Original Article

# *CYP2C19*2* Allele Carrier Status and Coronary In-stent Restenosis: Is There an Association?

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## Abstract

**Background and objective:** The *CYP2C19*2* allele is associated with reduced clopidogrel bioactivation, increasing the risk of complications after percutaneous coronary intervention (PCI), particularly stent thrombosis. Recently published data suggests that *CYP2C19*2* allele carriers have a higher risk for in-stent restenosis (ISR) after endovascular treatment. Very few studies have investigated the relationship between *CYP2C19*2* and coronary ISR, with no significant association reported. The objective of this study was to assess the relationship between *CYP2C19*2* allele carrier status and coronary ISR.

**Methods:** Patients with previous PCI with stenting and who were scheduled for elective PCI after coronary angiogram were recruited from the cardiac catheterization suite over a 12-month period. The angiography report of each patient was perused to identify patients requiring PCI due to ISR. For patients with angiography-confirmed ISR, date of previous PCI to the restenosed stent was noted. *CYP2C19*2* genotyping was undertaken using a *Taq*Man® Drug Metabolism assay. The association between *CYP2C19*2* allele carrier status and incidence of coronary ISR within 1 year was assessed using Fisher's exact test ($p < 0.05$ significance) and by calculating the odds ratio (OR) with a 95% confidence interval (CI).

**Results:** Of the 82 patients with previous PCI, 29 (35.4%) had angiography-confirmed ISR (12 carriers, 17 non-carriers of *CYP2C19*2*). In 13 (44.8%) of these patients, the restenosed stent was deployed within 1 year and the patients were on clopidogrel therapy at the time of repeat PCI (8 carriers, 5 non-carriers of *CYP2C19*2*). The association between *CYP2C19*2* allele carrier status and ISR within 1 year was not statistically significant (Fisher's exact $p = 0.067$; OR: 4.80, 95% CI: 0.98–23.54, $p = 0.053$).

**Conclusions:** Despite a higher proportion of *CYP2C19*2* allele carriers exhibiting ISR within 1 year compared to non-carriers, the association was not statistically significant. This result may be attributed to the small sample size, and larger prospective studies are recommended to further assess this association.

**Keywords:** Clopidogrel; Coronary in-stent restenosis; *CYP2C19*2* polymorphism; Percutaneous coronary intervention; Pharmacogenetic testing.

**Abbreviations:** BMS, bare metal stent; CI, confidence interval; CYP, cytochrome P; DES, drug-eluting stent; EM, extensive metabolizer; IM, intermediate metabolizer; ISR, in-stent restenosis; OR, odds ratio; PCI, percutaneous coronary intervention; PM, poor metabolizer.

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## Introduction

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor is the standard treatment for patients undergoing percutaneous coronary intervention (PCI) with stent deployment to reduce the risk of post-procedural thrombotic complications. This synergistic combination therapy is typically given for 3 months after PCI for bare metal stents (BMS) and for at least 1 year with drug-eluting stents (DES).[1–3] Whilst European guidelines tend to favor use of the newer $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor as first-line agents, provided there is no high risk of bleeding[2], American guidelines recommend these newer antiplatelet agents as po-

tential alternatives to clopidogrel.[3] Clopidogrel is still the most extensively used $P2Y_{12}$ receptor inhibitor after PCI, particularly due to more robust evidence, lower cost and decreased incidence of bleeding compared to the newer $P2Y_{12}$ receptor inhibitors.[4]

Clopidogrel is a thienopyridine inactive prodrug and requires biotransformation in the liver to form its pharmacologically active metabolite, which selectively and irreversibly antagonizes the $P2Y_{12}$ component of the adenosine diphosphate receptor on the platelet surface and consequently attenuates platelet aggregation.[5] Two sequential hepatic oxidative steps are involved in clopidogrel metabolism to the active metabolite,[5] with cytochrome P (CYP) 450 2C19 being the principal enzyme involved in both steps.[6] The CYP2C19 enzyme is encoded by a highly polymorphic gene and CYP2C19 single nucleotide polymorphisms have been identified as significantly and consistently associated with variability in clopidogrel response.[6–9]

