Original Research Article

New Concern: Drug-Drug Eluting Stent Interaction (DDESI) between Drugs Prescribed and Drug Eluting Stents (DESs) after Percutaneous Coronary Intervention (PCI) in Coronary Artery Disease (CAD) Patients: A Multicenter Cross-Sectional Observational Study

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ABSTRACT

Objective: This study was aimed to evaluate the interactions between commonly used drug eluting stents (DES) and prescribed medications in coronary artery disease (CAD) patients those underwent percutaneous coronary intervention (PCI).
Study design: Retro-prospective, Multicenter, Cross-sectional, Observational study.
Methodology: A total of 127 CAD patients those successfully underwent PCI with different DES were enrolled in this study. The study population were divided into 3 groups; i) Patients stented with Sirolimus DES (n=52), ii) Everolimus DES (n=46) and iii) Zotarolimus DES (n=29) respectively, the patients case report and drug chart were reviewed periodically up to one-year regular follow-up period and retro-prospectively analysed. Results were statistically analysed using Graph Pad Prism software version 7.01 to determine the statistical difference between each study group. $P<0.05$ was considered as significant. Baseline clinical characteristics, angiographic and procedural characteristics, commonly prescribed medications and the new medical terminology Drug-Drug Eluting Stent Interaction abbreviated as DDESI were compared.
Results: Out of 127 total populations, patients stented with Sirolimus DES reported less (0.85%) DDESI compared to Everolimus DES (2.54%) and Zotarolimus DES (1.69%) DDESI. Drugs such as aspirin, atorvastatin and clopidogrel were found to be three most commonly prescribed drugs to maximize benefits and minimize the complications in CAD patients those underwent PCI with different DES.
Conclusion: According to the available patients data and results obtained it is concluded that Sirolimus DES was found to be more suitable and safe when compared to Everolimus DES and Zotarolimus DES after the one year regular follow-up period in CAD patients post PCI.

Keywords: Coronary artery disease; Drug eluting stents; Sirolimus; Everolimus; Zotarolimus; Percutaneous coronary intervention; Drug interactions; DDESI.

1. INTRODUCTION

Coronary artery disease (CAD) has been remaining the first killer and the major cause of public health problems in the world [1]. An estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack

and stroke [2]. According to a WHO report in 2014, the age-adjusted cardiovascular disease mortality rates in India were 349 and 265 per 100 000 in men and women, respectively. These rates are more than two to three times higher than in USA (170 and 108 per 100 000 in men and women, respectively) [3]. Treatment goals for coronary heart disease (CHD) include heart-healthy lifestyle changes, medicines, medical procedures and surgery includes coronary interventions as angioplasty and coronary stent for widening the clogged arteries and coronary artery bypass grafting (CABG) for bypassing the clogged arteries and cardiac rehabilitation [4].

Drug eluting stents (DESs) have been widely used for CAD since Food and Drug Administration (FDA) approved use of first Drug eluting stent (DES) in April 2003 [5]. DES is a peripheral or coronary stent (a scaffold) placed into narrowed, diseased peripheral or coronary arteries in the heart that slowly release a drug to block cell proliferation [6], but may be associated with the hazard of late stent thrombosis. Local delivery of drugs using DESs provides both biological and mechanical solution and has emerged as a very promising approach and effective in management of in-stent restenosis (ISR). For local drug delivery to be successful, challenges to be addressed include decision on the most appropriate agent to be used [7, 8], determination of the proportion of systemic dose needed locally [9] and identification of a biocompatible vehicle that can deliver drug for the required therapeutic window [10, 11]. Four classes of drugs (anti-inflammatory, antithrombogenic, anti-proliferative and immunosuppressive) are candidate drugs to be used in DESs; these drugs inhibit one or more biochemical pathways leading to restenosis.

