*CYP2C19*2* Genetic Polymorphism and other Predictors for Coronary In-Stent Restenosis in Patients on Clopidogrel Therapy

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Introduction

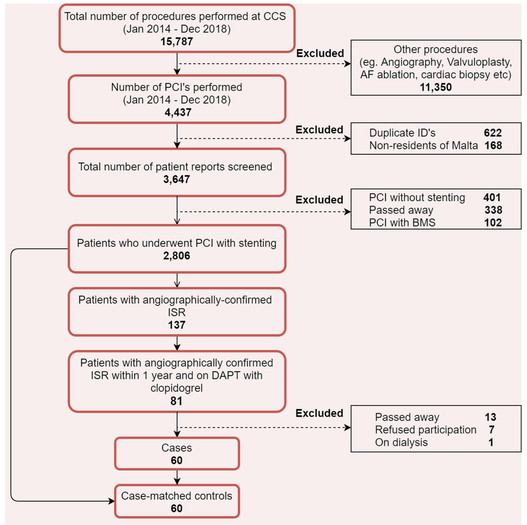
Dual antiplatelet therapy (DAPT) is the cornerstone therapy in patients undergoing percutaneous coronary intervention (PCI) to prevent atherothrombotic complications. Clopidogrel with aspirin is the most commonly prescribed DAPT.[1,2] Clopidogrel is a prodrug which requires hepatic activation by the cytochrome P 450 2C19 (CYP2C19) enzyme which is highly polymorphic. The loss-of-function **2* allele is the most common genetic polymorphism.[3] *CYP2C19*2* has been reported to significantly decrease the concentration of the active metabolite of clopidogrel leading to complications post-PCI, such as major adverse cardiovascular events.[3] In-stent restenosis (ISR), defined as ≥50% re-narrowing of a deployed stent, is a complication that may threaten the long term prognosis of PCI.[4] Few studies have been conducted to explore the association between *CYP2C19*2* and coronary ISR in patients receiving clopidogrel and conflicting findings have been reported.[5-8]

Aim

To study the association between the *CYP2C19*2* genetic polymorphism and incidence of ISR within 1-year post-PCI with drug eluting stent (DES) implantation in patients prescribed aspirin and clopidogrel.

Method

- A retrospective matched case-control study design with prospective follow-up was adopted.
- Patients who underwent PCI with stent implantation (January 2014-December 2018) at the Cardiology Department of the acute general hospital were screened. Patients with angiographically-confirmed DES-ISR within 1 year when aspirin and clopidogrel were identified (Cases) and patients with no documented ISR post-PCI in the study period (Controls) were case-matched for age, gender, diabetes and estimated glomerular filtration (eGFR) rate (Figure 1).
- Cases and controls were invited by the cardiologists for *CYP2C19*2* genotyping, which was undertaken at the Molecular Diagnostics Unit of the hospital using gradient polymerase chain reaction and reverse hybridization after ethics approval. Carriers of the *CYP2C19*2* allele were communicated to the cardiologists.
- The association between CYP2C19*2 and incidence of ISR was analysed using the Fisher's Exact test (univariate analysis) and binary logistic regression (multivariate analysis). Odds ratio (OR) was calculated and a p-value less than 0.05 was considered statistically significant.



BMS: Bare metal stent; **CCS;** Cardiac catheterisation suite; **DAPT:** Dual antiplatelet therapy; **ISR**: In-stent restenosis; **PCI:** Percutaneous coronary intervention

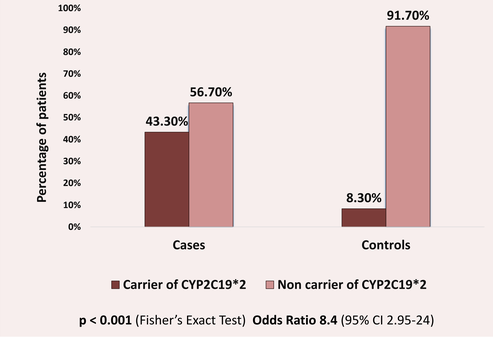
Figure 1: Patient recruitment flowchart

Results

- Sixty cases and 60 matched controls were enrolled.
- Patient and PCI characteristics are shown in Table 1.
- The majority of cases (n=58) had ISR in 1 stent.
- The most common site of ISR was the left anterior descending artery (n=21). Most ISR occurred after 7-8 months (n=20) and 9-12 months (n=22).
- The association between *CYP2C19*2* carrier status and ISR within 1 year post-PCI was statistically significant in the univariate (p<0.001) and multivariate analysis (p=0.001) (Figure 2).
- Other significant associations for ISR identified in the multivariate analysis were previous revascularisation (OR 38.6, p<0.001), heart failure (OR 17.7, p=0.012) and active smoking (OR 3.5, p=0.026) (Table 2).

Table 1: Patient demographics, clinical and PCI characteristics (N = 120)

Variable	Cases n = 60	Controls n = 60	p-value
Mean age in years ± SD	65 ±9.8	65 ±9.4	0.835
Male gender	51	51	1.000
Caucasian	59	59	1.000
Mean BMI in kg/m² ±SD	30 ± 4.7	31 ± 5	0.256
Positive family history of IHD	47	42	0.290
Previous revascularisation	54	24	< 0.001
Previous MI	29	15	0.008
Active smoker	32	19	0.016
Current alcohol Intake	30	14	0.002
Patient comorbidities			
Hypertension	37	48	0.027
Dyslipidaemia	22	47	< 0.001
Heart failure	15	2	0.007
Mean LVEF % ±SD	59 ±10	73 ±14	< 0.001
Diabetes mellitus	30	30	1.000
Renal impairment (eGFR <60 mL/min/1.73m²)	10	10	1.000
Mean eGFR ±SD	77 ±20	77 ±19	0.934
Reason for PCI			
IHD	40	27	0.016
NSTEMI	16	13	0.522
STEMI	4	20	<0.001
Type of PCI			
Emergency/Primary	31	35	0.465
Elective	29	25	0.465



p < 0.001 (Fisher's Exact Test) **Odds Ratio 8.4** (95% CI 2.95-24)

Figure 2: Correlation between *CYP2C19*2* and ISR (N = 120)

Table 2: Significant associations of ISR – Multivariate analysis

	p value	Odds Ratio
Previous Revascularisation	p<0.001	38.621
Carrier of *CYP2C19*2*	**0.001**	**22.612**
Heart failure (LVEF ≤50%)	0.012	17.717
Active smoking	0.021	3.489

Conclusions

- 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.
- Other significant associations of ISR identified were previous revascularisation, heart failure and active smoking.
- *CYP2C19*2* genotyping may be used as a tool together with consideration of non-genetic risk factors for precision antiplatelet therapy in patients undergoing PCI with DES implantation and prescribed aspirin and clopidogrel to decrease the risk of ISR.

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