The **2* variant allele is the most common *CYP2C19* loss-of-function allele, translating to decreased CYP2C19 enzyme activity, with an estimated prevalence of 29% to 35% in Asians and 15% in Caucasians and Africans.[7] Non-carriers of the **2* allele (homozygous *1/*1) are classified as extensive metabolizers (EMs), carriers of one **2* allele (heterozygous *1/*2) as intermediate metabolizers (IMs) and carriers of two **2* alleles (homozygous *2/*2) as poor metabolizers (PMs) of clopidogrel. EMs efficiently metabolize clopidogrel to the active form and show the highest levels of platelet inhibition with standard 75 mg clopidogrel dosing, while IMs and PMs show decreased inhibition of platelet aggregation.[8] The *CYP2C19*2* allele has been associated with reduced active clopidogrel metabolites and higher on-clopidogrel platelet reactivity, leading to a greater risk of adverse cardiovascular events in PMs and IMs compared to EMs. The strongest association was reported in patients with acute coronary syndrome undergoing PCI with stent implantation, where **2* allele carriers had an increased risk of stent thrombosis.[8,9]

In-stent restenosis (ISR) is another well-documented complication of PCI.[10] Although the rate of ISR decreased significantly with the use of DES compared to balloon angioplasty and BMS, it still persisted as a limiting factor for the long-term benefit of PCI, with an approximate rate of 10% in non-complex lesions.[2,11–15] ISR develops through different phases involving vascular smooth muscle cell migration and proliferation, resulting in neointimal hyperplasia.[12,15–19] DES-ISR typically occurs within 6 to 12 months after stent deployment,[11] causing partial reocclusion of the intervention site.[20] When manifested clinically as stable angina or ischemia, repeat target vessel revascularization is generally required.[2,21,22] Risk factors reported to influence the extent of ISR are lesion features, including chronic total occlusion, calcification, bifurcation, small vessel diameter and long stenosis; technical factors, namely stent material, width, length and location, comorbidities such as diabetes mellitus, as well as drug resistance and/or hypersensitivity.[12,15,20,21]

Very few studies have investigated the relationship between *CYP2C19*2* allele carrier status and ISR. Two studies published in 2014 demonstrated that the *CYP2C19*2* variant allele is a risk factor for peripheral and vertebral artery ISR in clopidogrel-treated patients.[23,24] With respect to coronary ISR, a 2015 case-match study in an Iranian patient population indicated that the prevalence of ISR during a 1-year period after PCI was higher in patients who were carriers of *CYP2C19*2*; however, the association did not reach statistical significance.[25] In contrast, in a recent study by Ruedlinger *et al.*,[26] undertaken in Chilean patients who underwent PCI, non-carriers of the *CYP2C19*2* allele had a higher incidence of ISR.

The objective of this study was to assess the relationship between *CYP2C19*2* allele carrier status and coronary ISR.

## Methods

### *Ethics approval*

The study protocol was approved by the University of Malta Research Ethics Committee (19/2013).

### *Study setting*

The study was undertaken at Mater Dei Hospital, an acute general hospital in Malta. Patients were recruited from the cardiac catheterization suite at the Department of Cardiology and genotyping was carried out at the Molecular Diagnostics Unit of the Department of Pathology.

### *Patient recruitment, sampling and data collection*

Patients ≥ 18 years of age, with a history of previous PCI with stent deployment and who were scheduled for elective PCI after coronary angiogram, were recruited from the cardiac catheterization suite at the time of PCI by non-probability sampling over a 12-month period, between 1 January and 31 December 2014. The coronary angiogram report of each patient was perused to identify patients requiring PCI due to angiography-confirmed ISR and those who had no ISR. For patients with angiography-confirmed ISR, the date of previous PCI to the restenosed stent was noted to establish if less than 1 year had elapsed since the previous PCI and if the patients were still on clopidogrel therapy.

After obtaining written informed consent, 5 mL of peripheral blood was collected from each patient in a purple-top EDTA vacutainer at the time of recruitment. A validated data collection form developed for the purpose of the study was completed for each patient to collect demographic information, cardiac risk factors, comorbidities, laboratory investigations and concomitant medications.

