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Original Article

The impact of generic form of Clopidogrel on cardiovascular events in patients with coronary artery stent: results of the OPCES study

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Abstract

BACKGROUND: To compare the early and late cardiovascular events as well as side effects of Osvix, a generic form of Clopidogrel versus Plavix regimens in patients with chronic stable angina, undergoing bare metal stent (BMS) or drug eluting stent (DES) placement, this study was carried out.

METHODS: A total of 442 patients with chronic stable angina who were scheduled for elective percutaneous coronary intervention (PCI) were included in a randomized, double blind, multi-centric clinical trial being performed in 6 distinct university hospitals in 5 cities of Iran from March 2007 to November 2009. Baseline, demographic and history of risk factors were recorded using the patients' medical charts. Stenting procedure was performed via transfemoral approach using low osmolar contrast agents. Patients underwent BMS or DES placements based on the physician selection and were randomly assigned to Osvix or Plavix groups. Patients were followed by telephone in 0 and 6 months intervals regarding the major adverse cardiovascular events (MACE) including death, myocardial infarction, in-stent thrombosis, stroke, target lesion revascularization, and target vascular revascularization. Angina episodes, bleeding, liver enzymes, neutrophils and platelets count were also assessed in these intervals.

RESULTS: There was not any significant difference between these two groups regarding the baseline characteristics. In the DES group, the 6-month mortality rate and the incidence of MACE in Osvix and Plavix groups were 0.9% and 1.9% ($p = 0.61$) and 1.8% and 4.9% ($p = 0.26$), respectively. During the follow up period after DES or BMS placement, there wasn't any significant difference regarding neutrophil and platelet counts or liver enzymes between study groups.

CONCLUSIONS: Using Osvix and Plavix are followed by similar major cardiovascular events and side-effect profile in patients undergoing PCI.

KEYWORDS: Cardiovascular Events, Coronary Artery Stents, OPCES.

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Intracoronary stenting is widely used to treat patients with coronary artery disease.[1,2] Current stents are thrombogenic, resulting in temporary or permanent risk of in-stent thrombosis.[2,3]

The short and long-term benefits of double anti-platelet therapy with aspirin and clopidogrel (a thienopyridine derivations that blocks platelet activation by selective and irreversible inhibiting ADP (P2Y12) receptor) have been established for patients with acute coronary syndromes and those undergoing percutaneous coronary intervention (PCI) with stents.[4-6]

This combination of drug therapy showed a significant absolute risk reduction in death, myocardial infarction and stroke in long term follow up of patients undergoing PCI.[7]

The prescription of clopidogrel seems to be increasing in Iran as a consequence of increasing prevalence of coronary heart disease (CHD) and stenting in Iran.[8] Premature discontinuation of thienopyridine therapy has been associated with a marked increase in the risk of stent thrombosis.[9-10] The American Heart Association, and the American College of Cardiology had stressed the importance of at least 12 months of dual antiplatelet therapy after drug eluting stents (DES) implantation, along with educating the patient and healthcare providers about the hazards of premature discontinuation.[11] The generic form of clopidogrel named "Osvix" has been produced by Osveh Pharmaceutical Company, an ex-Iran Merck Company. Osvix cost is 80% less than Plavix t at the time of study. Thus, its local production may lead to increase patient's compliance and saving costs.

Osvix in vivo and in vitro studies has been reported before.[12] Because of the same dissolution speed and realizing rate of Osvix, it received the Iranian Food and Drug Administration (FDA) approval for the treatment of patients undergoing PCI and stent implantation. This study was designed to compare the early and late major cardiovascular events and drug safety in patients who were treated with Osvix or Plavix after PCI with Bare Metal Stents (BMS) or DES placement as well as evaluation of changes in platelet and neutrophils counts and liver enzymes and major bleeding complication.

Methods

Study Population

OPCES is a bioequivalent, randomized, double blind, multi-centric clinical trial enrolling six centers in five cities of Iran. From March 2007 to November 2009, 442 patients were included in this study. Those centers that have the facility and requirements for stenting and also the tendency for research collaboration are included in this trial. The stent type selection was based on the cardiologist opinion. Patients were randomized at least 12 hours before planned PCI to receive a 300 mg loading dose of Plavix or Osvix (1:1) and followed by 75 mg/day for 30 days in BMS and 6 months in DES groups. All patients received daily aspirin therapy before PCI and were continued until one and six months in BMS and DES groups, respectively. External evaluation committee assessed the procedure of the study every six months.

The study was approved by the ethical committee of the Isfahan Cardiovascular Research Center, a WHO collaborating center and was registered in the Iranian registration clinical trial (IRCT138712111723N1). All patients provided written informed consents for participation.

