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Original Article

Efficacy and Safety of Dual Antiplatelet Therapy on Graft Patency After Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial

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ABSTRACT

Background: Early vein graft occlusion after coronary artery bypass grafting (CABG) is one of the major problems after the surgery which directly impacts its short- and long-term outcomes. One of the potential explanations is aspirin resistance. The aim of this study was to evaluate the efficacy and safety of dual antiplatelet therapy (DAPT) with clopidogrel and aspirin compared with aspirin alone on the reduction of early graft occ usion.

Methods: In a multicenter randomized controlled trial with a parallel design, from 2012 to 2015 among 1165 patients, we compared 140 candidates for CABG: 71 in the DAPT group (300 mg c of clopidogrel and 80–325 mg of aspirin) and 69 in the aspirin group. The primary outcome was graft patency assessed by coronary computed tomography angiography performed at 6 months' follow-up. Bleeding complications were considered the secondary outcome.

Results: Saphenous vein grafts were occluded in 10 (14.1%) patients in the DAPT and 11 (15.9%) in the control group (P = 0.758). After adjustments for study centers, the associations remained unchanged (OR [95% CI]: 1.49 [0.59–3.74]). Bleeding endpoints were also similar in the 2 groups (P > 0.05).

Conclusions: Our study did not demonstrate the superiority of the DAPT regimen over aspirin monotherapy in patients undergoing elective CABG. Larger multicenter studies may provide more evidence. ***(Iranian Heart Journal 2020; 21(1): 6-16)***

KEYWORDS: Coronary artery bypass, Platelet aggregation inhibitors, Aspirin, Clopidogrel

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Early vein graft failure is still one of the important caveats of coronary artery bypass grafting (CABG), which might translate to major cardiovascular events. Thrombosis, intimal hyperplasia, smooth muscle cell proliferation, and *de novo* atherosclerosis plaques have been suggested as a possible candidate for graft failure, among which thrombosis plays a crucial role in the early phase. By blocking cyclooxygenase-1, ASA inhibits platelet activity and decreases the rate of graft thrombosis. [1] Despite this protective approach, around 30% of venous grafts will become occluded in the first year after surgery, which may be considered aspirin resistant. [2, 3] This may be due to the inability of aspirin to inhibit all aspects of the platelet activation process and also the aspirin resistance phenomena. [4] To overcome these problems, it was suggested to add clopidogrel in order to lower the rate of early graft occlusion. To date, there is no clear consensus regarding the use of dual antiplatelet therapy (DAPT) after elective CABG. Several studies have investigated the clinical use of clopidogrel in the matter, but they have reached mixed results. Considering the abovementioned controversy, this study aimed primarily to evaluate the effects of a combination of clopidogrel and aspirin therapy on the reduction of early graft occlusion evaluated by coronary computed tomography (CT) angiography in patients with recent CABG.

METHODS

The study was an open-label multicenter randomized controlled trial with a parallel design. It was aimed to evaluate the superiority of DAPT of clopidogrel and aspirin compared with aspirin alone on the reduction of early graft occlusion in patients with recent CABG.

Study Participants and Settings

The study was conducted from May 2012 to December 2015 in 3 professional centers for cardiovascular diseases (Day General Hospital, Pars General Hospital, and Rajaie Cardiovascular, Medical, and Research Center) in Tehran, Iran. All the selected centers were referral private or teaching hospitals.

The study protocol was approved by the ethics committee of Karaj Islamic Azad University (Code: 030- 8/9/1390).

Inclusion Criteria:

1. Patients' age ≥ 18 y
2. Candidates for CABG

Exclusion Criteria:

1. Concomitant valve surgeries
2. Concomitant aortic surgery
3. Redo-CABG
4. Patients who did not take aspirin at least 48 hours before surgery
5. Clopidogrel use within 5 days before CABG
6. Any condition with increased bleeding risk, precluding DAPT
7. Significant bleeding in the first 4 hours after surgery, defined as continuous chest tube drainage > 100 cm^3 per hour on average in this time interval

Totally, 1165 patients who were candidated to undergo CABG were assessed for the eligibility criteria by a cardiologist. Every eligible patient was given a written informed consent form by the main investigator; and after signing the form, he/she was registered in the study.

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Study Groups and Randomization

The participants in this study underwent randomization (on a 1: 1 basis) via the permuted block method to either the DAPT group (clopidogrel and aspirin) or the aspirin monotherapy group within 24 hours after surgery. The process of random assignment was conducted in our data management center, located in one of the collaborating hospitals (Rajaie Cardiovascular, Medical, and Research Center) by the team members not involved in the conduction of the trial performed. Random sequence was generated using the permuted block randomization method (blocks of 4). After the registration of each patient in the trial, the nurse in charge called the center's data management center and asked for the assigned study group. According to the random sequence, the staff in the center announced the assigned group as Group A (DAPT) or Group B (control) to the nurse. The trial was open-label, and no masking was applied.