Drug interactions are one of the most common causes of side effects in poly-pharmacy [12]. A drug-drug interaction (DDI) may either increase or decrease the effects of one or both drugs, clinically significant interactions are often predictable and usually undesired [13]. Nowadays, Drug-drug interactions (DDIs) were found to be one of the major problems in pharmacotherapy worldwide, focus on identifying, resolving and preventing drug therapy problems are the important role of the pharmacy care practitioner. It is observed that several researchers established many DDIs between prescribed medications but there are no literatures available about the interactions between DESs like scaffolds and prescribed drugs after PCI, this makes me impress to design this basic observational study as a first attempt to invent and evaluate the new term Drug-drug eluting stents interactions first time in the world. Researchers, physicians particularly cardiologists like to use or invent abbreviations and acronyms, the use of abbreviations or acronyms is necessary to simplify and facilitate modern communication in our highly technical world [14]. Therefore, the new medical term Drug-Drug Eluting Stent interaction hereafter will be abbreviated as DDESI.

2. METHODOLOGY

2.1 Study Design

The present retro-prospective, multicenter cross-sectional observational study included CAD patients treated with different DESs within some selected hospitals (Vivekanandha Medical Care Hospital, Tiruchengode, Apollo Multi Speciality Hospital, Trichy, Sri Gokulam Hospital, Salem) of the three different parts in South India from the beginning of 2016-2017, the basic features of the selected DES are shown in Table 1.

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Table 1. Basic features of the drug eluting stents (DESs) studied

Eluting Drug	Brand name	Scaffold material	Nominal Size (Length x Diameter)	Strut thickness (µm)	Polymer material	Polymer thickness (µm)	Drug elution kinetics
Sirolimus	Cypher (Raptor & Raptorrail)	Stainless steel	18 x 3mm	140	PEVA, PBMA	12.6	80% within the first 4 weeks
Everolimus	Xience (V, Prime, Xpedition, & Alpine)	Cobalt-chromium	18 x 3mm	81	PBMA, PVDF-HFP	7.6	80% within the first 4 weeks
Zotarolimus	Resolute Onyx & Endeavor	Cobalt-alloy	18 x 3mm	91	PBMA, PHMA, PVP	5.6	85% within the first 8 weeks

PEVA: Poly-ethylene-co-vinyl acetate; PBMA: Poly-n-butyl methacrylate; PVP: Polyvinylpyrrolidone; PHMA: Poly-hexyl methacrylate; PVDF-HFP: Copolymer of vinylidene fluoride and hexafluoro-propylene.

2.2 Ethical approval

Ethical approval was gained through the main centre's Institutional Ethics Committee (IEC) with the approval number SVCP/IEC/JAN/2016/10 dated 27/01/2016. Hence it is a patients data analysis based study it was exempt from obtaining individual informed consent from each patient according to the Helsinki Declaration of 1964 revised in 2000 [15], but the objective of the present study was explained to all participants.

2.3 Study population

Totally N=127 (88 Male + 39 Female) CAD patients those successfully intervened with different DESs were included in this individual data based observational study. The study population were classified in to three groups i) Patients stented with Sirolimus DES; N=52 (38 Males + 14 Females), ii) Patients stented with Everolimus DES; N=46 (31 Males + 15 Females), and iii) Patients stented with Zotarolimus DES; N=29 (19 Males + 10 Females). The selection criteria include history of unstable angina (UA), chronic stable angina (CSA), myocardial infarction (MI) or the presence of high-risk factors for CAD etc.

2.4 Study protocol

The CAD patients who met the following inclusion criteria were included in this study. A number of variables that play a vital role in stent therapy were analysed. These include baseline patient characteristics, angiographic and procedural characteristics, stent characteristics, most commonly prescribed medications and DDESI. The pre and post PCI case reports and drug charts of the selected CAD patients were reviewed also other necessary details are collected from the patients via phone calls whenever required.

2.4.1 Inclusion criteria

Age 30 to 80 years old, both males and females, patients underwent angioplasty using at least one DES, patients underwent angioplasty with or without hypertension and diabetes mellitus, patients those already prescribed with medications like anti-hypertensive drugs, anti-hyperlipidemic drugs, anti-coagulants, vasodilators and oral hypoglycaemic agents

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either single or in combination at least one month before they subject to PCI and not reported for any DDI symptoms only were included in this study.

2.4.2 Exclusion criteria

Patients with age <30 and >80, pregnancy, lactation, critically ill patients, patients with life style modification alone, patients those received only percutaneous transluminal coronary angioplasty (PTCA) without stent implantation, patients those received bare metal stents (BMS) not DES, patients with complex lesions and who received multiple types of stents concurrently, and patients who were diagnosed with acute MI (NSTEMI) and underwent coronary artery bypass grafting (CABAG) were excluded from this study.