Study participants

Patients were eligible for enrollment if they were ≥ 18 years of age, had chronic stable angina and selected for stenting in a coronary artery with diameter ≥ 2.5mm. Exclusion criteria included previous treatment with a clopidogrel or warfarin for any reason, history of allergy or any contraindication to clopidogrel, high-risk patients (e.g., severe left ventricular dysfunction with ejection fraction less than 30%, stenting of saphenous vein grafts or internal mammary artery), total vessel occlusion without myocardial viability in DES and large thrombus in angiography before PCI.

Study Protocol

All the patients underwent complete history and physical examination. Baseline and demo-

graphic information including sex, age, indications for stenting, morphology, length, and diameter of stent, previous cardiac interventions, and left ventricular ejection fraction based on echocardiography reports were recorded according to the patients' medical charts. History of smoking, hypercholesterolemia, hypertriglyceridemia, high blood pressure, diabetes mellitus and family history of premature coronary heart disease (CAD) in first relatives were also recorded. All the patients underwent electrocardiography and echocardiography before the intervention. Blood samples were drawn from each patient before the intervention to measure the platelet and neutrophil counts as well as liver enzymes. Patients who were selected for stenting were randomly assigned to receive a 300 mg loading dose of Plavix (n = 221) or Osvix (n = 221) (1:1 randomization ratio) 12 hours before the procedure followed by 75 mg/day for 30 days in BMS and 6 months in DES groups. All patients received daily aspirin therapy three days before PCI and were continued until one and six months in BMS and DES groups, respectively. External evaluation committee assessed the procedure of the study every six months. The laboratory assessment was performed for all patients before the study, then one month after PCI for patients with BMS and one and six months after PCI for patients with DES. Follow up to assess clinical end points including MACE were done. Blood samples were taken in one month and six months in BMS and DES groups to measure platelets, neutrophils, alanine aminotransferase (ALT), and aspartate aminotransferase (AST).

Angioplasty procedure

Coronary angiography was performed according to standard techniques. Unfractionated heparin, 100 unit/kg was administered immediately before the procedure. PCI was considered successful when a residual diameter stenosis was less than 20% with thrombolysis in myocardial infarction (TIMI) flow less than III. TIMI III means contrast material flows briskly into and clears rapidly from the distal segment or good distal runoff.[13]

TIMI grade 3 flows were obtained. Patient's angiographic films were reviewed by two independent cardiologists to collect appropriate data. Coronary angiography lesions were classified into three types. Type A included lesions with the following characteristics: discrete (<10 mm length), concentric, readily accessible, non-angulated segment, smooth contour, little or no calcium, less than totally occlusive, not ostial in location, no major side branch involvement, and absence of thrombus. Type B included lesions of tubular (10-20 mm length), eccentric, moderate tortuosity of proximal segment ≥ 45, irregular contour, moderate to heavy circulation, total occlusion, ostial location, bifurcation lesion requiring double guide wire, and some thrombus present. Type C involved diffuse (> 20 mm length), excessive tortuosity of proximal segment, extremely angulated segments (≥ 90), with total occlusion >3 months old, inability to protect major side braches, and degenerated side branches with friable lesions.

Study end points

MACE which is the primary endpoint of this study included death, Q wave and non-Q wave MI, stroke, target lesion revascularization (TLR), target vascular revascularization (TVR), in-stent thrombosis. Cardiovascular death was considered as any death with a cardiovascular cause and included those deaths following a cardiovascular procedure (for example, PCI), cardiac arrest, MI, pulmonary embolus, stroke, hemorrhage or death due to unknown cause. Non- cardiovascular death was defined as death due to a clearly documented non-cardiovascular cause (e.g., trauma, infection, malignancy). MI was defined by symptoms suggestive of infarction, electrocardiographic changes, and positive cardiac enzymes. In-stent thrombosis was classified in three groups; definite: the presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion; probable: unexplained deaths within 30 days after procedure or acute myocardial infarction

involving the target-vessel territory without angiographic confirmation; possible: all unexplained deaths occurring at least 30 days after the procedure. Stroke defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours. Secondary endpoints included changes of platelet or neutrophil number or liver enzymes, hospitalization for angina, and major bleeding.

All primary and secondary end points were assessed during hospitalization and after 30 days in BMS and six months in DES group. The academic research consortium definitions were used for stent thrombosis.[14]

Statistical analysis

Results were reported as mean ± standard deviation (SD) for the quantitative variables and percentages for the categorical variables. The groups were compared using the chi-square test (or Fisher's exact test if required) for categorical variables and the t-test or Mann-Whitney U test for the continuous variables. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for windows.

