CYP2C19*2 genetic polymorphism and incidence of in-stent restenosis in patients on clopidogrel: A matched case-control study

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Abstract

Background: The cytochrome P450 2C19 *2 (CYP2C19*2) genetic polymorphism is associated with reduced clopidogrel bioactivation, increasing the risk of atherothrombotic complications after percutaneous coronary intervention (PCI). In-stent restenosis (ISR) is a complication that limits the long-term prognosis of PCI.

Objective: To investigate the association between CYP2C19*2 and ISR within one-year after PCI in patients prescribed dual antiplatelet therapy (DAPT) with aspirin and clopidogrel Setting: Acute general hospital, Malta Main outcome measure: Association between CYP2C19*2 and drug-eluting stent (DES)-ISR within one-year post-PCI in patients on DAPT with aspirin and clopidogrel

Method: Sixty patients with angiographically-confirmed DES-ISR within one year when on DAPT with aspirin and clopidogrel were retrospectively identified (cases) and 60 patients with no documented ISR post-PCI in the study period (controls) were case-matched for age, gender, diabetes and estimated glomerular filtration rate value. Cases and controls were invited by cardiologists for CYP2C19*2 genotyping. The association between CYP2C19*2 and ISR was analysed using the Fisher's Exact test and binary logistic regression.

Results: Twenty-six (43.3%) cases and 5 (8.3%) controls were carriers of CYP2C19*2 , while 34 (56.7%) cases and 55 (91.7%) controls were non-carriers of CYP2C19*2 . The association between CYP2C19*2 carrier status and DES-ISR within one-year post-PCI was statistically significant ($p<0.001$) in both the univariate and multivariate analysis.

Conclusion : The proportion of CYP2C19*2 carriers who presented with DES-ISR within one-year post-PCI while on clopidogrel was significantly higher compared to patients with no documented ISR.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended as the gold standard therapy after percutaneous coronary intervention (PCI) with drug eluting stent (DES) placement to prevent atherothrombotic complications. [1] Recent European guidelines advocate for the more potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel over clopidogrel to prevent recurrence of adverse cardiac thrombotic events. [2, 3]

Yet, clopidogrel remains the most frequently prescribed $P2Y_{12}$ inhibitor post-PCI due to its lower cost and fewer reported bleeding events compared to the other $P2Y_{12}$ inhibitors. [4–6] Clopidogrel is a second-generation thienopyridine prodrug that requires hepatic activation principally by the cytochrome P450 2C19 (CYP2C19) enzyme to exert its effect of inhibiting platelet aggregation and activation through selective and irreversible adenosine diphosphate binding. [7–9] Despite treatment with standard doses of

clopidogrel, there are patients who persist to experience recurrent cardiovascular episodes due to inadequate platelet inhibition. [10–12]

This interpatient variability in clopidogrel response could be attributed to genetic factors such as the *CYP2C19*2* loss-of-function allele. [13–18] Presence of the *CYP2C19 *2* allele has been reported to significantly decrease the concentration of the active metabolite of clopidogrel, resulting in the reduction of platelet inhibitory activity and increasing the risk of platelet aggregation and thrombotic complications, including stent thrombosis. [8, 13–19]

In-stent restenosis (ISR), defined as gradual re-narrowing of the stented coronary vessel diameter by ≥ 50% determined via coronary angiography, is another complication that may arise after PCI with stent placement, and limits the long-term prognosis of the PCI. [20, 21] Few studies have been conducted to explore the association between the *CYP2C19 *2* allele and incidence of coronary ISR in patients receiving clopidogrel, and conflicting findings have been reported. [22–26] Three studies showed a higher frequency of ISR in carriers of *CYP2C19*2* however the correlation was not statistically significant [22–24] while another study reported a lower incidence of ISR among carriers of *CYP2C19*2.*[25] These studies concluded that the findings could be attributed to a small sample size and recommended further analysis.