2.5 Statistical analysis

Statistical analysis was done by using Graph Pad Prism software version 7.01 and results were expressed as Mean ± SEM for numerical variables and as percentage (%) for categorical variables. Column statistics followed by student t test was performed to compare the statistical difference between various groups, $P<0.05$ was considered as statistically significant.

3. RESULTS

3.1 Baseline patient characteristics

A total of 127 patients were included in the study it is found that 52 patients were treated with Sirolimus DES, 46 patients were treated with Everolimus DES and 29 patients were treated with Zotarolimus DES, several clinical baseline patient characteristics and its significance was determined as shown in Table 2.

Table 2. Baseline patient characteristics

Baseline Patient Characteristics	Patients treated with Sirolimus DES (n=52)	Patients treated with Everolimus DES (n=46)	Patients treated with Zotarolimus DES (n=29)	*P*-value
Age	56.17±8.79	58±11.33	58.11± 8.15	-
Male	73.08 %	67.39 %	65.52 %	0.0089
Female	26.92 %	32.61 %	34.48 %	0.0398
History of CAD	21.43 %	07.69 %	11.11 %	0.0832
Smoking	25.00 %	07.69 %	13.88 %	0.0920
Alcoholic	21.43 %	07.69 %	08.34 %	0.1080
Single vessel disease	48.57 %	56.92 %	39.44 %	0.124
Multi vessel disease	51.35 %	43.07 %	60.33 %	0.0109
IWMI	25.00 %	19.23 %	30.55 %	00168
ASMI	30.35 %	15.38 %	16.66 %	0.0468
AWMI	17.86 %	19.23 %	13.88 %	0.088
IPMI	01.79 %	0 %	0 %	0.4226
Stable angina	44.64 %	76.92 %	77.78 %	0.029
Unstable angina	10.71 %	23.08 %	19.44 %	0.0402
Diabetics	23.21 %	42.31 %	36.11 %	0.0265
Hypertension	32.14 %	38.46 %	33.33 %	0.0031
Hypercholestremia	03.57 %	03.84 %	13.88 %	0.1716
Renal failure	0 %	0 %	02.77 %	0.4226

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Heart failure	03.57 %	0 %	02.77 %	0.1899
Arrhythmia	01.79 %	07.69 %	05.55 %	0.1009
Hyperthyroidism	01.79 %	0 %	0 %	0.4226

3.1.1 Gender wise distribution of the study population

In this study population male was higher in patients treated with Sirolimus DES (73.08%) then Everolimus DES (67.39%) and Zotarolimus DES (65.52%) but female population was found to be high in Zotarolimus DES (34.48%) compared to Everolimus DES (32.61%) and Sirolimus DES (26.92%).

3.1.2 Age wise distribution of the study population

Age is categorized in to six variables and each group is compared with each variable, among 127 populations, the incidence of CAD was mostly occurred in patients at the age of 51-60.

3.1.3 Coronary artery disease background of the study population

The CAD background of the study population of 127 patients was divided into two groups: i) patients with the history of CAD and ii) patients without the history of CAD. Among the study population patients without the history of CAD were found to be more in Everolimus DES (92.30%) then Zotarolimus DES (88.88%) and Sirolimus DES (78.47%).

3.1.4 Social habits wise distribution of the study population

Social habits of 127 populations were analysed and categorized to smoker, alcoholic, both and none. All the above four categories were found to be high in patients treated with Sirolimus DES; smoker (25%), alcoholic (21.43%), both (14.29%), none (39.28%) then in patients treated with Zotarolimus DES; smoker (13.88%), alcoholic (8.34%), both (2.78%), none (75%). In Everolimus DES group; smoker was (7.69%), alcoholic (7.69%), both (11.54%) and none (73.08%) it is found to be lowest among all the three groups.

3.1.5 Patients with Target vessel diseases (TVD)

CAD was classified into single vessel disease (SVD) and multi vessel disease (MVD). The SVD was found to be high in patients treated with Everolimus DES (56.92%) then in Sirolimus DES (48.57%) and Zotarolimus DES (39.44%) but MVD was found to be more in patients treated with Zotarolimus DES (60.33%) when compared to Sirolimus DES (51.35%) and Everolimus DES (43.07%).