Results

The total study population represents a group of 442 patients (mean age 59 ± 9.5 years) with stable angina pectoris in whom PCI was performed. Among them, 225 participants implanted BMS and the rest implanted DES. A total of 224 patients treated with Osvix (110 patients in BMS and 114 patients in DES) and 218 subjects were treated with plavix (115 patients in BMS and 103 patients in DES). The patient characteristics in the two groups are shown in Table 1. Except male to female ratio that was higher in the Osvix than the Plavix group, the two drug groups were comparable with respect to baseline characteristics, clinical data especially left ventricular ejection fraction, and medical history. There were significantly more frequent hypertensive patients in the Osvix than in the Plavix group (P <0.01), but no other significant differences were seen in patient characteristics between the two groups (Table 2). Besides, in both groups with DES and BMS, there was no significant difference in the type of coronary lesion, direct stenting, stent length and stent diameter (table 3).

Table 1. Baseline characteristics and clinical data of all participants based on Plavix or Osvix use

	Total (n = 442)	Osvix (n = 224)	Plavix (n = 218)	P value
Men/Women	295 (66.7)	153 (68.3)	142 (65.1)	0.48
Age (year)	59.02 ± 9.56	58.88 ± 9.15	59.17 ± 9.99	0.75
Body mass index (kg/m^2)	26.59 ± 4.12	26.41 ± 3.91	26.78 ± 4.33	0.34
LVEF (%)				
> 50	284 (65.3)	147 (66.5)	137 (64.0)	
41-50	100 (23.0)	53 (24.0)	47 (22.0)	0.44
31-40	41 (9.4)	15 (6.8)	26 (12.1)	
PCI	32 (7.2)	15 (6.7)	17 (7.8)	0.65
CABG	1 (0.2)	0 (0.0)	1 (0.5)	0.49
Medical history				
Cigarette smoking †	79 (18.1)	42 (18.9)	37 (17.3)	0.89
Hypertension ‡	275 (64.4)	157 (71.7)	118 (56.7)	<0.01
Hyperlipidemia §	289 (70.0)	149 (72.3)	140 (67.6)	0.30
Diabetes ‖	106 (24.5)	51 (23.2)	55 (25.9)	0.51
Myocardial infarction ¶	237 (53.6)	116 (51.8)	121 (55.5)	0.43
Congestive heart failure #	6 (1.4)	3 (1.3)	3 (1.4)	0.99
Cerberovascular disease	8 (1.8)	4 (1.8)	4 (1.8)	0.99

Data are presented as mean ± SD or number (%) where applicable.

† Cigarette smoking: person smoking at least 1 cigarette (or cigar, pipe) per the last month.

‡Hypertension: Systolic blood pressure > 140 mmHg or diastolic > 90 mmHg or hypertensive drug

§Hyperlipidemia: LDL cholesterol ≥ 1.0 mg/dl, triglycerides ≥ 150 mg/dl and HDL ≤ 40 mg/dl or on treatment of hyperlipidemia

Table 2. Recorded characteristics and clinical data of all patients based on their stent type.

		Osvix (n = 224)	Plavix (n = 218)	P value
Female gender	DES*	71 (62.3)	71 (68.9)	0.30
	BMS†	82 (74.5)	71 (61.7)	0.04
Age (yr)	DES	59.89 ± 9.58	58.39 ± 10.00	0.26
	BMS	57.85 ± 8.59	59.88 ± 9.96	0.10
Body mass index (kg/m^2)	DES	26.69 ± 3.59	26.77 ± 3.76	0.89
	BMS	26.10 ± 3.92	26.80 ± 4.81	0.24
Previous intervention				
Percutaneous coronary intervention (%)	DES	9 (7.9)	9 (8.7)	0.82
	BMS	6 (5.5)	8 (7.0)	0.64
Coronary artery bypass graft	DES	0	0	-
	BMS	0 (0.0)	1 (0.9)	0.99
Left ventricular ejection fraction (%)				
> 50	DES	69 (61.6)	67 (66.3)	
	BMS	78(71.6)	70(61.9)	0.65
41-50	DES	32(28.6)	21(20.8)	
	BMS	21(19.3)	26(23.0)	
31-40	DES	9 (8.0)	10 (9.9)	
	BMS	6 (5.5)	16 (14.2)	0.13
< 30	DES	2 (1.8)	3 (3.0)	
	BMS	4 (3.7)	1 (0.9)	
Medical history				
Cigarette smoking‡	DES	15 (13.3)	13 (13.1)	0.79
	BMS	27 (24.8)	24 (20.9)	0.69
Hypertension§ (%)	DES	85 (77.3)	55 (54.5)	<0.01
	BMS	72 (66.1)	63 (58.9)	0.28
Hyperlipidemia‖	DES	83 (79.8)	63 (67.0)	0.04
	BMS	66 (64.7)	77 (68.1)	0.59
Diabetes ¶	DES	35 (30.7)	30 (30.3)	0.95
	BMS	16 (15.1)	25 (22.1)	0.18
Myocardial infarction	DES	63 (55.3)	55 (53.4)	0.78
	BMS	53 (48.2)	66 (57.4)	0.17
Congestive heart failure	DES	2 (1.8)	0 (0.0)	0.50
	BMS	1 (0.9)	3 (2.6)	0.62
Cerbrovascular disease	DES	2 (1.8)	2 (1.9)	0.99
	BMS	2 (1.8)	2 (1.7)	0.99