The patients who were randomized in the DAPT group received a loading dose of 300 mg (4 tablets) of clopidogrel (Plavix ®, Sanofi-Aventis Co) within 24 hours after surgery and a maintenance dose of 75 mg/d was continued for 30 days in combination with 80–325 mg of aspirin. The patients who were assigned to the control group received aspirin (80 mg/d). For both groups, aspirin was recommended for lifelong treatment.

Study Endpoints

The primary endpoint was graft patency evaluated by CT angiography 6 months after surgery. A graft was considered patent if no significant stenosis (≥ 70%) was detected by CT angiogram; otherwise, it was regarded as occluded.

The secondary endpoints were:

1) The amount of chest tube output in the early postoperative period, defined as the amount of the bloody fluid drained. The chest tube drainage was considered significant when its amount exceeded 100 cm^3 per hour on average for a 4-hour interval in the intensive care unit (ICU) after surgery.

2) The need for blood transfusions with either of the following criteria:

a. ≥ 2 units of packed red blood cells

b. ≥ 2 units of fresh frozen plasma

c. ≥ 5 units of platelets

3) In-hospital mortality, defined as cardiac death in the postoperative period and during hospitalization as a secondary endpoint of the study.

After undergoing surgery, the patients were discharged to the ICU, where they were visited every day by the principal investigator or eligible cardiologists and assessed for the study endpoints.

Data Collection and Follow-up

All the data related to the patients' characteristics, intervention, and bleeding complications from the index event until discharge were recorded in a CRF by a trained and qualified study coordinator (SC). During the time of hospitalization, all the participants were monitored in terms of the amount of chest tube drainage and blood product transfusion.

Afterward, the patients were asked by the study coordinator to refer for a visit at 1 month's follow-up. Treatment adherence was evaluated, along with any complication, by the principal investigator.

Six months after surgery, CT-angiography was performed to evaluate graft patency. During the recruitment for imaging follow-up, the patients who refused to attend this examination were asked to give the reason for not attending and cases of death were reported when available.

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After CT angiography for the participant, all data about the number and type of involved graft vessel(s) were saved in the CRF.
All the CT angiographic examinations were double-checked by the radiologist involved in the study.

Statistical Analysis

The data were analyzed via the intention-to-treat approach. The data were described as the mean (± the standard deviation) for the interval variables with normal distributions, the median (interquartile ranges) for the interval variables without normal distributions, and count (%) for the categorical variables. Fitness of the distribution of the interval variables to normal distribution was assessed using the one-sample Kolmogorov–Smirnov test. Associations between DAPT and other variables were determined using the Student *t*-test for the interval variables with normal distributions, the Mann–Whitney *U* test for the interval variables without normal distributions and the ordinal variables, and the Pearson χ^2 test (or the Fisher exact test, as needed) for the nominal variables. A *P* value $\leq$ 0.05 was considered statistically significant.
Adjusted associations between the primary endpoint (graft occlusion) and DAPT were investigated using a multivariate binary logistic model. The study center was considered a covariate, and other covariates in the model were chosen if a significant *P* value was detected in the bivariate statistical analysis.
The statistical analyses were performed via IBM SPSS Statistics 19 for Windows (IBM Inc, Armonk, NY) and Stata 11 (Stata Inc, Texas, USA).

RESULTS

Baseline and Background Data

The study was conducted from May 2012 to December 2015 in 3 centers for cardiovascular diseases in Tehran, Iran. In total, 1165 patients were assessed primarily for the inclusion criteria. Among them, 740 did not satisfy the inclusion criteria and 209 did not participate and sign the informed consent form. The remaining 216 patients were randomly assigned to the 2 study arms (108 in each group). Nonetheless, due to a nurse's error, 3 patients were misclassified and, therefore, 111 participants received DAPT and 105 received aspirin only. Finally, 140 (65%) participants (71 in the intervention group and 69 in the control group) remained until the end of the study and their relevant data were used in the statistical analysis. Seventy-six (35%) patients quit the study as they chose not to undergo CT angiography or could not complete the follow-up course. The study participants' flow diagram is presented in Figure 1.
Table 1 depicts a comparison of the background characteristics between the 2 groups: the patients who agreed to undergo CT angiography (ie, those who were entered in the final analysis) and the patients who did not. The results showed that the 2 groups were similar in several aspects; thus, it can be concluded that the acceptance of CT angiography was random in the study participants. The participants' characteristics were compared between the study groups, and the results are presented in Table 2. The findings suggested that the patients were roughly similar in the 2 study groups.