3.1.6 Patients with Myocardial infarction

Myocardial infarction (MI) is categorized into Inferior Wall Myocardial Infarction (IWMI), Anterioseptal Myocardial Infarction (ASMI), Anterior Wall Myocardial Infarction (AWMI) and Infero-posterior Wall Myocardial Infarction (IPWMI or IPMI). The IWMI patients are treated more with Zotarolimus DES (30.55%) but ASMI patients were highly treated with Sirolimus DES (30.35%) on the other hand AWMI patients also treated more with Everolimus DES (19.23%) when compared to other two DESs and it is found that only (1.79%) of IPMI patients treated with Sirolimus DES.

3.1.7 Patients with Angina pectoris

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Angina pectoris is categorized into stable angina and unstable angina. Patients treated with Sirolimus DES had (44.64%) of stable angina and (10.71%) of unstable angina but patients received Everolimus DES shows (76.92%) stable angina and (23.08%) unstable angina and Zotarolimus DES treated patients had (77.78%) stable angina and (19.44%) of unstable angina before subject to PCI.

3.1.8 Pattern of Co-morbidities among study population

Out of 127 patients, 99 patients had one or more co-morbid condition and 28 patients did not have any co-morbidity before subject to angioplasty. Out of 99 patients with co-morbidities, in Sirolimus DES treated patients (23.21%) had diabetics, (32.14%) hypertension, (3.57%) hypercholestremia, (3.57%) congestive heart failure, (1.79) arrhythmia and (1.79%) hyperthyroidism but in patients treated with Everolimus DES (42.31%) had diabetics, (38.46%) hypertension, (3.84%) hypercholestremia and (7.69%) arrhythmia. On the other hand, in Zotarolimus DES implanted patients it is found that (36.11%) had diabetics, (33.33%) hypertension, (13.88%) hypercholestremia, (2.77%) renal insufficiency, (2.77%) congestive heart failure and (5.55%) arrhythmia.

3.2 Angiographic features and procedural characteristics

In this study population, in most of patients it is found that lesions were more often occurred in the left anterior descending (LAD) coronary artery then in left circumflex and right coronary arteries (RCA) and all the lesions were highly treated with Zotarolimus DES (58.33%) when compared to Everolimus DES (46.15%) then Sirolimus DES (44.64%) and the distribution of these lesions was comparable with each other in all the three groups as shown in Table 3.

Table 3. Angiographic and procedural characteristics

Angiographic and Procedural characteristics	Patients treated with Sirolimus DES (n=52)	Patients treated with Everolimus DES (n=46)	Patients treated with Zotarolimus DES (n=29)	*P*-value
ISR location as a unit				
LAD coronary artery	44.64 %	46.15 %	58.33 %	0.0075
Left circumflex	33.92 %	07.69 %	33.33 %	0.1154
Right coronary artery	26.78 %	42.30 %	22.22 %	0.0708
Others	0	07.69 %	08.33 %	16.02
No. of Stent as a unit				
Patient with One DES	87.05 %	88.46 %	94.44 %	0.006
Patient with Two DES	12.05 %	11.54 %	05.55 %	0.0453

3.2.1 Route of Stent intervention in the study population

The route by which these stents were introduced in to the coronary artery was analysed and categorized into two major routes i) through right radial artery route and ii) through right femoral artery route but it is found that right femoral artery route was mostly preferred in all cases in all the three groups.

3.2.2 Patients treated with different number of DES

Patients treated with both one DES and two DES were included in this study, out of 127 cases, (94.44%) of patients implanted with single and (5.55%) of patients stented with double Zotarolimus DES which is found to be highly significant when compared to patients

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implanted with (88.46%) single and (11.54%) double Everolimus DES followed by patients stented with (57.5%) single and (12.5%) double Sirolimus DES.