* DES: Drug eluting stent
†BMS: Bare metal stent
‡Cigarette smoking: Person smoking at least 1 cigarette (or cigar, pipe) in the last month.
§Hypertension: Systolic blood pressure > 140 mmHg or diastolic > 90 mmHg or on hypertensive drug
‖Hyperlipidemia: LDL cholesterol ≥ 1.0 mg/dl, triglycerides ≥ 150 mg/dl and HDL ≤ 40 mg/dl or on treatment of dyslipidemia

Table 3. Coronary angiography and stent characteristics of patients and drug type used

Angiography stent	Osvix (n = 224)	Plavix (n = 218)	P value
Drug eluted Stent†			
Diseased disease coronary (%)			
LAD	84 (80.0)	75 (75.8)	0.73
RCA	13 (12.4)	16 (16.2)	
LCX	8 (7.6)	8 (8.1)	
Type of lesion			
A	24 (23.1)	16 (16.3)	
B	54 (51.9)	44 (44.9)	0.09
C	26 (25.0)	38 (38.8)	
Direct stenting (%)	41 (39.4)	37 (37.8)	0.81
Stent length (mm)	25.90 ± 8.17	25.23 ± 8.33	0.57
Stent diameter (mm)	2.92 ± 0.29	2.98 ± 0.26	0.14
Bare metal stent MS‡			
Type of diseased coronary (%)†			
LAD	45 (45.0)	64 (58.7)	0.11
RCA	34 (34.0)	31 (28.4)	
LCX	21 (21.0)	14 (12.8)	
Type of lesion§			
A	65 (64.4)	60 (55.6)	0.42
B	31 (30.7)	42 (38.9)	
C	5 (5.0)	6 (5.6)	
Direct stenting (%)	61 (65.6)	67 (64.4)	0.86
Stent length (mm)	14.56 ± 3.94	15.02 ± 4.54	0.44
Stent diameter (mm)	3.17 ± 0.39	3.12 ± 0.37	0.31

Data are presented as mean ± SD or number (%) where applicable
† DES: Drug eluting stent
‡BMS: Bare metal stent
§Type of lesion:

