



SYSTEMATIC REVIEW

REVISED CYP2C19 polymorphism and coronary in-stent restenosis: A systematic review and meta-analysis [version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

Background: In-stent restenosis (ISR) remains a major drawback in coronary stenting. The association between the CYP2C19 loss of function (LOF) gene and the prevalence of ISR after coronary stenting remains controversial. Previous studies have produced conflicting results and have been limited by their small population sizes.

We conducted this systematic review and meta-analysis to determine the association between the presence of the CYP2C19 LOF gene and the prevalence of ISR.

Methods: A systematic online database search was performed until April 2021. The primary outcome was ISR and assessed using OR with 95% CI. Publication bias was assessed using the Newcastle Ottawa Scale. I^2 was applied to examine heterogeneities among the studies.

Results: A total of 284 patients (four non-randomized controlled trial studies) were included in this study. Two hundred and six patients had wild-type genotypes, while 78 patients had the LOF genotype. Among the 78 patients with the LOF gene, 40 patients had an ISR. Meanwhile, of the 206 patients with a wild-type gene, 69 patients had an ISR. The LOF gene was associated with a higher risk of ISR (OR 95% CI = 2.84 [1.54–5.24], $p = 0.0008$). A major limitation in our study was the small

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number of previous studies and small sample sizes.

Conclusions: Patients with LOF genes, regardless of the allele variation, treated with clopidogrel, had a higher risk of developing ISR after coronary stenting.

Keywords

CYP2C19, polymorphism, coronary in-stent restenosis, systematic review, clopidogrel

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REVISED Amendments from Version 1

In this second version of the manuscript, we edited one sentence about the association of CYP2C19 LOF gene with clopidogrel in the abstract research background. It also contains minor corrections of some mistypes. Finally, we corrected the inconsistency in writing the title of the bibliography in the reference list.

Any further responses from the reviewers can be found at the end of the article

Introduction

Despite the fact that the prevalence of in-stent restenosis (ISR) has decreased gradually, consistent with stent evolution, ISR remains a major drawback in coronary stenting.¹ ISR is defined as stenosis with a diameter > 50% at the stent segment or its edges. In the stent era, ISR is primarily a result of neointimal hyperplasia. Stent implantation causes injury to endothelial cells and induces several complex biological responses, including the activation, proliferation, and migration of smooth muscle cells (SMC) into the endovascular lumen. Vascular smooth muscle cells (VSMCs) play a crucial role in the pathogenesis of vascular diseases, including vascular inflammation and restenosis following angioplasty.² Stent implantation also stimulates the release of thrombogenic and vasoactive cytokines.³

An animal study conducted by Niu *et al.* revealed that expression of the P2Y₁₂ receptor in the vessel wall promoted atherogenesis and VSMC migration from media to intima. Direct activation of P2Y₁₂ also mediates VSMC proliferation.⁴ Furthermore, thrombin-induced P2Y₁₂ is known to enhance mitogenesis in human SMC.⁵ Clopidogrel has long been used as a P2Y₁₂ inhibitor.

Clopidogrel is converted to an active metabolite by the enzyme CYP2C19. The genes encoding the CYP enzyme are polymorphic, and several variants have been related to increased or decreased activity of the drug. Based on the genetic polymorphism of CYP2C19, wild-type homozygote CYP2C19*1*1 is a powerful metabolizer. However, carriers of CYP2C19 LOF alleles (*2, *3, *4, *5) are poorer metabolizers.⁶ Several studies have been conducted to assess the association between ISR events and CYP2C19 polymorphism.⁷⁻¹⁰ However, the results are conflicting. Therefore, this study aims to conduct a meta-analysis regarding the association between CYP2C19 LOF genes and ISR events.

Methods

This study was conducted following Cochrane's methodology and PRISMA guidelines.¹¹ It is registered in the PROSPERO database, registration number: 293424.

Search strategy

We performed a systematic search of several online databases (Scopus, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, and Research Gate) for all studies on CYP2C19 polymorphism and in-stent restenosis. We used the terms "coronary restenosis" AND "in-stent restenosis" AND "gene polymorphism" AND "CYP2C19" AND "genotype".

