

Impact of early (3 months) dual antiplatelet treatment interruption prior to renal transplantation in patients with second-generation DES on perioperative stent thrombosis and MACEs

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ABSTRACT

Objective: Early cessation of dual antiplatelet therapy (DAPT) is related to stent thrombosis (ST). The use of second-generation everolimus- and zotarolimus-eluting stents is associated with low restenosis rates and short duration of clopidogrel usage. Non-cardiac surgery in recently stent-implanted patients is associated with major adverse cardiac events (MACEs). Chronic renal failure patients awaiting renal transplantation may also undergo coronary stent implantation prior to surgery. Here we aimed to investigate the safety of early (3 months) DAPT interruption in second-generation drug-eluting stent (DES)-implanted renal transplant recipients.

Methods: In total, 106 previously stent-implanted chronic renal failure patients who underwent renal transplantation were retrospectively enrolled. Three groups were formed according to stent type and the duration of DAPT: early-interruption (3 months from DES implantation), late-interruption (3–12 months from DES implantation), and bare-metal stent (BMS; at least 1 month from BMS implantation) groups.

Results: Comparison among BMS, DES-early and DES-late groups indicated no difference in ST, myocardial infarction, death, and MACEs. In addition, no difference was observed in ST ($p=0.998$), myocardial infarction ($p=0.998$), death ($p=0.999$), and MACEs ($p=0.998$) between DES-early and DES-late groups.

Conclusion: Early (3 months) interruption of antiplatelet treatment with second-generation stents before renal transplantation seems to be safe and does not lead to increase in the occurrence of ST and MACEs. (*Anatol J Cardiol* 2017; 18: 391-6)

Keywords: percutaneous coronary intervention; drug-eluting stents; non-cardiac surgery; stent thrombosis; chronic renal failure

Introduction

Clopidogrel together with acetylsalicylic acid is the standard combination used in dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) for preventing sub-acute stent thrombosis (ST) (1). Drug-eluting stents (DESs) have mostly replaced bare-metal stents (BMSs) because they are associated with lower restenosis rates, despite there being safety concerns about late ST risk (2, 3). It has been proposed that delayed endothelialization associated with DES implantation can extend thrombosis risk. Discontinuation of thienopyridine therapy has been reported as the major determinant of ST (4). Sirolimus- and paclitaxel-eluting stents as the first-generation DESs were replaced by second-generation DESs because of their lower ST and restenosis rates (5). The superiority of everolimus- and zotarolimus-eluting stents has been shown in previous trials (6, 7).

Recently, minimum duration of DAPT in patients with stable

coronary artery disease treated with DES has decreased from 12 to 6 months (8,9). Early discontinuation of clopidogrel, even 3 months of DAPT was found to be non-inferior to 12 months, without significantly increasing ST risk (10). Non-cardiac surgery is often required in patients taking DAPT. It is still a challenge to balance between ischemia and bleeding risks (11). Approximately, 20%–23% of these patients undergo non-cardiac surgery within 2 years of procedure. The time from coronary stenting to surgery is associated with MACEs, mainly in cases in which surgery is performed in the first 6 months after coronary procedure (12). ST has a worse prognosis than de novo coronary obstruction. Discontinuation of DAPT is a strong predictor of ST (13). In this respect, non-cardiac surgery after second-generation DES implantation is an issue that needs to be investigated.

Chronic renal failure (CRF) and end-stage renal disease (ESRD) patients requiring hemodialysis are associated with increased cardiovascular mortality. ESRD patients with ischemic

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Table 1. Baseline features of the study group

Clinical features	Stent groups			P
	BMS (n=24)	DES-Early (n=41)	DES-Late (n=41)	
	n (%)	n (%)	n (%)	
Age, years	58.17±5.4	54.44±6.6	56.63±6.9	² 0.07
Gender, male	18 (75%)	27 (65.9%)	27(65.9%)	¹ 0.700
Diabetes mellitus	11 (45.8%)	16 (39%)	16 (39%)	¹ 0.865
Hypertension	21 (87.5%)	21 (87.5%)	31 (75.6%)	¹ 0.509
Hyperlipidemia	18 (75%)	28 (68.3%)	33 (80.5%)	¹ 0.447
Current smoking	8 (33.3%)	12(29.3%)	13 (31.7%)	¹ 0.938
Prior PCI	6 (25%)	6 (25%)	11 (26.8%)	¹ 0.875
Prior CABG	4 (%16.7)	3 (7.3%)	2 (4.9%)	¹ 0.243
LV EF (%), mean±SD	56.33±8.46	59.66±6.36	58.49±5.68	² 0.155
Clinical presentation	0 (%0)	2 (4.9%)	4 (9.8%)	¹ 0.282
NSTEMI	15 (62.5%)	30 (73.2%)	29 (70.7%)	
SAP	9 (37.5%)	9 (2%)	8 (19.5%)	
USAP				