Aim of the study

The aim of this study was to investigate the association between *CYP2C19*2* carrier status and the incidence of ISR within one-year post-PCI in patients prescribed DAPT with aspirin and clopidogrel.

Ethics approval

The study was approved by the University of Malta Faculty of Medicine and Surgery Research Ethics Committee (Ref No. FRECMDS_1819_59).

Method

Study setting and design

The study was undertaken at the Department of Cardiology, Phlebotomy Clinic and the Molecular Diagnostics Unit (MDU) of the Department of Pathology at Mater Dei Hospital, the main acute general hospital in Malta. A retrospective matched case-control study design was adopted (January 2014-December 2018). Prospective follow-up was applied for patients who underwent PCI between January and December 2018, who were followed-up for any ISR occurrence until December 2019.

Patient recruitment

The list of procedures performed at the Cardiac Catheterisation Suite (CCS) between January 2014 and December 2018 (N = 15,787) was obtained and screened. Patients were screened using the

Cardiovascular Information Management System (CVIS) at five intervals: 1,3,6,9 and 12 months post-PCI. Procedures other than PCI, and patients who were non-residents of Malta and could not be recruited for genotyping or followed-up were excluded. From the identified list of PCIs, duplicate patients and patients who passed away and could not be recruited for genotyping or followed-up were not considered. The inclusion criteria were patients ≥ 18 years, PCI with DES, prescribed DAPT with aspirin and clopidogrel for 12 months, any gender, any ethnicity. Further exclusion criteria were patients who underwent PCI with ballooning only or with bare-metal stenting, DAPT less than 12 months, patients with severe liver impairment, and patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2.

Patients (n = 137) with angiographically-confirmed ISR were identified and narrowed down to 81 patients with angiographically-confirmed ISR within one-year post-PCI and on clopidogrel. Patients who passed away after this screening process, patients who refused participation, and one patient on haemodialysis, were excluded at this stage. A total of 120 patients; 60 cases, and 60 case-matched controls selected using CVIS were included as the study population. Cases were patients with angiographically-confirmed ISR within 1 year of DES placement while on DAPT with aspirin and clopidogrel, and Controls were patients with no history of angiographically-documented ISR post-PCI, and case-matched for age, gender, diabetes mellitus and eGFR value (Fig. 1). **'Insert** Fig. 1 **here'**

Patients who met the study criteria (cases and controls) were invited via telephone by the responsible consultant cardiologist or a physician delegate to present at the CCS for *CYP2C19*2* genotyping. A brief description of the research study and what was expected from the patient was provided, and a date and time for a meeting with the investigator was set if they agreed to participate. Informed written patient consent was obtained and a data collection form developed and validated for the purpose of the study was completed. The data collection form collects patient demographic information, cardiac risk factors and social history, relevant comorbidities and investigations, angiographic factors, current medications prescribed and CYP2C19*2 genotype results. For each patient, a 5ml peripheral blood sample was collected by a physician or phlebotomist in a purple-top ethylenediaminetetraacetic acid (EDTA) vacutainer. The vacutainers were stored at the MDU between 2°C and 8°C prior to genomic DNA extraction.

Genomic DNA extraction and CYP2C19*2 genotyping

Genomic DNA extraction was performed using the QIAamp® DNA Mini QIAcube Kit (Qiagen®) on the automated QIAcube® robotic workstation. Extraction was performed from a 200µL sample of whole blood collected from each patient, and was stored at -20°C until genotyping. *CYP2C19*2* genotyping was performed for cases and controls with gradient polymerase chain reaction using the Eppendorf Mastercycler® gradient, and reverse hybridisation using the Autoimmun Diagnostika (AID) GmbH (Germany) RDB 2070X/2071X *CYP2C19*2* genotyping kits. Patients were categorised into *CYP2C19*2* carriers, which included carriers of one or two **2* alleles, and non-carriers of *CYP2C19*2*.