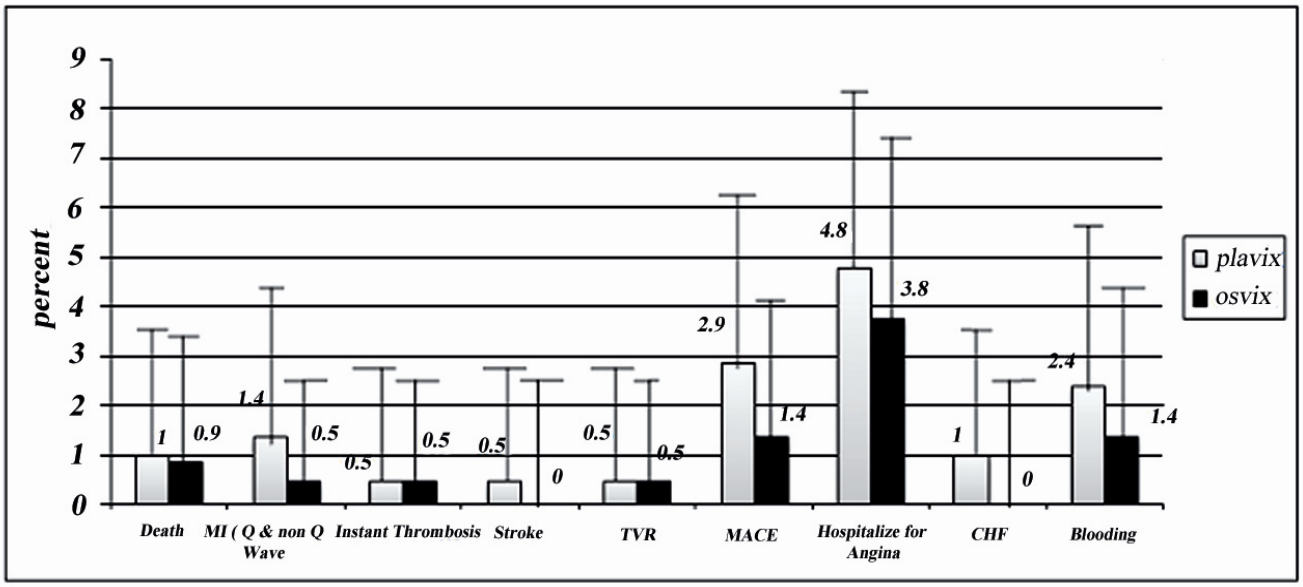


Figure 1. Frequency and 95% confidence intervals of events following Osvix or Plavix placement in bare-metal or drug eluting stents patients

Figure 1 shows the frequency and 95% confidence intervals of events such as death, instant thrombosis, MACE rate, and MI following Osvix or Plavix placement in Bare-metal or drug eluting stents patients.

There was no significant difference regarding MACE rate in patients treated with Osvix compared with Plavix (Figure 1). The study groups had the same frequency of MI, thrombosis, stroke and TVR (Figure 1). Regarding changes in laboratory variable, no significant changes were found concerning liver enzymes, platelet and neutrophil counts between the two drug regimens in both DES and BMS groups (Figures 2 and 3).

Discussion

OPCESS is the first randomized trial to compare the effect of a generic form of clopidogrel on MACE after coronary stenting in Iran. Increased platelet activity has been shown to increase cardiovascular complications in acute coronary syndrome (ACS), and subsequent to PCI.[15] Various studies have demonstrated that administration of antiplatelet drugs such as aspirin, ticlopidine and clopidogrel reduce short and long-term cardiovascular events in patients suffering ACS or undergoing PCI.[16] We studied the short and long-term cardiovascular complications, including death, myocardial infarction, stroke, TLR and TVR in patients treated with Osvix (300 mg bolus, and 75 mg/daily maintenance) or Plavix (300 mg bolus, and 75 mg/daily maintenance). Assessment of secondary endpoints such as angina, heart failure (HF),

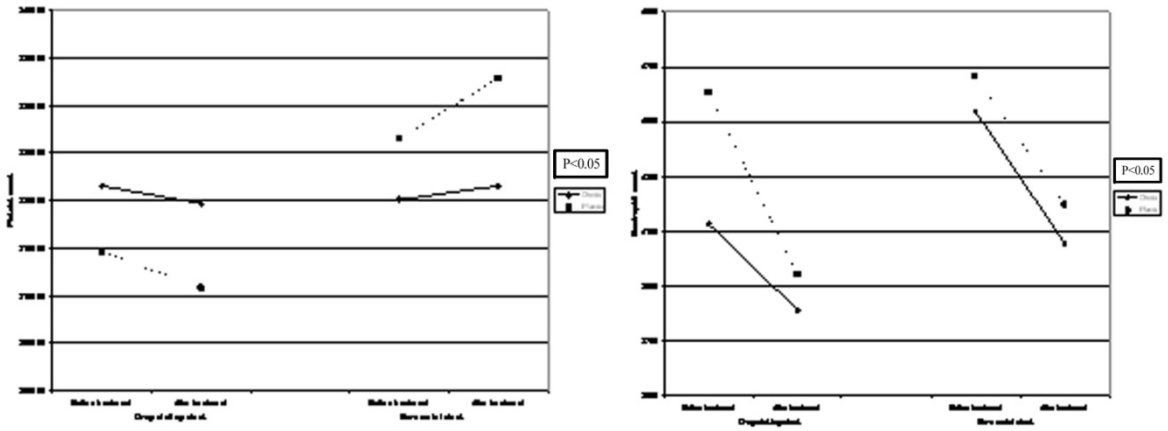


Figure 2. Changes of serum platelet and neutrophil counts following Osvix and Plavix regimens in patients who underwent bare-metal or drug eluting stenting