### *CYP2C19*2 genotyping*

Genomic DNA was extracted using the QIAamp® DNA Mini Kit on the fully automated QIAcube (Qiagen) from 200 µL of the anticoagulated whole blood sample obtained at the time of recruitment. The *Taq*Man® (Thermo Fisher Scientific) allelic discrimination assay (rs4244285, C_259866767_70), which involves DNA amplification and homogeneous solution hybridization using fluorescence resonance energy transfer, was used for *CYP2C19*2* genotyping on the 7500 Applied Biosystems real-time PCR system. Using a 96-well PCR plate, each well had a final volume of 25 µL consisting of genomic DNA, an allele-specific probe labelled with VIC® dye and another labelled with 6FAM™ dye, forward and reverse primers and *Taq*Man® Universal PCR Master Mix. The PCR reaction was performed as an initial denaturation at 95 °C for 10 minutes, followed by 50 denaturation cycles at 92 °C for 15 seconds and annealing/extension at 60 °C for 90 seconds. Patients were genotyped as carriers or non-carriers of the *CYP2C19*2* allele.

### *Statistical analysis*

Data was analyzed using IBM SPSS Statistics 24. Distribution between patients who presented with coronary angiography-confirmed ISR at the time of recruitment and patients with no ISR was

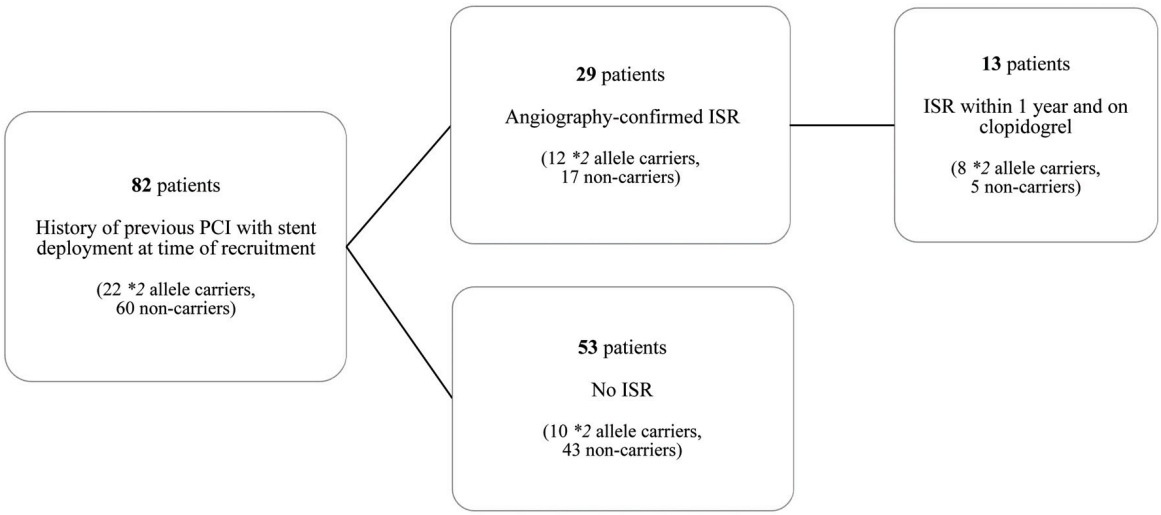


**Fig. 1.** In-stent restenosis at time of recruitment (*N* = 82). Abbreviations: ISR, in-stent restenosis; PCI, percutaneous coronary intervention.

tested using the one-way ANOVA test for continuous variables and the Pearson's chi-square test for categorical variables, with a 95% confidence interval (CI). Continuous variables were presented as mean ±standard deviation, and categorical variables were presented as number of patients and percentage (%). The association between *CYP2C19*2* allele carrier status and incidence of coronary ISR within 1 year was assessed with cross-tabulations and the Fisher's exact test and by calculating the odds ratio (OR) with a 95% CI. A *p*-value less than 0.05 was considered statistically significant.