Eligibility criteria

The criteria included were observational studies or randomized controlled trials (RCTs), which examined the association between gene polymorphism and coronary restenosis after stent implantation. Exclusion criteria included case reports, case series, studies in languages other than English, and non-human studies. Two reviewers (V. and HBPP) independently screened the search results according to the inclusion and exclusion criteria. Any discrepancies were settled through discussion with a third investigator (YP) until a consensus was reached.

Quality assessment

The RCTs were evaluated based on Cochrane methodological criteria. However, the quality of observational studies was evaluated using the Newcastle – Ottawa Scale.¹²

Endpoint

The primary endpoint was in-stent restenosis after stent implantation regardless of the type of previous stent.

Statistical analysis

Statistical analysis was carried out using RevMan 5.4 software (RRID:SCR_003581). All outcomes were assessed as an odds ratio (OR) with a 95% confidence interval (CI). A P-value equal to or less than 0.05 was considered statistically significant. I^2 assessed heterogeneity. I^2 values less than 25% were defined as low heterogeneity; I^2 values between 25%

and 50% were defined as moderate heterogeneity, and I^2 values greater than 50% were defined as high heterogeneity. A fixed-effects model was used in cases of low or moderate heterogeneity. However, a random-effects model was used when heterogeneity was high.

Results

The initial search identified a total of 43 studies. Of these 43 studies, one article did not contain full text, and 13 studies were duplicates, leaving 29 studies. Of the remaining studies, 20 were excluded due to irrelevant titles or abstracts. Furthermore, five full-text articles were categorized as case reports, reviews, letters to the editor, or did not provide data for calculation. Finally, four observational studies were included in the qualitative synthesis (Figure 1). A total of 284 patients were included in the study. Two hundred and six patients had wild-type genotypes, while 78 patients had a LOF genotype. The quality of the four observational studies is shown in Table 1.