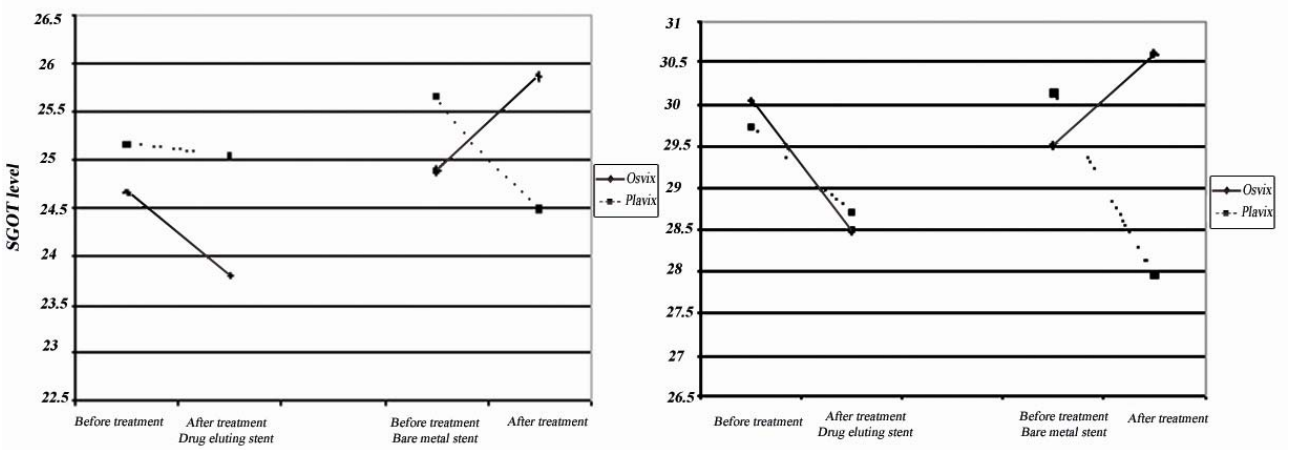
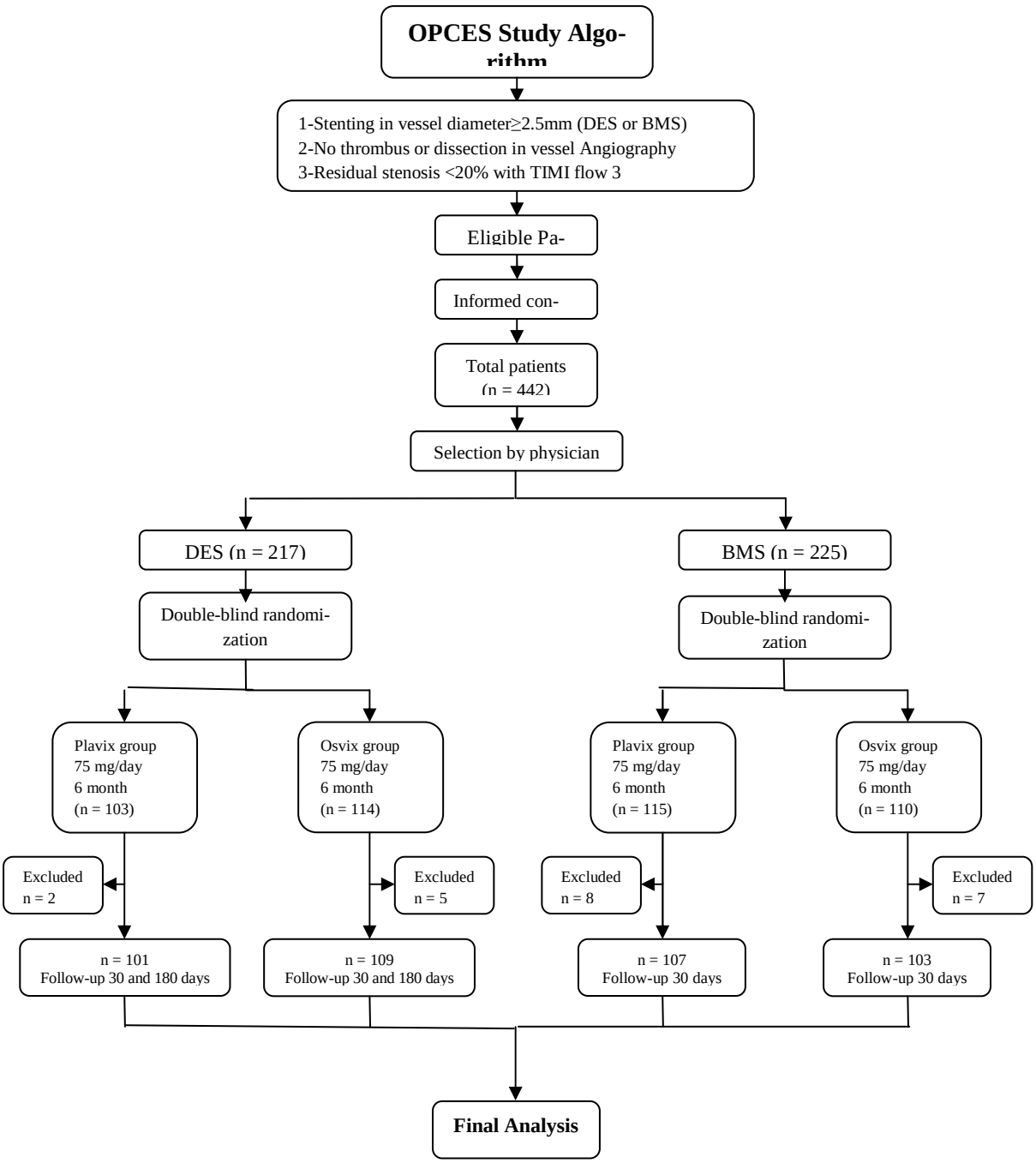