## Results

Two hundred and fifty-two (30%) patients out of the total 843 patients (including first PCI and history of PCI patients) who underwent PCI between 1 January and 31 December 2014 were recruited. Of the 252 patients, 82 (32.5%) had a history of previous PCI with stent deployment and were included in the study. Out of these 82 patients, 29 (35.4%) were undergoing repeat PCI due to angiography-confirmed ISR (Fig. 1). Twenty-five patients had DES-ISR, while 4 patients had BMS-ISR. The most commonly affected coronary vessels were the left anterior descending artery (*n* = 9), right coronary artery (*n* = 7) and saphenous venous graft (*n* = 6). Three patients had ISR in a bifurcation lesion. The characteristics of the patients with ISR and those with no ISR were similar ($p > 0.05$), except for *CYP2C19*2* allele carrier status and renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$), which were significantly higher in the patients with ISR ($p < 0.05$) (Table 1). In 13 (44.8%) of the 29 patients with ISR, the restenosed stent was deployed within 1 year and the patients were

**Table 1. Patient characteristics (*N* = 82)[a]**

| | ISR, *n* = 29 | No ISR, *n* = 53 | *p*-value 95% CI |
|---|---|---|---|
| Age | 64.83±9.896 | 64.45±8.915 | 0.862 |
| Male sex | 25 (86.2) | 40 (75.5) | 0.250 |
| Caucasian ethnicity | 28 (96.6) | 53 (100) | 0.174 |
| Carrier of *CYP2C19*2* allele | 12 (41.4) | 10 (18.9) | 0.028* |
| eGFR <60, as mL/min/1.73$m^2$ | 12 (41.4) | 9 (17.0) | 0.016* |
| Active smoking | 7 (24.1) | 13 (24.5) | 0.967 |
| BMI ≥30[b], as kg/$m^2$ | 18 (64.3) | 24 (50.0) | 0.226 |
| Hypertension | 25 (86.2) | 49 (92.4) | 0.363 |
| Diabetes mellitus | 19 (65.5) | 30 (56.6) | 0.429 |
| Dyslipidemia | 26 (89.7) | 50 (94.3) | 0.435 |
| ≥2 previous PCI | 12 (41.4) | 19 (35.8) | 0.624 |
| >1 vessel stented | 10 (34.5) | 13 (24.5) | 0.337 |
| Previous bypass graft surgery | 11 (37.9) | 12 (22.6) | 0.142 |

[a]Values are expressed as number of patients (%), except age which is expressed as mean ±standard deviation; [b](%) is out of a total of 28 patients for ISR and out of 48 patients for no ISR. *Reaching statistical significance ($p < 0.05$). Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ISR, in-stent restenosis; PCI, percutaneous coronary intervention.

**Table 2.** *CYP2C19*2* **allele carrier status versus ISR within 1 year: Cross-tabulation**

| | | | ISR within 1 year | | Total |
|---|---|---|---|---|---|
| | | | Yes | No | |
| Carrier of *CYP2C19*2* allele | Yes | Number of patients | 8 | 4 | 12 |
| | | Percentage | 66.7 | 33.3 | 100.0 |
| | No | Number of patients | 5 | 12 | 17 |
| | | Percentage | 29.4 | 70.6 | 100.0 |
| | | *Total* | 13 | 16 | 29 |
| $p$ = 0.067 (Fisher's exact 2-sided). Odds ratio: 4.80, 95% confidence interval: 0.98–23.54, $p$ = 0.053. | | | | | |

Abbreviation: ISR, in-stent restenosis.

on clopidogrel therapy at the time of repeat PCI (Fig. 1).

Of the 29 patients with ISR, 12 were carriers and 17 were non-carriers of the *CYP2C19*2* allele. Eight (66.7%) of the 12 **2* allele carriers had ISR within 1 year and were on clopidogrel therapy at the time of repeat PCI. Only 5 (29.4%) out of the 17 non-carriers presented with ISR within 1 year. Although the difference between the two proportions (37.3%) is large, the association between *CYP2C19*2* allele carrier status and ISR within 1 year was not statistically significant (Fisher's exact $p$ = 0.067; OR: 4.80, 95% CI: 0.98–23.54, $p$ = 0.053) (Table 2).

## Discussion

The findings from this study show that despite a higher proportion of *CYP2C19*2* allele carriers exhibiting coronary ISR within 1 year compared to non-carriers, and **2* allele carriers being 4.08-times more likely to exhibit ISR than non-carriers, the association between *CYP2C19*2* allele carrier status and development of coronary ISR was not statistically significant ($p > 0.05$). Our findings are similar to Nozari *et al.*[25] who reported that the prevalence of ISR after PCI was higher in **2* allele carriers but without a statistically significant relationship, and contrast to Ruedlinger *et al.*,[26] who identified non-carriers of the **2* allele with higher incidence of coronary ISR.