3.3 CAD patients and medications

3.3.1 Commonly prescribed medications in CAD patients

Medications such as HMG-CoA reductase inhibitors (86.3%), aspirin (75.2%), proton pump inhibitors (60.7%), platelet P2Y12 inhibitors (47.6%) and ACE inhibitors (44.8%) are more commonly prescribed medications but GP IIb/IIIa receptor inhibitors (4.9%), aldosterone antagonists (2.1%) and morphine sulfate (1.9%) are found to be less commonly prescribed medications in CAD patients before and after they subject to PCI, other commonly prescribed medications also shown in the Fig. 1.

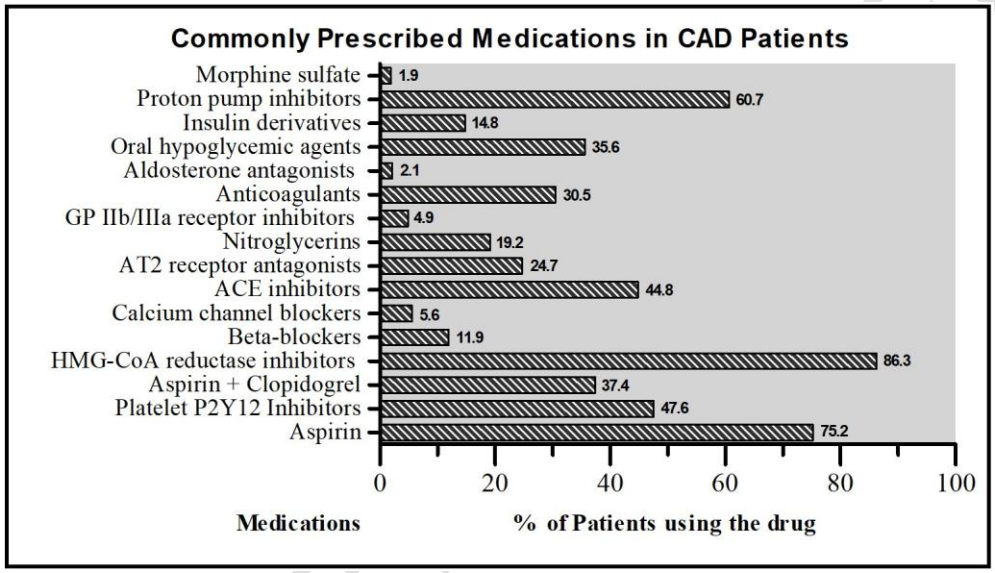

Fig. 1. Commonly prescribed medications in CAD patients

3.3.2 Most commonly prescribed drugs in CAD patients before and after PCI

In all the three groups most commonly prescribed drugs are aspirin, atorvastatin, clopidogrel, pantoprazole, nicorandil, alprazolam, ramipril, telmisartan, glyceryl trinitrate and isosorbide dinitrate. Among all drugs it is found that aspirin is more prevalent in patients with Sirolimus DES (94.64%) and Everolimus DES (80.76%), but in patients treated with Zotarolimus DES atorvastatin (100%) is more prevalent which is found to be highest then Sirolimus DES (87.50%) and Everolimus DES (73.07%) next to that clopidogrel was highly prescribed, it is found that aspirin, atorvastatin and clopidogrel are the three most commonly prescribed drugs in all the three study groups at least two months before they considered as suitable candidate for PCI, and the patients recommended to continue the same drugs after the completion of PCI procedures with or without little dose adjustments as shown in Table 4.

Table 4. Most commonly prescribed drugs in CAD patients before and after PCI

Drugs	Patients treated with Sirolimus DES (n=52)	Patients treated with Everolimus DES (n=46)	Patients treated with Zotarolimus DES (n=29)	*P*-value

Aspirin	94.64 %	80.76 %	83.33 %	0.0024
Atorvastatin	87.50 %	73.07 %	100 %	0.0079
Clopidogrel	91.05 %	69.23 %	80.55 %	0.0061

3.4 Drug-Drug Eluting Stents Interactions (DDESIs)

Out of 127 patients, (2.54%) of Everolimus DES treated patients and (1.69%) of Zotarolimus DES treated patients reported less significant DDESIs after they underwent PCI procedure but Sirolimus DES intervened patients (0.85%) does not reported for any significant DDESI as shown in Fig. 2. It is found that the observed drug interactions are mostly occurred in elderly patients particularly those suffering with chronic non-curable illness like hypertension, diabetes mellitus or both, variations from person to person were also seen this is may be due to several factors like age, allergies, body mass index, diseases, drug dosage, genes, gender, physiology and lifestyle, but serious results of drug interactions and its outcomes like death, disability, permanent impairment of organs, congenital anomaly, life-threatening and hospitalization were not observed in any patients.