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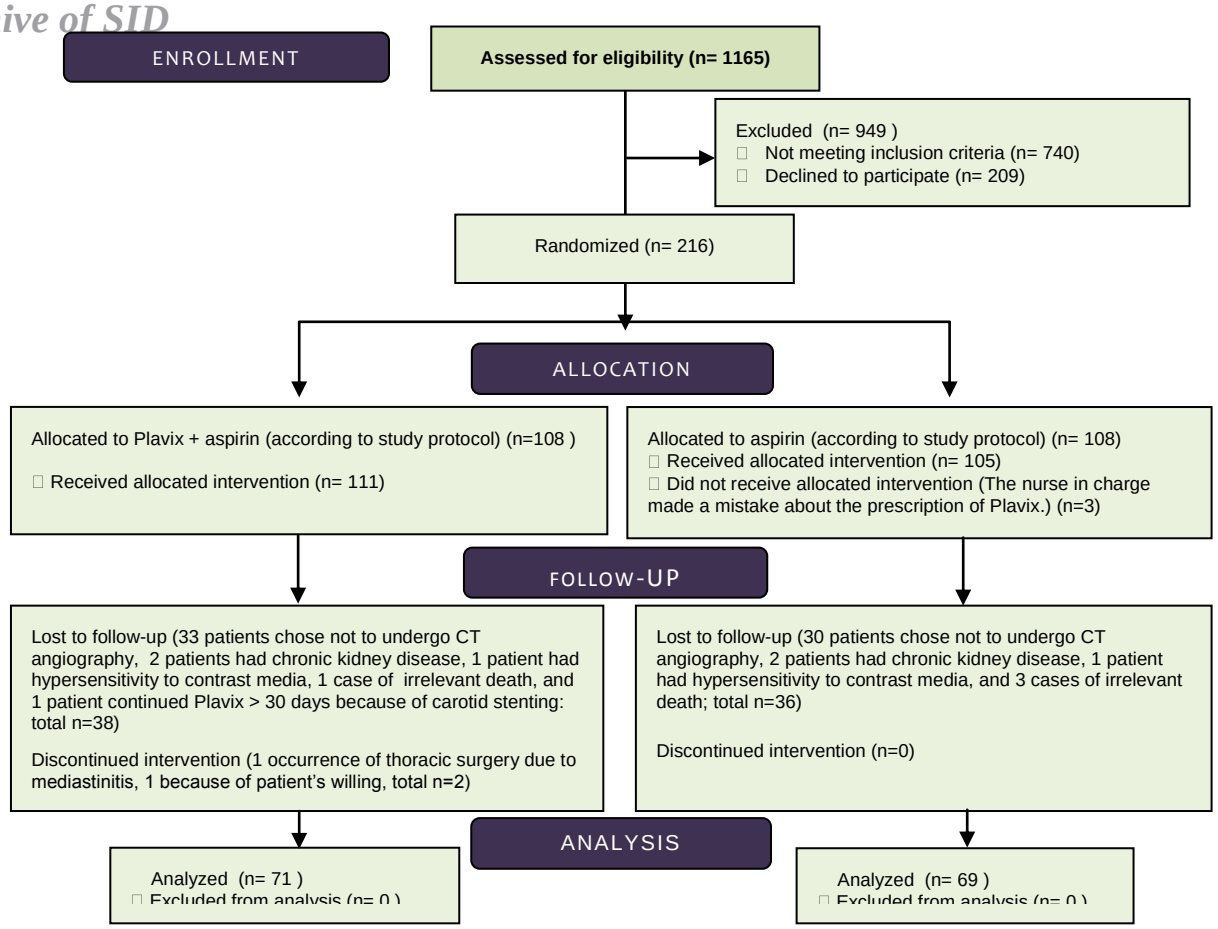

Figure 1. CONSORT Flow Diagram

Table 1. Comparison of the patients'characteristics between the group that underwent CTA and the group that did not

	CTA Performed (n=140)	CTA NOT Performed (n=76)	*P* value
Study Group [a]			0.714
Intervention	71 (50.7%)	40 (52.6%)	
Control	69 (49.3%)	35 (46.1%)	
Gender [a]			0.144
Male	113 (80.7%)	54 (71.1%)	
Female	27 (19.3%)	21 (27.6%)	0.198
Age (y) [b]	62 (±9.4)	61 (±9.7)	
Center [a]			0.428
1	28 (20%)	11 (14.5%)	
2	33 (23.6%)	15 (19.7%)	
3	79 (56.4%)	49 (64.5%)	
History of MI [a]	72 (51.4%)	40 (52.6%)	0.790
Family history [a]	58 (46.4%)	29 (38.2%)	0.503
Hypertension [a]	82 (58.6%)	52 (68.4%)	0.121
Dyslipidemia [a]	95 (67.9%)	48 (63.2%)	0.568
Diabetes [a]	57 (40.7%)	28 (36.8%)	0.629
Smoking [a]	77 (55%)	44 (57.9%)	0.730
Coronary Vessel Stenosis [a]			0.583
Single vessel	13 (9.3%)	4 (5.3%)	
Two vessels	29 (20.7%)	17 (22.4%)	
Three vessels	98 (70%)	54 (71.1%)	
LVEF (%) [b]	47 (±10.8)	46 (±10.3)	0.882