According to Mitra and Agrawal,[12] the overall pathogenesis of ISR is not entirely understood and "prevention of ISR appears to be a multipronged attack as no therapeutic magic bullet exists to block all the processes in one go". In clinical practice, the importance of ISR is well-known.[10] Reducing the incidence of ISR is crucial, since ISR limits the long-term benefit of PCI by affecting the quality of life of the patient due to physical limitations caused by angina,[26] and augments health care costs due to the need for repeat revascularisation.[27,28]

Stent implantation causes injury to the arterial vessel wall, stimulating platelet activation through a number of pathways,[17,29,30] hence the rationale for prescribing antiplatelet therapy after PCI. Platelets are reported to be involved in the pathophysiology of ISR,[12,18,29,30] so the higher proportion of *CYP2C19*2* allele carriers exhibiting coronary ISR within 1 year compared to non-carriers may be explained in terms of inadequate platelet inhibition after PCI when these decreased clopidogrel responders are treated with clopidogrel. Recommendations for *CYP2C19* genotype and clopidogrel therapy state that a more potent $P2Y_{12}$ receptor inhibitor with no or little interindividual response variability, such as prasugrel or ticagrelor, unless contraindicated, rather than clopidogrel, should be prescribed in carriers of the *CYP2C19*2* allele, while non-carriers should be prescribed clopidogrel at the standard 75 mg dose.[8,31]

The $p$-value is highly dependent on the sample size and it is very unlikely to obtain statistical significance when the sample size is small, unless the difference between the proportions is considerable. The Fisher's exact $p$-value obtained in our study (0.067) exceeds the 0.05 level of significance by only a small margin, despite the very small sample size (29 patients with ISR). Compared to our study, Nozari *et al.*[25] had a larger sample of patients with ISR (50 patients) and a higher $p$-value (0.273) was obtained. Hence, given the small sample size, the findings from our study should not be ignored. Since the $p$-value obtained in our study exceeds the 0.05 level of significance by only a small margin, it is likely that a slightly larger sample size would have yielded a significant association between the two categorical variables.

The restricted sample size in this study limited power of the data and the ability to draw definite conclusions. Larger prospective case-control studies are recommended to further assess this reported association, which may open up new possible explanations of the pathophysiology of ISR and substantiate the role of *CYP2C19*2* genotyping with respect to antiplatelet therapy in patients undergoing PCI. The possibility that measured and unmeasured clinical and angiographic factors that may predispose to ISR development, such as lesion features, technical details of the PCI and comorbidities, which may have contributed to this association cannot be excluded. One measured predisposing factor is renal impairment, which was significantly higher in patients with ISR. This association is supported by other studies that have linked renal insufficiency with increased incidence of coronary ISR.[32–36] On the other hand, in a study by Best *et al.*,[37] ISR was not increased with chronic kidney disease.

## Future research prospective

ISR is a limiting factor for the long-term benefit of PCI. When manifested clinically, repeat target vessel revascularization is generally required. The higher proportion of *CYP2C19*2* allele carriers exhibiting ISR within 1 year compared to non-carriers is an interesting finding regarding the pharmacogenetic implications of clopidogrel and the incidence of coronary ISR. Larger prospective studies are recommended to assess this finding further, which may open up new possible explanations of the pathophysiology of ISR and support the utilization of *CYP2C19*2* genotyping for the personalization of antiplatelet therapy in patients undergoing PCI.

## Conclusions

The higher proportion of *CYP2C19*2* allele carriers exhibiting

ISR within 1 year compared to non-carriers is an interesting finding regarding the association of clopidogrel metabolism and the prevalence of coronary ISR. Since no significant association was found, which may be attributed to the small sample size, larger prospective studies are recommended to further assess this association.

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## Conflict of interest

The authors have no conflict of interest related to this publication.

## Author contributions

Study design (FW, AF, LMA), clinical support (RGX, AF), performance of experiments and laboratory support (FW, GZ, CB), data analysis (FW, LC, LMA), manuscript writing (FW). All authors reviewed and approved the manuscript.

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