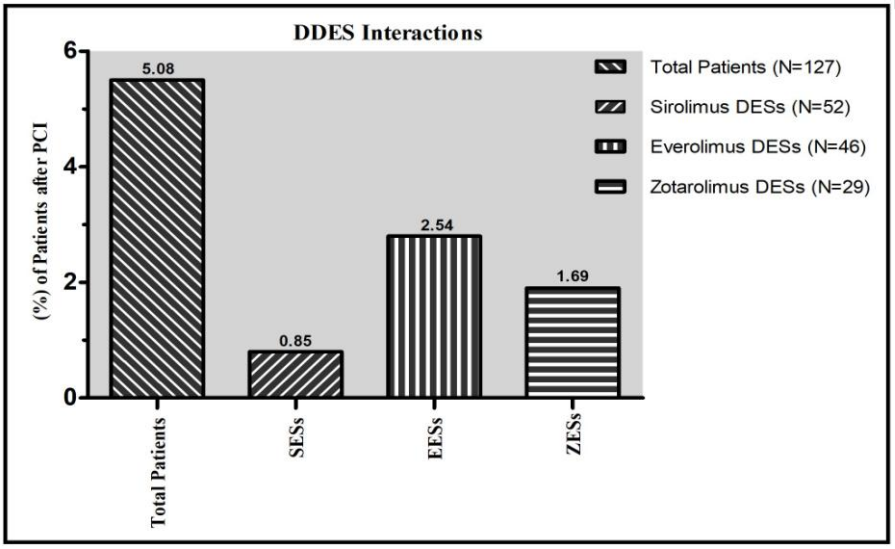

Fig. 2. Drug-drug eluting stents interactions (DDESIs)

4. DISCUSSION

All the three groups are well matched, males are found to be more in all groups, the incidence of CAD are mostly occurring in the age group of 51-60 years old. Among the study population patients without the history of CAD after PCI were found more, smokers and alcoholics were more prevalent in Sirolimus DES, higher proportion of the patients with Sirolimus DES had multi vessel coronary disease but patients with Zotarolimus DES had both single vessel disease and multi vessel coronary disease. The ASMI had higher prevalence in patients with Sirolimus DES but AWMI had higher prevalence in patient with Everolimus DES, also IPMI had greater prevalence in patient with Sirolimus DES before subject to PCI. Higher proportion of all the three groups had stable angina, diabetes mellitus, hypertension but arrhythmia was more prevalent only in Everolimus DES. While comparing angiographic and procedural characteristics few significant differences exist between treatment groups with respect to lesion characteristics. Lesions were mostly located in the LAD, left circumflex and RCA and significantly comparable with each other in all the three

groups but lesions were found to be more often occurred in the LAD coronary artery then other arteries. At the same time all the lesions were effectively treated with Sirolimus, Everolimus and Zotarolimus DES respectively. Right femoral route was mostly preferred in all the three groups to introduce DES into the body and single stent was mostly used in all groups then multiple stents.

Based on the study carried out, aspirin, atorvastatin and clopidogrel are the three most commonly prescribed drugs to maximize benefits and reduce the other complications in patients those underwent PCI. Aspirin is more prevalent in patients with Sirolimus and Everolimus DES but in case of Zotarolimus DES implanted patients atorvastatin was more prevalent. Aspirin is widely used anti-platelet agent in CAD patients; it is effective, safe and inexpensive and is recommended for most of patients undergoing PCI. Aspirin produces beneficial action with intervened DES without increasing the risk of bleeding there by patients will survive more. Clopidogrel has been shown to reduce the rates of cardiac events. Atorvastatin reduces thrombin generation after PCI, these three drugs are considered to be highly necessary for the maintenance of normal cardiac function after angioplasty.