Action taken after genotyping

Genotype results were communicated to the respective consultant cardiologist. Thirty-one letters (26 cases and 5 controls who were *CYP2C19*2* allele carriers) were presented to six consultant cardiologists. The letters included patient identity, genotype result with genotype-guided antiplatelet recommendations based on the Clinical Pharmacogenetics Implementation Consortium (CPIC®) guidelines for CYP2C19 genotype and clopidogrel therapy.[8] The decision to switch from clopidogrel therapy to an alternative $P2Y_{12}$ inhibitor, if recommended, was left to the cardiologist's discretion.

Statistical analysis

Data analysis was carried out using IBM SPSS® Statistics version 27.0. Continuous variables (age, BMI, eGFR) were described by means and standard deviations (SD), and categorical variables were described by frequencies and percentages (%). The difference between two proportions z-test was used to compare percentages between cases and controls; the independent samples *t-test* was used to compare mean scores between these two groups; and the Fisher's exact test was used to investigate the association between *CYP2C19*2* and ISR. For all three tests, a 0.05 level of significance was used, where p-values less than 0.05 were considered statistically significant.

A binary logistic regression model was fitted to relate the occurrence of ISR with ten risk factors. The risk factors included: previous revascularisation, *CYP2C19*2* carrier status, heart failure, active smoking, dyslipidaemia, hypertension, > 1 stent implantation, BMI ≥ 30 kg/m^2, positive family history of ischaemic heart disease, and current alcohol intake. P-values were computed for each risk factor, where p-values less than 0.05 were considered statistically significant. The odds ratios (OR) which measure the association between risk exposure and occurrence of ISR were provided for the significant risk factors.

Results

Of the 60 cases and 60 controls recruited, the mean age of the patients in both groups was 65 years with an equal number of patients (n = 30) with diabetes in both groups and a mean eGFR of 77 $ml/min/1.73m^2$ in both groups ($p > 0.05$). A higher number of cases underwent previous revascularisation, had previous myocardial infarction, were active smokers and current alcohol consumers ($p < 0.05$) (Table 1).

Table 1
Patient characteristics, comorbidities and PCI characteristics (N = 120)

Variable	Cases n = 60	Control n = 60	p-value
Patient characteristics			
Mean age in years ± SD	**65 ± 9.8**	**65 ± 9.4**	**0.835**
Male gender	**51**	**51**	**1.000**
Caucasian ethnicity	59	59	1.000
Mean BMI in kg/m^2 ± SD	30 ± 4.7	31 ± 5	0.256
Positive family history of IHD	47	42	0.290
Previous PCI	54	24	< 0.001
Previous CABG	16	7	0.036
Previous MI	29	15	0.008
Active smoker	32	19	0.016
Current alcohol intake	30	14	0.002
Comorbidities			
Hypertension	37 (61.6%)	48 (80 %)	0.027
Dyslipidaemia	22 (36.6%)	47 (78.3%)	< 0.001
Heart failure	15 (25%)	2 (3.3%)	0.007
LVEF mean % ±SD	59 ± 10	73 ± 14	< 0.001
Diabetes mellitus	**30 (50%)**	**30 (50%)**	**1.000**
Renal Impairment (eGFR < 60 mL/min/1.73m^2)	**10 (16.6%)**	**10 (16.6%)**	**1.000**
Reason for PCI			
Ischaemic Heart Disease	40 (66.6%)	27 (45%)	0.016
Non-ST-Elevation MI	16 (26.7%)	13 (21.7%)	0.522
ST-Elevation MI	4 (6.7%)	20 (33.3%)	< 0.001

BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; eGFR: Estimated Glomerular Filtration Rate; IHD: Ischaemic Heart Disease; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention

Variable	Cases n = 60	Control n = 60	p-value
Type of PCI			
Emergency/Primary	31 (51.7%)	35 (58.3%)	0.465
Elective	29 (48.3%)	25 (41.7%)	0.465
Single-stent PCI	31 (51.7%)	41 (68.3%)	0.062
Multi-stent PCI	29 (48%)	19 (37%)	0.062

BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; eGFR: Estimated Glomerular Filtration Rate; IHD: Ischaemic Heart Disease; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention

The most common comorbidities were hypertension and dyslipidaemia. A significantly higher proportion of patients with hypertension and dyslipidaemia was observed in the control group compared to the cases group ($p < 0.05$). A significantly higher proportion of patients with heart failure was observed in the cases compared to the controls ($p < 0.05$), with a mean LVEF of 59% in the cases and 73% in the controls ($p < 0.001$). The majority of cases and controls were undergoing PCI due to ischaemic heart disease ($p < 0.05$). Patient characteristics are detailed in Table 1. **'Insert** Table 1 **here'**

For the cases group, the most commonly affected coronary vessel which required repeat PCI due to ISR was the left anterior descending artery (n = 21, 33.3%). The mean time from PCI to the presentation of ISR was 8 months, with 10–12 months being the most common duration (n = 22, 36.7%). The majority of cases (n = 58, 96.6%) had ISR requiring repeat PCI in only one stent. Unstable angina was the most common presentation of ISR (n = 32, 53.3%). The majority of the cases (n = 39, 65%) had ISR in a second-generation DES (Table 2). **'Insert** Table 2 **here'**

Table 2
Angiographic factors for cases (n = 60)

Variable	Number of cases (%)
Coronary vessel affected with ISR	
Left anterior descending artery	21 (33.3%)
Right coronary artery	12 (19%)
Circumflex artery	10 (16%)
Grafts	7 (11%)
Obtuse marginal artery	5 (8%)
Left main artery	3 (4.8%)
Diagonal artery	2 (3.2%)
Intermediate artery	2 (3.2%)
Posterior descending artery	1 (1.5%)
Time of presentation of ISR from PCI (months)	
> 1–3	5 (8.3%)
4–6	13 (21.7%)
7–9	20 (33.3%)
10–12	22 (36.7%)
ISR presentation	
Unstable Angina	32 (53.3%)
ST-Elevation Myocardial Infarction	15 (25%)
Non-ST-Elevation Myocardial Infarction	13 (21.7%)
Drug-eluting stent generation	
First generation (paclitaxel, sirolimus)	11 (18.3%)
Second generation (zotarolimus, everolimus)	39 (65%)
Third generation (biolimus)	10 (16.7%)
Stenosed stent dimensions	
Mean length in mm ± SD	18.02 ± 7.10
Mean diameter in mm ± SD	2.78 ± 0.40

Out of the 120 patients, 89 (74%) patients were non-carriers of the *CYP2C19*2* (homozygous*1/*1) and 31 (25.8%) were carriers of the *CYP2C19*2* allele; 31 patients were genotyped as heterozygous *1/*2, and one patient was genotyped as homozygous *2/*2 and belonged to the cases group. A significantly higher proportion of cases (n = 26, 43.3%) were carriers of the *CYP2C19*2* allele compared to controls (n = 5, 8.3%) ($p < 0.001$). Six patients were switched from clopidogrel to prasugrel after developing ISR; 3 patients were genotyped as carriers of CYP2C19*2, and 3 patients were genotyped as non-carriers.

The Fisher's exact test revealed that the association between *CYP2C19*2* carrier status and coronary ISR within one-year post PCI was statistically significant ($p < 0.001$, OR = 8.4). Carriers of the *CYP2C19*2* allele were 8.4 times more likely to develop ISR than non-carriers (Fig. 2). **'Insert** Fig. 2 **here'.** Binary logistic regression analysis identified four significant risk factors of ISR within one-year post-PCI; namely previous revascularisation, carrier of *CYP2C19*2*, heart failure and active smoking (Table 3). '**Insert** Table 3 **here'**

Table 3
Significant associations of the incidence of ISR in the multivariate analysis

Variable	**p-value**	**Odds Ratio**
Previous Revascularisation	0.000	38.621
Carrier of CYP2C19*2	**0.001**	**22.612**
Heart Failure	0.012	17.717
Active Smoker	0.026	3.489