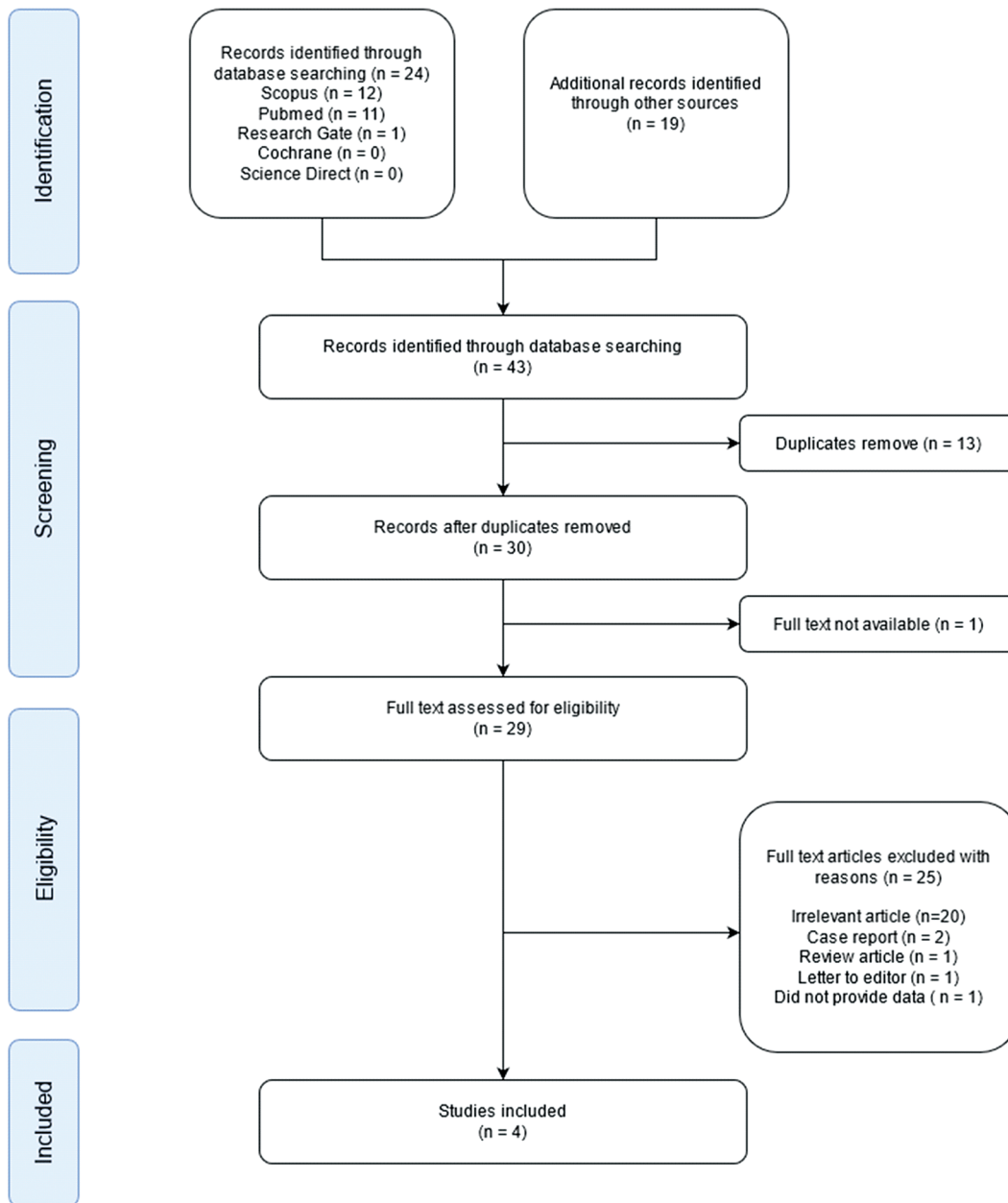


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of study selection.

Table 1. Newcastle – Ottawa scale indicating the quality of each included study.

	Selection	Comparability	Outcome	Total score	Overall grade
Da Costa <i>et al.</i> (2020) ⁷	*	0	**	3	Poor
Zhang <i>et al.</i> (2020) ⁸	**	*	**	5	Fair
Wirth <i>et al.</i> (2018) ⁹	**	*	***	6	Fair
Nozari <i>et al.</i> (2015) ¹⁰	**	*	***	6	Fair

Asterisks indicate the star rating according to the Newcastle-Ottawa Scale.

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain.
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain

Patient characteristics

The patients included in the studies had similar characteristics; they were predominantly male (62%–72%) (Table 2), with a mean age range of 60–66 years, except for the study by Da Costa *et al.*, which did not report their patients’ characteristics.⁷ The patients in the Wirth *et al.* study had the highest proportion of diabetes and hypertension compared to the other studies.⁹

Genotype characteristics

In most of the studies examined, the wild gene (*1*1) was dominant (in 65%–89% of patients) (Table 2). Only in the study by Da Costa *et al.* was the wild gene the minority (in only 25% of patients).⁷ The four selected studies examined different LOF genes. The study by Nozari *et al.* showed the heterozygote *1*2 LOF gene.¹⁰ In contrast, the study by Da Costa *et al.* examined LOF heterozygote *1*2 and homozygote *2*2 genes without clearly specifying the percentage.⁷ The study by Zhang *et al.* only mentioned that the LOF gene has a *2 or *3 allele.⁸ The study by Wirth *et al.* stated that the LOF gene has a *2 allele.⁹

Stent characteristics

Da Costa *et al.* did not state clearly the stent type used in their study.⁷ However, Zhang *et al.* only used drug-eluting stents (DES).⁸ Meanwhile, Wirth *et al.* and Nozari *et al.* used bare-metal stents (BMS) and DES in their studies without clearly stating the percentages (Table 2).^{9,10}

Table 2. Included studies and baseline characteristics.

