. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet (London, England)* 2021;**397**:1470–1483.
43. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, Vescovo GM, Cavallari LH, Bikdeli B, Ten Berg J, Mehran R, Gibson CM, Crea F, Pereira NL, Sibbing D, Angiolillo DJ. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *Eur Heart J* 2022;**43**:959–967.
44. Tornyos D, Balint A, Kupo P, El Abdallaoui OEA, Komocsi A. Antithrombotic therapy for secondary prevention in patients with non-cardioembolic stroke or transient ischemic attack: a systematic review. *Life (Basel)* 2021;**11**:447.
45. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, Collet J-P, Cuisset T, De Luca G, De Luca L, Farb A, Franchi F, Gibson CM, Hahn J-Y, Hong M-K, James S, Kastrati A, Kimura T, Lemos PA, Lopes RD, Magee A, Matsumura R, Mochizuki S, O'donoghue ML, Pereira NL, Rao SV, Rollini F, Shirai Y, Sibbing D, Smits PC, Steg PG, Storey RF, Ten Berg J, Valgimigli M, Vranckx P, Watanabe H, Windecker S, Serruys PW, Yeh RW, Morice M-C, Angiolillo DJ. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the academic research consortium. *Circulation* 2023;**147**:1933–1944.

46. Galli M, Angiolillo DJ. De-escalation of antiplatelet therapy in acute coronary syndromes: why, how and when? *Front Cardiovasc Med* 2022;**9**:1–13.
47. Galli M, Costa F, Navarese EP. De-escalation versus shortening of DAPT. *Eur Heart J Cardiovasc Pharmacother* 2024:pvae019. https://doi.org/10.1093/ehjcvp/pvae019.
48. Kang J, Rizas KD, Park KW, Chung J, Van Den Broek W, Claassens DMF, Choo EH, Aradi D, Massberg S, Hwang D, Han J-K, Yang H-M, Kang H-J, Chang K, Ten Berg JM, Sibbing D, Koo B-K, Kim H-S. Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis. *Eur Heart J* 2023;**44**:1360–1370.
49. Bangalore S, Singh A, Toklu B, Dinicolantonio JJ, Croce K, Feit F, Bhatt DL. Efficacy of cilostazol on platelet reactivity and cardiovascular outcomes in patients undergoing percutaneous coronary intervention: insights from a meta-analysis of randomised trials. *Open Heart* 2014;**1**:e000068.
50. Galli M, Laborante R, Occhipinti G, Zito A, Spadafora L, Biondi-Zoccai G, Nerla R, Castriota F, D'Amario D, Capodanno D, Jeong YH. Impact of ethnicity on antiplatelet treatment regimens for bleeding reduction in acute coronary syndromes: a systematic review and pre-specified subgroup meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2024;**10**:158–69. https://doi.org/10.1093/ehjcvp/pvad085