Discussion

Findings from this research demonstrated a significant association between the presence of the *CYP2C19*2* allele and ISR within one-year post-PCI in both the univariate (OR 8.4, $p < 0.001$) and multivariate analysis (OR 22.6, $p = 0.001$). The risk of developing ISR within one-year post-PCI on clopidogrel therapy was shown to be significantly higher in *CYP2C19 *2* carriers than in non-carriers and the signal observed in the previous study by Wirth et al.[24] was confirmed. A recent study by Zhang et al[26] supports these findings, where significantly higher rates of ISR were observed in carriers of the *CYP2C19* loss-of-function alleles (*1/*2, *1/*3) on standard dose clopidogrel compared to non-carriers.

Further to *CYP2C19*2* carrier status, the multivariate analysis in the present study identified a significant association between non-genetic factors namely previous revascularisation, heart failure and active smoking and incidence of ISR. The finding with respect to previous revascularisation is in accordance with three previous studies, where history of PCI was identified as an independent predictor of DES-ISR. [27–29] As regards heart failure, a similar significant association between heart failure and ISR was reflected in two previous studies. [27, 30] Conflicting evidence on the effect of smoking on ISR has been reported. Similar to the present study, smoking was observed to be a significant predictor of ISR in two

studies [31, 32], while three other studies found no association. [33–35] Conversely, it has also been reported that smoking may have a 'protective effect' contributing to decreased high platelet reactivity while on clopidogrel therapy and enhanced clinical benefit of clopidogrel in smokers compared to non-smokers, a phenomenon described as the "smoker's paradox". [27, 36–38]

A higher number of cases compared to controls in the present study underwent PCI with multiple stenting, however there was no statistically significant association between ISR and a higher number of stents implanted. This finding contrasts with other studies which demonstrated that the number of stents deployed was an independent predictor of ISR. [30,39–42] This association may be due to the increased probability of vessel trauma causing intimal hyperplasia increases with the increase in number of stents deployed [43, 44]. Vessel trauma caused by an increase in the number stents deployed may precipitate the initiation of the inflammation cascade, causing the recruitment of platelets, neutrophils and fibrin, along with the proliferation of smooth muscle and fibroblasts, leading to the development of ISR. [45–47]

Twenty-six percent of the present study cohort were carriers of one or two *CYP2C19 *2* alleles. These patients had an 'Actionable' genotype with regards to clopidogrel and were eligible for *CYP2C19* genotype-guided intervention according to guidance from the CPIC and the Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group (DPWG), which recommend carriers of *CYP2C19*2* to be prescribed alternative $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) instead of clopidogrel, if there is no-contraindication. [8, 48] Clopidogrel is the only $P2Y_{12}$ inhibitor available on the Maltese National Health Service (NHS) and prasugrel and ticagrelor are available on the private market for out-of-pocket purchase. Inaccessibility, along with the price of alternative antiplatelet therapy, may have caused prescription hesitancy among cardiologists in the present study.

Over the past decade, clinical decision-making with respect to personalisation of antiplatelet therapy in patients undergoing PCI incorporating pharmacist-led CYP2C19 genotyping along with the consideration of non-genetic risk factors, has been implemented in various institutions, predominantly in the USA. This has come into effect as a result of the increasing reports of improved clinical and economic outcomes, access to guidance from entities such as the CPIC and DPWG, availability of alternative antiplatelet agents to clopidogrel, and the availability of rapid CYP2C19 genotyping. [5, 49–63]