Author (year)	Da Costa <i>et al.</i> (2020) ⁷	Zhang <i>et al.</i> (2020) ⁸	Wirth <i>et al.</i> (2018) ⁹	Nozari <i>et al.</i> (2015) ¹⁰
Study type	Cross-sectional	Retrospective cohort	Retrospective cohort	Case match study
Sample size (n)	24	78	82	100
Wild gene (%)	6 (25.0)	51 (65.4)	60 (73.2)	89 (89)
LOF gene (%)	18 (75.0)	27 (34.6)	22 (26.8)	11 (11)
LOF gene type	*1*2/ *2*2	allele *2 or *3	allele *2	*1*2
Stent type	Not clear	DES	BMS & DES	BMS & DES
Clopidogrel dose	Not clear	75 mg/day	Not clear	75 mg/day
Total ISR event	13	17	29	50
BMS – ISR	Not clear	N/A	4	30
DES – ISR	Not clear	17	25	20
Age (years)	N/A	66.69 ± 6.2	64.58 ± 9.2	60.09 ± 10.29
Male (%)	N/A	49 (62.8)	65 (79.2)	72 (72)
Diabetes mellitus (%)	N/A	25 (32.0)	49 (59.8)	26 (26)
Hypertension (%)	N/A	54 (69.2)	74 (90.2)	51 (51)
Dyslipidemia (%)	N/A	N/A	76 (92.7)	62 (62)
Smoking (%)	24 (100)	32 (41.0)	20 (24.4)	20 (20)

Abbreviations: LOF: loss of function; ISR: In-stent restenosis; BMS: bare metal stent; DES: drug eluting stent.

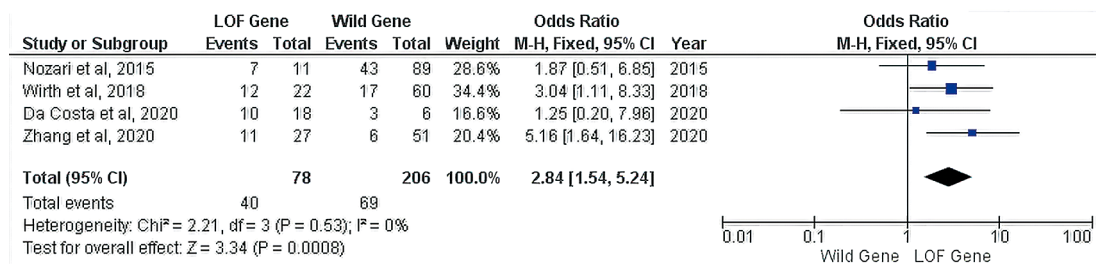


Figure 2. Forest plot of the correlation between the CYP2C19 genotype and ISR risk.

Reported outcomes

From all of the studies, the only incidence of ISR can be calculated quantitatively. However, regardless of the time of presentation from the stent implantation to ISR detection, it is known that there were forty incidents of ISR in the 78 patients with LOF genes and 69 incidents of ISR in the 206 patients with a wild gene. Furthermore, our analysis found an increased risk of ISR was observed in patients with a LOF gene (OR 95% CI = 2.84 [1.54–5.24], P = 0.0008) (Figure 2).

Discussion

The response to clopidogrel differs from person to person. Many investigations have been conducted to determine the biological components involved in this variance. Polymorphisms in the liver cytochrome isozyme P450 (CYP2C19, CYP3A4, and CYP3A5), as well as the P2Y12 receptor itself, seem to be the major cause of variation.^{13,14} The ability of the LOF gene to reduce the clopidogrel response in platelets was the first to be revealed, as seen by enhanced platelet aggregation in terms of CYP2C19 polymorphisms.¹³

Numerous studies have found that CYP2C19 polymorphisms vary greatly among ethnic groups. In comparison to the white population (25%–35%) and the black population (35%–45%), the Asian population (55–70%) exhibited a greater prevalence rate of the LOF CYP2C19 allele variation (CYP2C19 *2 and *3). In comparison to the white population (18%), the Asian population (4%) exhibited a lower frequency of the CYP2C19 GOF variant allele (CYP2C19 *17).¹⁴