¹ Pearson chi-square; ²One Way ANOVA
NSTEMI - acute coronary syndrome (ACS) without ST-segment elevation myocardial infarction; SAP - stable angina pectoris; SD - standard deviation; USAP - unstable angina pectoris

heart disease treated with PCI may still benefit from renal transplantation (14). Here we aimed to evaluate the safety of early (3 months) DAPT interruption in preoperative ESRD patients undergoing transplantation proposed to be at high risk. This study mainly aimed to determine the effect of early interruption of DAPT on the rates of ST and MACEs.

Methods

The study group included patients who underwent PCI with DESs or BMSs for stable angina pectoris or unstable angina pectoris and acute coronary syndrome without ST-segment elevation myocardial infarction before renal transplantation from 2010 to 2016 at our institution. The patients who received ticagrelor or prasugrel were excluded to assess only early interruption of DAPT comprising aspirin and clopidogrel. Other exclusion features were ST-segment elevation myocardial infarction and first-generation DESs. The study was approved by the local ethics committee. Three groups were formed according to stent type and DAPT time before surgery. The second-generation DES group comprised patients who received everolimus- (Xience, Abbott Vascular, Santa Clara, California and Promus, Boston Scientific, Natick, Massachusetts) and zotarolimus-eluting stents (Resolute, Medtronic, Santa Rosa, California). The BMS group comprised patients who received Integrity (Medtronic Inc.) and Gazelle (Boston Scientific) stents. Within each stent group, pa-

tients were categorized based on their timing of DAPT interruption: early-interruption (3 months from DES implantation), late-interruption (3–12 months from DES implantation), and BMS (at least 1 month from BMS implantation) groups.

Clinical information and data on coronary angiography, stent procedures, and postoperative follow-up of the patients were obtained retrospectively. The data acquired from hospital files were evaluated by an independent investigator who was not related to the study purpose. All patients were on routine hemodialysis for CRF and received a standard regimen of 100-mg aspirin and 600-mg clopidogrel prior to PCI and 100-mg aspirin/day and 75-mg clopidogrel/day thereafter. Stent type and selection were determined by the operator. Troponin levels in CRF patients were evaluated consecutively. Increases in troponin levels were interpreted as myocardial infarction. DAPT, comprising aspirin and clopidogrel, was interrupted 5–7 days before renal transplantation. Low-molecular weight heparin was implemented during this period, even for anticoagulation needed for planned hemodialysis. The patients did not receive perioperative medication with steroids. All patients underwent renal transplantation from living donors. Patient selection for renal transplantation was largely dependent on the renal transplantation team. In this regard, some patients who underwent PCI with second-generation DESs 3 months prior to surgery were prepared for renal transplantation because of available living donors and evidence-based safety of second-generation DES. After the surgery, DAPT was re-initiated in cooperation with surgeons mostly 5 days after

Table 2. Comparison of study groups according to angiographic and procedural features

Angiographic and procedural features		Stent groups			P
		BMS	DES-Early	DES-Late	
		(n=24) n (%)	(n=41) n (%)	(n=41) n (%)	
Clopidogrel usage duration, month,	Median (25%-75%)	1 (1-2)	3(3-3)	9 (7-12)	¹ 0.001**
Number of stent per patient		15 (62.5%)	23 (56.1%)	27 (65.9%)	² 0.879
	1	7 (29.2%)	14 (34.1%)	12 (29.3%)	
	2	2 (8.3%)	4 (9.8%)	2 (4.9%)	
Number of diseased vessel per patient		14 (58.3%)	25 (61%)	28 (68.3%)	² 0.851
	1	8 (33.3%)	14 (34.1%)	10 (24.4%)	
	2	2 (8.3%)	2 (4.9%)	3 (7.3%)	
Stent diameter, mm	Mean±SD	*3.44±0.53	2.92±0.31	2.92±0.28	³ 0.001**
	Stent length, mm	Mean±SD	*18.29±6.28	21.33±4.12	

¹Kruskall-Wallis Test; ²Pearson chi-square; ³One Way ANOVA

surgery. The total duration (before and after transplantation) of DAPT interruption was 10–12 days.