Figure 3. Changes of serum aspartate aminotransferase and alanine aminotransferase levels following Osvix and Plavix regimens in patients who underwent bare-metal or drug eluting stenting

major hemorrhagic episodes, and reduction of platelet or neutrophil counts and liver enzyme changes revealed no significant difference between the two treated groups. Reduced systolic performance and ageing are among important factors underlying MACE in these patients. However, the frequency distribution of age, sex and left ventricular systolic function were similar in Osvix and Plavix groups. Tavazzi showed that concomitant disease and CVD risk factors can increase MACE.[17] Whereas these risk factors were evenly distributed in the two groups in this randomized clinical trial; a higher frequency of hypertension in the Osvix group was seen ($p = 0.001$) (Table 2). Kang and colleagues demonstrated that hypertension does not affect short and long-term cardiovascular complications of PCI.[18] Patients in Osvix group showed nonsignificant lower MACE rate than the Plavix group ($p < 0.05$). Thus, it can be concluded that Osvix has at least similar CVD complications as Plavix. Alidoosti and colleagues showed that the type of vessel selected for PCI did not affect the short and long term complications of the procedure.[19] In our study, the frequency distribution according to the vessel elected for angioplasty was the same in both groups. Various studies have demonstrated an increase in short and long term post-angioplasty complications in patients with complex lesions: the worse the anatomy and morphology of the lesion, the more difficult the procedure and the poorer the outcomes.[20,21] In our study, the frequency distribution of the type of coronary lesion elected for angioplasty was not significantly different in the Osvix and Plavix groups. In separate studies, Singh and Pompa showed that the length and diameter of stents are directly, and inversely proportional to TLR.[22,23] In our study, the stent length and diameter, as well as angioplasty technique had similar distribution in both groups, although the rate of TVR was low in our study as shown by results. This may have been due to the short follow-up period (one month for non-pharmacological stents and six months for pharmacological stents). TVR was seen in two of our patients who underwent CABG a day after unsuccessful angioplasty. Based on comparison of frequency distribution of patients according to MACE in the preceding one and six months for BMS and DES stents, respectively, the incidence of MACE including death was similar in the Osvix and Plavix groups. The incidence of MI was 0.4% in the Osvix and 1.4% in the Plavix groups with no significant difference. In-stent thrombosis occurred in 0.4% of Osvix and 0.5% of Plavix groups. We found the same results regarding stroke, TVR and overall MACE. No significant difference was observed between the two groups in regard to episodes of angina, HF and bleeding which suggest no inferiority of Osvix compared to Plavix. Although the occurrence of events was not significantly different in the two groups, the distribution of findings revealed an up-sloping trend in complications in the Plavix group. Thus, it may be concluded that Osvix was not associated with more complications than Plavix in patients who underwent PCI. Safety of antiplatelet drugs is of great importance and must be assessed against possible side-effects. Gurbel demonstrated that including clopidogrel in the therapy of unstable angina patients, significantly reduced mortality from MACE. Although clopidogrel may significantly increase the risk of bleeding, its benefits have been shown to outweigh the risks.[24] Yusuf and colleagues showed that adding clopidogrel to aspirin reduced MACE but increased the risk of bleeding.[25] However, in our study, the rate of major bleeding in Osvix and Plavix groups who were treated with aspirin too, were not significant. During our follow-up period, mean platelet counts did not change significantly in either groups (Plavix, $p = 0.80$ and Osvix, $p = 0.99$) or between them ($p = 0.87$). However, neutrophil counts were reduced significantly in the two groups ($p < 0.001$), but the trend of change in counts was not significantly different between the two groups. The above findings showed that adverse hematological effects (thrombopenia or neutropenia) did not increase in the Osvix group as compared to the Plavix group.