A study by Mega *et al.* involving 1,477 acute coronary syndrome patients, with primary outcomes characterized by death from nonfatal myocardial infarct (MI), nonfatal stroke, and other cardiovascular causes, showed a significantly higher rate of LOF polymorphism (12.1% versus 8%; P = 0.01) than wild-type CYP2C19.¹⁵ For 450 days after clopidogrel therapy, similar results were reported for the rate of stent thrombosis (2.6% versus 0.8%; P = 0.02). Another study of 259 patients using clopidogrel medication for one month after their first MI found that individuals with CYP2C19 polymorphisms had considerably poorer five-year survival (HR = 3.69; 95% CI = 1.69–8.5; P = 0.0005), which was linked to considerably poorer clinical outcomes following coronary stenting.¹⁶ In another study, 552 individuals were revealed to have the wild-type CYP2C19 allele, and 245 had at least one of two alleles. Patients who were homozygous for the wild-type gene had considerably lower platelet aggregation levels than those with two alleles (11% versus 23%; P < 0.0001).¹⁷

The present study showed a significant association between ISR risk and the LOF gene. The odds of ISR were 2.8% higher in the LOF gene compared to the wild gene. The wild gene can metabolize clopidogrel more effectively than the LOF gene. Zhang *et al.* and Nozari *et al.* stated that they used clopidogrel 75mg in their study.^{8,10} Moreover, Zhang *et al.* also had a third group of patients with the LOF gene who were administered a double dose of clopidogrel (150 mg). There were no significant differences in this group compared to patients with the wild gene who were given a normal dose of clopidogrel (75 mg).⁸

The first choice for a clopidogrel resistance management strategy is to increase the dose of clopidogrel, with the current loading dose for clopidogrel being 300 mg. A larger loading dosage of 600 mg was compared to a lower loading dosage of 300 mg in two studies. Cuisset *et al.* randomly selected 292 patients undergoing stenting for non-ST elevation myocardial infarction (STEMI) to receive a loading dose of either 300 mg or 600 mg 12 hours before percutaneous coronary intervention (PCI). One month after the intervention, all patients were administered aspirin 160 mg and clopidogrel 75 mg daily. The 600 mg loading dosage group demonstrated reduced adenosine diphosphate (ADP) induced platelet aggregation and P-selection expression compared to the 300 mg loading dosage group.

Furthermore, there were fewer cardiovascular incidents in the 600 mg loading dosage group after one month (7 vs 18 events; P = 0.02).¹⁸ One hundred and forty-eight patients undergoing elective PCI were randomly assigned to three

groups in a study conducted by L'Allier *et al.* Group A patients were administered 75 mg clopidogrel on the morning of the procedure and 300 mg clopidogrel a day (≥ 15 hours) before the procedure. Group B patients were administered 600 mg clopidogrel in the morning (≥ 2 hours) of the procedure. Meanwhile, group C patients were administered 600 mg clopidogrel on the morning of the procedure and 600 mg clopidogrel a day before the procedure. Group C revealed substantially higher relative inhibition of peak and final ADP-stimulated platelet aggregation than groups A and B. Thus, it appears that a successive 600 mg/dose of clopidogrel bolus resulted in more substantial platelet inhibition than a single loading dosage.¹⁹

The effectiveness of a daily maintenance dosage of clopidogrel 150 mg in patients undergoing elective PCI was examined in a study by Angiolillo *et al.* Both groups of patients continued medication for 30 days before returning to the regular dose. ADP-induced platelet aggregation (20 μ M) was higher in 75 mg clopidogrel/day patients than in 150 mg clopidogrel/day individuals (64% versus 52.1%; $P < 0.001$).²⁰ The VerifyNow test evaluated relative platelet aggregation in response to 5 μ M ADP (45.1% vs 65.3%; $P < 0.001$), and platelet function inhibition (60 versus 117; $P = 0.004$) was substantially improved in patients who received clopidogrel 150 mg compared to those given 75 mg.²⁰

A larger trial of 153 individuals with a low clopidogrel response (platelet reactivity index 69%) to 75 mg/day or 150 mg/day ($n = 95$ or $n = 58$) clopidogrel found similar results. After two weeks of therapy, clopidogrel 150 mg/day was linked with a considerably lower platelet reactivity index than 75 mg/day (43.9% versus 58.6%; $P < 0.001$). After switching to clopidogrel 150 mg/day for two weeks, 20 out of 31 patients in the 75 mg/day group were responsive (platelet reactivity was 69%).²¹ Overall, the outcomes of this study point to the possibility of employing higher clopidogrel bolus and maintenance dosages.