The implementation of CYP2C19-guided antiplatelet therapy has been reported to result in better platelet inhibition and decreased adverse cardiac outcomes compared to patients who did not undergo CYP2C19-guided antiplatelet adjustments, in whom significantly poorer outcomes were observed. [51, 56, 57, 59, 60, 62] Although improved outcomes for patients have been reported, none of the evidence-base resulted from large, prospective clinical trials. As a result, the American Heart Association/American College of Cardiology and European Society of Cardiology guidelines do not presently recommend implementation of routine CYP2C19 pharmacogenetic testing to tailor DAPT. [64, 65] The recent large multi-site TAILOR-PCI trial showed very promising results and provided a signal supporting the benefit of *CYP2C19* genotype-guided antiplatelet therapy.[66] Moreover, a sub-study from the POPular genetics trial showed that the

genotype-guided group was non-inferior to standard therapy with regards to thrombotic events, with a reduction in thrombotic events in the genotype-guided group and a lower incidence of bleeding and ischaemia.[6] With the emerging evidence of the positive impact of CYP2C19 genotype-guided antiplatelet therapy selection on patient outcomes, particularly post-PCI, pharmacist-led pharmacogenetic programs hold great potential to optimise therapy and decrease adverse outcomes. [67]

The authors acknowledge the following limitations. The lower number of cases than controls with dyslipidaemia identified in clinical records did not match the patients' medication history of statin therapy. This could be due to statins being prescribed for secondary prevention post-PCI and not to treat diagnosed dyslipidaemia or due to underreporting, causing discrepancies in the data collected. Low-density lipoprotein cholesterol and triglyceride levels were not recorded; hence this discrepancy could not be verified. Moreover, the correlation between lipid profile parameters and ISR would have been interesting to explore if recorded. Adherence to clopidogrel was not evaluated in this study and could be another factor that affects predisposition to ISR.

Conclusion

The risk of developing ISR within one-year post-PCI on clopidogrel therapy was significantly higher in *CYP2C19 *2* carriers than in non-carriers. Other significant associations identified to increase the risk of ISR were previous revascularisation, heart failure and active smoking. Pharmacist-led *CYP2C19*2* genotyping may be used as a tool together with consideration of non-genetic risk factors to achieve precision antiplatelet therapy and decrease the risk of ISR.

Declarations

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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Tables

Table 1. Patient characteristics, comorbidities and PCI characteristics (N=120)

Variable	Cases n=60	Control n=60	p-value
Patient characteristics			
Mean age in years ±SD	**65 ±9.8**	**65 ±9.4**	**0.835**
Male gender	**51**	**51**	**1.000**
Caucasian ethnicity	59	59	1.000
Mean BMI in kg/m^2 ±SD	30 ±4.7	31 ±5	0.256
Positive family history of IHD	47	42	0.290
Previous PCI	54	24	<0.001
Previous CABG	16	7	0.036
Previous MI	29	15	0.008
Active smoker	32	19	0.016
Current alcohol intake	30	14	0.002
Comorbidities			
Hypertension	37 (61.6%)	48 (80 %)	0.027
Dyslipidaemia	22 (36.6%)	47 (78.3%)	<0.001
Heart failure	15 (25%)	2 (3.3%)	0.007
LVEF mean % ±SD	59 ±10	73 ±14	<0.001
Diabetes mellitus	**30 (50%)**	**30 (50%)**	**1.000**
Renal Impairment (eGFR <60 mL/min/1.73m^2)	**10 (16.6%)**	**10 (16.6%)**	**1.000**
Reason for PCI			
Ischaemic Heart Disease	40 (66.6%)	27 (45%)	0.016
Non-ST-Elevation MI	16 (26.7%)	13 (21.7%)	0.522
ST-Elevation MI	4 (6.7%)	20 (33.3%)	<0.001
Type of PCI			
Emergency/Primary	31 (51.7%)	35 (58.3%)	0.465
Elective	29 (48.3%)	25 (41.7%)	0.465
Single-stent PCI	31 (51.7%)	41 (68.3%)	0.062

Multi-stent PCI	29 (48%)	19 (37%)	0.062

BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; eGFR: Estimated Glomerular Filtration Rate; IHD: Ischaemic Heart Disease; LVEF: Left Ventricular Ejection Fraction; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention

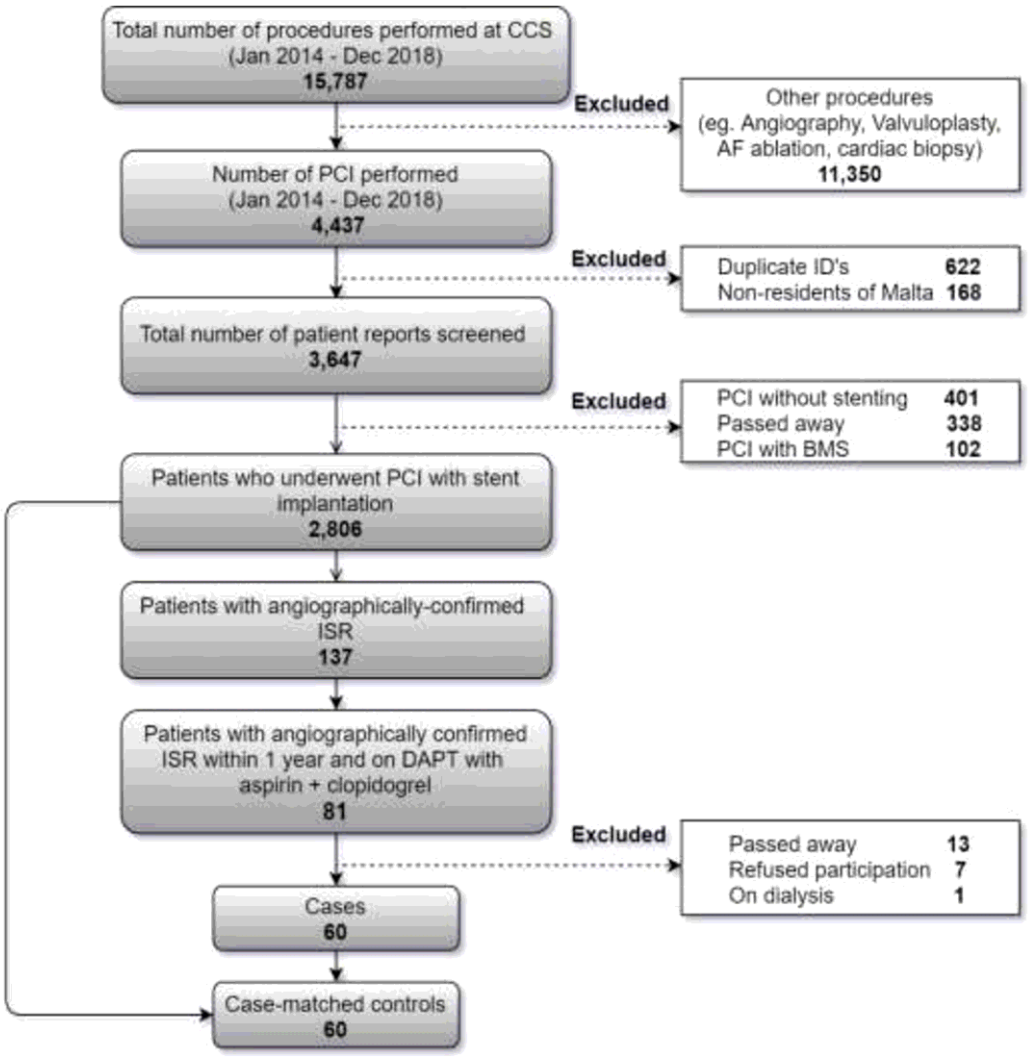
Table 2. Angiographic factors for cases (n=60)