We noted some limitations to our study, the most important of which was the small study population. However, the power of the study was enough to achieve the main and secondary objectives of the study. We recommend future studies to be carried out with larger study population. The other important limitation was that the angiographies were performed by different cardiologists in different centers. Thus, interobserver variability was inevitable.

In conclusion, our data demonstrated the safety of Osvix in improving clinical outcome compared to Plavix after coronary stenting in BMS or DES using patients. The frequency of MACE, non-cardiac events or adverse hematological changes did not increase with Osvix compared to Plavix patients which suggest it's safety. However, due to more cost advantages of Osvix regimen over Plavix, administration of Osvix among Iranian patients is preferable.



Conflict of Interests

This study was partly supported by grants from the Osveh Pharmaceutical Company, an ex-Iran Merck Company, Tehran, Iran. No potential conflict of interest relevant to this article was reported.

Authors' Contributions

AKH designed the study and drafted this manuscript, MP designed the study, MO, GKM, MN, AKH, MH, FR, SHS, and JK Carried the study, MGH drafted the manuscript and tables, HZ helped in designing the study and carried the study, AAT helped in designing the study, BS data analysis and drafted the tables, MGH helped in designing the study, MRKH and FN helped in statistical analysis, EKH and MJ helped in Data gathering, and NS helped in designing the study, revising the manuscript procedures, and drafting the manuscript. All authors read and approved the final manuscript.

References

1. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996; 348(9038): 1329-39.
2. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000; 102(6): 624-9.
3. Galla JM, Lincoff AM. The role of clopidogrel in the management of ischemic heart disease. Curr Opin Cardiol 2007; 22(4): 273-9.
4. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998; 339(23): 1665-71.
5. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ 1994; 308(6921): 81-106.
6. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358(9281): 527-33.
7. Steinhubl SR, Berger PB, Mann JT, III, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 288(19): 2411-20.
8. Sarraf-Zadegan N, Sayed-Tabatabaei FA, Bashardoost N, Maleki A, Totonchi M, Habibi HR, et al. The prevalence of coronary artery disease in an urban population in Isfahan, Iran. Acta Cardiol 1999; 54(5): 257-63.
9. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005; 293(17): 2126-30.
10. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA 2007; 297(2): 159-68.
11. Grines CL, Bonow RO, Casey DE, Jr., Gardner TJ, Lockhart PB, Moliterno DJ, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Catheter Cardiovasc Interv 2007; 69(3): 334-40.
12. Souri E, Jalalizadeh H, Kebriaee-Zadeh A, Shekarchi M, Dalvandi A. Validated HPLC method for determination of carboxylic acid metabolite of clopidogrel in human plasma and its application to a pharmacokinetic study. Biomed Chromatogr 2006; 20(12): 1309-14.
13. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med 1985; 312(14): 932-6.
14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115(17): 2344-51.

15. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006; 354(16): 1706-17.
16. Tavazzi L. Clinical epidemiology of acute myocardial infarction. Am Heart J 1999; 138(2 Pt 2): S48-54.
17. Kang DG, Jeong MH, Ahn Y, Chae SC, Hur SH, Hong TJ, et al. Clinical effects of hypertension on the mortality of patients with acute myocardial infarction. J Korean Med Sci 2009; 24(5): 800-6.
18. Alidoosti M, Salarifar M, Kassaian SE, Zeinali AH, Dehkordi MR, Fathollahi MS. In-hospital and late clinical outcomes of direct stenting strategy versus stenting after predilatation for the treatment of coronary artery lesions. Indian Heart J 2008; 60(4): 318-24.
19. Stone GW, Aronow HD. Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy. Mayo Clin Proc 2006; 81(5): 641-52.
20. Singh M, Rihal CS, Lennon RJ, Garratt KN, Holmes DR, Jr. Comparison of Mayo Clinic risk score and American College of Cardiology/American Heart Association lesion classification in the prediction of adverse cardiovascular outcome following percutaneous coronary interventions. J Am Coll Cardiol 2004; 44(2): 357-61.
21. Popma JJ, Leon MB, Moses JW, Holmes DR, Jr., Cox N, Fitzpatrick M, et al. Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. Circulation 2004; 110(25): 3773-80.
22. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999; 99(18): 2364-6.
23. Gurbel PA, Kandzari DE. Stent thrombosis associated with first-generation drug-eluting stents: issues with antiplatelet therapy. Neth Heart J 2007; 15(4): 148-50.
24. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345(7): 494-502.