ST, MACE, death, cardiac death, and MI rates were compared among groups. Death was defined as death due to all causes, cardiac or otherwise. Death of patients due to a cardiac cause or without a non-cardiac cause was considered as cardiac death. MI was defined as increase in cardiac enzyme levels above the upper normal limit associated with ischemic symptoms or electrocardiographic changes. It was specifically described as perioperative MI. After renal transplantation, creatinine levels returned to normal levels. In this respect, evaluations of troponin levels were not influenced by CRF anymore during postoperative period. Definite and probable ST based on the Academic Research Consortium definition was considered as ST. MACEs comprised death, ST, and MI in hospital.

Table 3. Stent thrombosis and clinical outcomes of the study groups

Clinical outcomes	Stent groups			P
	BMS	DES-early	DES-late	
	(n=24) n (%)	(n=41) n (%)	(n=41) n (%)	
Stent thrombosis	1 (4.2%)	0 (0%)	1 (2.4%)	0.465
Cardiac death	1 (4.2%)	0 (0%)	0 (0%)	0.178
Death	2 (8.3%)	1 (2.4%)	1 (2.4%)	0.411
MI	1 (4.2%)	1 (2.4%)	2 (4.9%)	0.840
MACE	2 (8.3%)	2 (4.9%)	3 (7.3%)	0.840

Pearson chi-square

Statistical analysis

All statistical analyses were performed using SPSS software (version 20.0, SPSS Inc, Chicago, IL, USA). Continuous variables were presented as mean±standard deviation or median (25%-75%). Number of cases and percentages were used for categorical data. Kolmogorov–Smirnov test was used to determine the normality of distribution. Independent sample test and one-way ANOVA were used for analyzing normally distributed continuous variables. Kruskal–Wallis test was used for analyzing non-normally distributed continuous variables. Intergroup comparisons of categorical data were performed using Pearson chi-square and Fisher’s exact tests. A p value of <0.05 was considered to indicate statistical significance.

Results

The study population comprised 106 renal transplant patients with a history of coronary stent implantation. According to the stent type and DAPT duration, three groups were formed and compared. Early-interruption (3 months) and late-interruption DES groups (3–12 months) were equal in population size, whereas the BMS group had less number of patients. No statistically significant difference was found between groups in terms of age, sex, diabetes mellitus, hypertension, hyperlipidemia, current smoking status, prior PCI history (history of PCI before index PCI), and prior coronary artery bypass grafting history, left ventricular ejection fraction, and clinical presentation. Baseline characteristics of study groups are listed in Table 1.

Stent diameter was statistically different between groups (p=0.001). Post-hoc analysis revealed that BMS diameter was

Table 4. Evaluation of DES-early and DES-late groups according to clinical end points

Clinical end-points	Stent groups		P
	DES-Early	DES-Late	
	(n=41) n (%)	(n=41) n (%)	
Stent thrombosis	0 (0%)	1 (2.4%)	0.998
Cardiac death	0 (0%)	0 (0%)	–
Death	1 (2.4%)	1 (2.4%)	0.999
MI	1 (2.4%)	2 (4.9%)	0.998
MACE	2 (4.9%)	3 (7.3%)	0.998

Fisher's Exact Test

larger than DES diameters in early- and late-interruption groups. Stent length was also different between groups ($p=0.017$). Post-hoc analysis revealed the BMS length was shorter than DES length in early- ($p=0.032$) and late- ($p=0.023$) interruption groups. Angiographic and procedural features are depicted on Table 2.

Clinical outcomes, including ST, death, cardiac death, MI, and MACE, were not different among the three groups. Although Pearson chi-square was not applicable due to low number of variables, the test was executed to show non-significance. The results are presented in Table 3. Comparison of our primary objective between early- and late-interruption DES groups also revealed no difference in clinical endpoints, as shown in Table 4.