Variable	Number of cases (%)
Coronary vessel affected with ISR	
Left anterior descending artery	21 (33.3%)
Right coronary artery	12 (19%)
Circumflex artery	10 (16%)
Grafts	7 (11%)
Obtuse marginal artery	5 (8%)
Left main artery	3 (4.8%)
Diagonal artery	2 (3.2%)
Intermediate artery	2 (3.2%)
Posterior descending artery	1 (1.5%)
Time of presentation of ISR from PCI *(months)*	
>1-3	5 (8.3%)
4-6	13 (21.7%)
7-9	20 (33.3%)
10-12	22 (36.7%)
ISR presentation	
Unstable Angina	32 (53.3%)
ST-Elevation Myocardial Infarction	15 (25%)
Non-ST-Elevation Myocardial Infarction	13 (21.7%)
Drug-eluting stent generation	
First generation (paclitaxel, sirolimus)	11 (18.3%)
Second generation (zotarolimus, everolimus)	39 (65%)
Third generation (biolimus)	10 (16.7%)
Stenosed stent dimensions	
Mean length in mm ±SD	18.02 ±7.10
Mean diameter in mm ±SD	2.78 ±0.40

Table 3. Significant associations of the incidence of ISR in the multivariate analysis

Variable	p-value	Odds Ratio
Previous Revascularisation	0.000	38.621
Carrier of *CYP2C19*2*	**0.001**	**22.612**
Heart Failure	0.012	17.717
Active Smoker	0.026	3.489

Figures



BMS: Bare-metal stent; CCS: Cardiac Catheterisation Suite; DAPT: Dual antiplatelet therapy; DES: Drug-Eluting Stent; ISR: In stent Restenosis PCI: Percutaneous Coronary Intervention

Figure 1

Patient recruitment flowchart

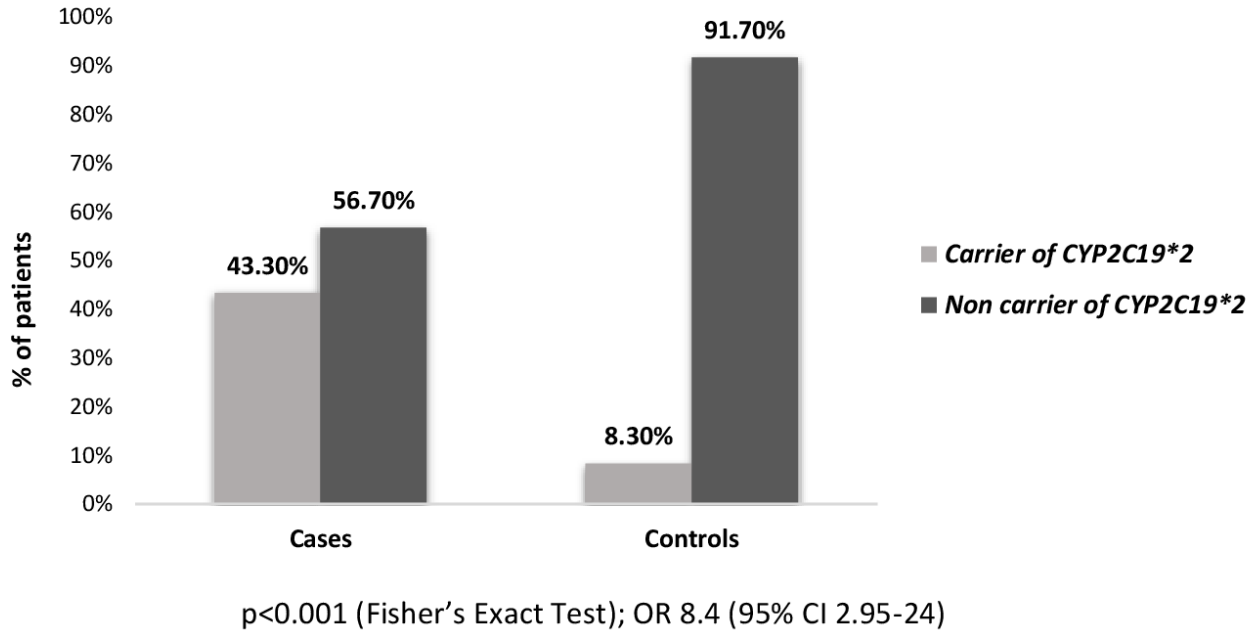


Figure 2

Association between CYP2C19*2 status and ISR by univariate analysis (N=120)