Other alternative drugs include prasugrel, ticagrelor and cilostazol. Although there is limited evidence to suggest that using prasugrel interacts with proton pump inhibitors (PPIs) via cytochrome P450, a study of TRITON-TIMI 38 and PRINCIPLES 44 showed that PPIs did not affect the efficacy of prasugrel. Thus, the use of PPIs with prasugrel is preferable. Ticagrelor is a new platelet aggregation inhibitor. Ticagrelor, like clopidogrel, binds to P2Y₁₂, which acts as an antagonist to the ADP receptor on platelets, preventing platelet aggregation.

Unlike clopidogrel, ticagrelor reversibly binds to P2Y₁₂ and does not displace ADP from the receptor, allowing it to target 2-MeS-ADP-induced signalling. Furthermore, because ticagrelor does not need hepatic enzymatic activation, it is more consistent in reducing platelet aggregation. It has a lower risk of medication interactions and is not affected by CYP polymorphisms.²²

Cilostazol suppresses cAMP degradation in platelets by inhibiting platelet aggregation via phosphodiesterase-3-blockers. As a result, cilostazol may be an option for people who are resistant to clopidogrel. In patients receiving contemporary stent-based percutaneous procedures, using cilostazol in combination with clopidogrel and aspirin may minimize restenosis cerebral and cardiac side effects.²³ As a result, cilostazol is more beneficial than clopidogrel at high maintenance dosages. However, cilostazol was terminated more often in this trial due to the adverse effects.

Shim *et al.* randomly categorized 400 patients who underwent successful PCI with DES into triple antiplatelet therapy (clopidogrel, cilostazol, and aspirin) and dual antiplatelet therapy (clopidogrel and aspirin) groups. They reported a significant decrease in clopidogrel resistance in the triple antiplatelet group (19.7% versus 40%, $P < 0.001$). As a result, the rate of clopidogrel resistance in patients undergoing PCI with DES can be reduced.²⁴ Several trials compared the effectiveness and safety of using cilostazol with aspirin and clopidogrel in dual antiplatelet therapy (DAPT). Cilostazol combination therapy has significant advantages in major cardiac side effects, death from any cause, cardiac death, target lesion revascularization, and in-segment restenosis. Benefits are reported in patients with clopidogrel resistance.²³

Several limitations were evident in the present study. First, regarding the association between the LOF gene and ISR, there were limited studies with small sample sizes, which may have limited statistical power. Second, none of the studies included were RCTs. Third, varying types of LOF genes were included in the studies, and some studies did not state clearly whether they were examining homozygote LOF genes or heterozygote LOF genes. Fourth, the studies utilized different stent types and did not clearly state the percentage of BMS and DES used in their studies, as we know that BMS have a higher tendency to form ISR. Fifth, none of the studies used intracoronary imaging. Furthermore, individual patient-level data were not available.

Conclusions

In conclusion, the present study supports the theory that, in patients who have undergone coronary stenting and been treated with clopidogrel, the presence of the LOF gene increases their risk of ISR. Furthermore, larger-scale studies are required to examine appropriate strategies in patients with the LOF gene who have undergone coronary stenting.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'CYP2C19 polymorphism and coronary in-stent restenosis: A systematic review and meta-analysis'. <https://doi.org/10.6084/m9.figshare.19312115>.¹¹

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0)

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Version 2

Reviewer Report 06 May 2024

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Fazli Rabbi Awan 

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I have read this article with great interest. It is well written study. Though, the sample size (number of papers used in this meta-analysis) was small as less literature has been available, authors were careful to draw any generalized conclusions. They have hinted towards ISR correlatoin with the risk (loss of function) genotype of the investigated gene. Overall, it is a good read.