Discussion

The present single-center study investigated the safety of early DAPT interruption in renal transplant patients perioperatively and established no increase in ST rates. Therefore, ST risk should be considered against surgical bleeding in early cessation of treatment. Shorter duration of DAPT has been evaluated in several randomized controlled trials. These studies aimed to show non-inferiority of shorter duration against longer duration treatment in clinical endpoint of ST. EXCELLENT and ISAR-SAFE trials showed that 6 months of clopidogrel therapy had no effect on endpoints irrespective of DES generation (15). In addition, SECURITY trial indicated non-inferiority of 6-month versus 12-month DAPT following second-generation DES implantation in terms of the incidence of cardiac death, MI, stroke, and definite/probable ST (16). In ITALIC trial, rates of bleeding and thrombotic events were not significantly different between 6- and 24-month DAPT after PCI with everolimus-eluting DES (17). Lower duration, even 3 months of treatment, was compared with zotarolimus-eluting stent in RESET and OPTIMIZE trials. ST risk did not increase with 3-month DAPT compared with that by 12-months DAPT in these two trials (7,10). In comparison, studies on longer DAPT indicated lower rates of very late ST, myocardial infarction, and MACEs but higher bleeding rates with 30-month DAPT than with 12-month DAPT (18). It should be noted that bleeding risk was reduced with shorter DAPT (8).

In contrast to some previous studies involving BMS- and DES-implanted patients without discrimination of stent generation, our study aimed to compare 3-month DAPT in second-generation DES-implanted patients with 12-month treatment in these patients as well as with BMS-implanted patients. Less ST is observed with second-generation DES. There is growing evidence that ST does not increase with a shorter period, even 3–6 months, of DAPT after the use of these stents (19, 20). In the previous guideline recommendations, the optimal duration is longer, mostly related to the use of first-generation DES (21). DAPT duration before non-cardiac surgery has been reduced because of increase in the availability of safety data and usage of second-generation DES (13). Moreover, recent 2017 European Society of Cardiology Dual Antiplatelet Therapy guideline recommended that DAPT should not be stopped during the first month of therapy because of elective non-cardiac surgery. After 1 month, if aspirin can be continued, cessation of clopidogrel should be considered (9). We noted that both aspirin and clopidogrel were interrupted in our trial.

The study population in our trial is unique as it comprises high-risk CRF patients undergoing renal transplantation. The rate of restenosis in patients with CRF is high when even DESs are implanted. More complex, calcific lesions and multi-vessel diseases are more common in these patients (22). Unfavorable clinical outcomes with second-generation DES are still prevalent (23). Previous studies have indicated that CRF is significantly associated with increased definite or probable ST in patients undergoing PCI with DES (24). Even though atherosclerotic burden of these patients seemed to higher, 3-month DAPT and early interruption of this treatment did not increased ST and MACE rates. Comparison among BMS, DES-early, and DES-late groups in terms of study endpoints indicated no difference in ST, death, MI, and MACEs. DES-early and DES-late groups also showed no difference in these endpoints. This finding supports the findings of the previous studies and demonstrates the safety of short-term usage of clopidogrel with second-generation DES. Another study by Mehran et al. (25) has also demonstrated that brief interruption of DAPT because of surgery does not result in elevated thrombosis risk. Approximately 10–12 days of interruption of DAPT in our study confirmed this finding.

Stent size and diameter have important effects on MACEs following PCI with stents. In our study, BMS diameter was larger and length was shorter than those of DES. This difference can be mainly explained by health insurance system in Turkey. In fact, BMS may be as good as DES in larger diameters (26). Hsieh et al. (27) proposed that 3.75 mm would be the cut-off value for the use of BMS. Second-generation DES has been shown to be more preferable over BMS in small vessels. Moreover, this effect is more distinct than that of first-generation DES. In terms of stent length, the effect on clinical outcome may not be significant with second-generation DES (28). With smaller size and longer length, we encountered one ST with these new-generation stents. We only experienced one ST in BMS group. A patient implanted with

3.5x18-mm BMS in the right coronary artery underwent surgery 2 months later, which eventually led to the death of the patient. One non-fatal ST in a patient implanted with a relatively long DES (3x40 mm in the left anterior descending artery) occurred in the DES-late group. DES-early group did not present ST, but one patient in this group developed myocardial infarction due to an artery different from the stent-implanted coronary artery. A non-cardiac death also contributed to the MACEs in this group.

Study limitations

This study had the following limitations. It was a retrospective analysis and liable to bias in patient data selection. In addition, the study was a single-center trial, with a population size not sufficiently large to draw certain conclusions. ST, which was our primary endpoint, is relatively rare after PCI for elective procedures. Hence, large-scale, prospective, randomized trials are needed to confirm our study results. The non-inferiority of 3-month DAPT with patients preoperatively implanted with second-generation DES should be investigated to obtain definite conclusions.

Conclusion

Three-month usage of DAPT and interruption before surgery with second-generation stents can be safe, with no increase in ST and MACE rates in renal transplant recipients. However, larger population and randomized studies are needed to determine optimum duration.

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Battal Gazi Barlas, from EFSAD's collections.