CAD patients with mild to moderate disease severity at initial and considered as not suitable for PCI immediately but prescribed for their major complications with medications like anti-hypertensive drugs, anti-hyperlipidemic drugs, anti-coagulants, vasodilators and oral hypoglycaemic agents either alone or in combination at least one month before they subject to PCI and not reported for any DDI between drugs prescribed before PCI with DES and advised to continue the same medications with or without optimal dose titration after PCI with DES is the important inclusion criteria for the selection of the patients for this study, as well as all the identified drug interactions in DES implanted CAD patients are reported only after the PCI. Therefore, the possibility of any DDI is less and all the determined drug interactions are considered to be DDESIs.

Due to this strong evidence of DDESIs it may be included in the classification of drug interactions. Therefore, I have derived the definition for the new medical term Drug-drug eluting stent interaction and it is defined as “interaction between the drug prescribed and drug which is coated on the stent during elution after percutaneous coronary intervention leads to alternations in pharmacokinetic and/ or pharmacodynamics actions of one drug produced by another drug”. The term Drug-Drug Eluting Stent Interaction hereafter will be abbreviated as DDESI and this acronym may be included in the medical terminology and used in medical dictionary of current advanced modern medical world, also I have classified the different categories of DDESI and its directions are given in Table 5.

Table 5. Different Categories of Drug-drug eluting stent interaction

DDESI Categories	Directions
Minor	Interaction is Mild or Non-significant (Monitoring may be required)
Major	Potential for Moderate or Significant interaction (Monitoring is required)
Serious	Potential for Severe interaction (Regular monitoring is required or alternate medication may be prescribed)
Contraindicated	High risk for Very severe or Dangerous interaction (Never use this combination of drugs)

The DDESI were analysed to monitor the effect of drugs in patients intervened with different DES. It is found that DES along with prescribed medications does not associated with any

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major DDESI like bleeding, increased or decreased blood concentration, stent thrombosis, restenosis, cardiovascular related death and other clinical manifestations. Among all groups, patients treated with Sirolimus DES does not showed any significant DDESI but patients treated with Everolimus and Zotarolimus DES reported less significant DDESI. Therefore, according to the results obtained Sirolimus DES was considered as more superior due to its less affinity towards the commonly co-prescribed medications particularly aspirin, atorvastatin and clopidogrel compared to Everolimus and Zotarolimus DES in South Indian CAD patients after they underwent PCI according to the monitoring parameters studied.

5. CONCLUSION

It is observed that Sirolimus DES does not produce any serious DDESI with prescribed medications according to the available first one year follow-up records of the patients obtained from the study centres, but few patients those stented with Everolimus and Zotarolimus DES reported chest pain and increased blood flow during the course of medications with optimal dose, according to the available resources it might be a suspected interaction between atorvastatin and Zotarolimus as well as Everolimus because all statins will increase the level or effect of immunosuppressant by P-glycoprotein (MDR1) efflux transporter mechanism. Everolimus may also increase the serum concentration of CYP3A4 substrates which have high risk with inhibitors but advanced screening techniques and molecular level studies are recommended to explore the exact molecular mechanisms behind these DDESI.

Although, the observed DDESI are considered to be less significant and falls in minor DDESI category, however these DDESI can be managed by avoiding combination drug therapy, adjusting the dose of main drug, adjusting the time of intake of two drugs, monitoring the combination therapy or modify the prescription with alternate drug and by educating the patients about potential DDESIs. The data derived from this study as well as total evidence available up to date does not support the impact of any clinically significant pharmacokinetic and/ or pharmacodynamic major DDESI between the drugs prescribed such as aspirin, atorvastatin, clopidogrel and Sirolimus DES. Therefore, it is concluded that Sirolimus DES was found to be more suitable and safe when compared to Everolimus and Zotarolimus DES in CAD patients those initially considered as not suitable for PCI but prescribed with medications include aspirin, atorvastatin and clopidogrel to minimize the disease outcomes later recommended for PCI according to the study carried out.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Author hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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DEFINITIONS, ACRONYMS, ABBREVIATIONS

DDESI: Drug-Drug eluting stent interaction.

DDESIs: Drug-Drug eluting stents interactions.

Drug-Drug eluting stent interaction: It is defined as “interaction between the drug prescribed and drug which is coated on the stent during elution after percutaneous coronary intervention leads to alternations in pharmacokinetic and/or pharmacodynamic actions of one drug produced by another drug”.

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