I only found one typing mistake:
P-selection should be P-selectin

and either use, vs or verses throughout.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genetics of Metabolic and Cardiovascular Disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 23 March 2024

<https://doi.org/10.5256/f1000research.134740.r249956>

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Vaiva Lesauskaitė 

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1. There is no information from which year publications were searched for systematic literature review in the search strategy.
2. Authors chose odds ratio as the effect size. But they use the terms "correlation" and "risk" in the results sections. No statistical methods were used to calculate correlation or risk. Terms must be corrected according to used statistical methods.
3. Two models (Fixed effect model and random effect model) are mentioned in the Methods chapter, but only the results of fixed effect are presented in the Results chapter. Why random effect model was not included in the results?.
4. The use of the fixed-effect model for the analysis is not acceptable because the analyzed results are gained from different types of studies, and studies are taken from different countries. Authors indicated that choice of fixed-effect model was based on the absence of heterogeneity. But only four studies are included in the meta-analysis, thus the power of the test of heterogeneity is low. Thus, authors don't give sufficient evidence that the studies really represent a single population, and all studies measure the same effect, which is different due to sampling error.
5. To edit Fig.5. It is not clear which group is assigned as a treatment group in the research. Usually, the same side for treatment and control group is used in the table and in the Forest plot. Authors changed these sides, and it is not clear if the conclusion is correct.
6. Newcastle - Ottawa Scale is used to assess the quality of the publication in the systematic literature review, but it is not suitable for estimation of the publication bias for the meta-analysis as it is indicated in the abstract of the review. At least Funnel plot has to be presented to show that there is no publication bias.
6. Table 2 line Age - it is not clear what numerical characteristics are presented "?±?" mean±SD?

SE?

7. The statement "The odds of ISR were 2.8% higher in the LOF gene compared to the wild gene" is not correct. OR 2,8 means increase in 2,8 folds or 280 percents.

8. The novelty and significance of meta analysis results are not disclosed in Discussion

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

No

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the 'living' method appropriate and is the search schedule clearly defined and justified? ('Living Systematic Review' or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular pathology, pharmacogenomics,;

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Version 1

Reviewer Report 04 April 2022

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Dyana Sarvasti

Department of Internal Medicine, Faculty of Medicine, Widya Mandala Catholic University, Surabaya, Indonesia

This meta-analysis study is interesting and useful, although it only involves four non-randomized

controlled trials. It can be used as additional knowledge about the management of antiplatelet therapy use in patients undergoing PCI who are suspected of having the presence of the CYP2C19 LOF gene. Unfortunately, the research objectives related to the use of antiplatelets are not fully described in the abstract, even though in the discussion and conclusions there are many mentions of the relationship between LOF genes, ISR, and various types of antiplatelets, especially clopidogrel. If possible, the association of the CYP2C19 LOF gene with antiplatelet use (clopidogrel) should also be addressed in the research objectives in the abstract.

In addition, there are some mistypes that need to be corrected. Here are some points related to this:

1. In table 2, it appears that “**Cross sectional**” is missing a hyphen. Consider adding the hyphen(s).
2. In abbreviations in table 2, It appears that “**bare metal**” is missing a hyphen. Consider adding the hyphen(s).
3. In abbreviations in table 2, It appears that “**drug eluting**” is missing a hyphen. Consider adding the hyphen(s).
4. There is an inconsistency in writing the title of the bibliography in the reference list. Sometimes it is written in lower case, sometimes in upper case. Consider making corrections.

Thank you for your kind attention.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Partly

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

If this is a Living Systematic Review, is the ‘living’ method appropriate and is the search schedule clearly defined and justified? (‘Living Systematic Review’ or a variation of this term should be included in the title.)

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular Prevention and Rehabilitation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 02 Jun 2022

Ivana Purnama Dewi

Dear Dyana Sarvasti, M.D

Thank you for your kind review
We will make some corrections regarding your suggestions

Best regards,
Yusra Pintaningrum, M.D

Competing Interests: No competing interests were disclosed.

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