Results are presented as: a: count (%), b: mean (±standard deviation).
CTA, Computed tomography angiography; MI, Myocardial infarction; LVEF, Left ventricular ejection fraction

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Table 2. Comparison of characteristics between the patients who were entered in the analysis (ITT) (N=140)

	Plavix-Aspirin (n=71)	Aspirin (n=69)	*P* value
Gender [a]			
Male	57 (80.3%)	56 (81.2%)	0.895
Female	14 (19.7%)	13 (18.8%)	
Age (y) [b]	62 (±8.4)	61 (±10.4)	0.423
History of MI [a]	31 (43.7%)	41 (59.4%)	0.062
Family history [a]	33 (52.4%)	25 (40.3%)	0.176
Hypertension [a]	44 (62%)	38 (55.1%)	0.407
Dyslipidemia [a]	50 (70.4%)	45 (65.2%)	0.501
Diabetes [a]	24 (33.8%)	33 (47.8%)	0.121
Smoking [a]	40 (56.3%)	37 (53.6%)	0.884
Coronary Vessel Stenosis [a]			
Single vessel	5 (7%)	8 (11.6%)	0.317
Two vessels	18 (25.4%)	11 (15.9%)	
Three vessels	47 (67.6%)	50 (72.5%)	
LVEF (%) [c]	50 (45-55)	50 (35-55)	0.172
Emergent operation [a]	3 (4.2%)	1 (1.4%)	0.324
Number of grafts [c]	2 (2-3)	2 (2-3)	0.399
Hemoglobin (g/dL) [b]	13.4 (2.8)	13.7 (2.4)	0.171

Results are presented as: a: count (%), b: mean (standard deviation), c: median(Q1-Q3).
MI, Myocardial infarction; LVEF, Left ventricular ejection fraction

In-Hospital Events

The patients were assessed in terms of bleeding, transfusion, and other outcomes and the comparative results are presented in Table 3. There was no statistical difference in the chest tube drainage between the 2 groups ($P > 0.05$). The incidence of significant bleeding leading to blood product transfusion was similar between the 2 groups. However, the amount of RBC transfused to the intervention group was less than that transfused to the control group ($P < 0.05$). No death was reported during this period.

Table 3. Comparison of the findings during hospitalization between the study treatment groups (ITT)

	Plavix-Aspirin (n=71)	Aspirin (n=69)	*P* value
Chest tube drainage (cm^3)			
First day after surgery [b]	400 (250 - 500)	400 (250 - 541.5)	0.541
ICU period [b]	500 (350 - 700)	500 (325 - 725)	0.828
Ward [b]	0 (0 - 0)	0 (0 - 0)	0.555
Total [b]	600 (350 - 750)	500 (350 - 875)	0.602
Need for transfusion [a]	42 (59.2%)	47 (68.1%)	0.271
Hemoglobin before transfusion [c] (g/dL)	10.6 (2.4)	10.9 (2.7)	0.169
In Transfused Patients:			
Units of packed RBCs [b]	1 (1 - 2)	2 (1 - 3)	0.004
Volume of packed RBCs (cm^3) [b]	250 (250 - 500)	500 (250 - 775)	0.005
Units of FFP [b]	3 (1.5 - 3)	3 (1.75 - 3)	0.894
Volume of FFP (cm^3) [b]	450 (300 - 450)	450 (275 - 450)	0.789
Units of platelet [b]	3 (2 - 4)	3 (2 - 4)	0.515
Volume of platelet (cm^3) [b]	150 (100 - 200)	150 (100 - 200)	0.515
Units of whole blood [b]	1 (1 - 1)	3 (3 - 3)	0.317
Volume of whole blood (cm^3) [b]	350 (350 - 350)	900 (900 - 900)	0.317
Re-operation because of bleeding [a]	0 (0%)	1 (1.4%)	0.493
Hospitalization (days after surgery)	6 (6 - 7)	7 (6 - 8)	0.223
Mortality [a]	0	0	-

Results are presented as: a: count (%), b: median (Q1-Q3), c: mean (standard deviation).
FFP, Fresh frozen plasma; RBC, Red blood cells

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Six Months After Surgery

After discharge, there were no records of bleeding, ischemic events, or mortality.

Graft Occlusion

As the primary endpoint of the study, the occlusions of venous (and arterial) grafts were measured via coronary CT angiography. Saphenous vein grafts were occluded in 10 (14.1%) patients in the DAPT group and 11 (15.9%) patients in the control group (P = 0.758). Arterial graft occlusion was observed in 5 (7%) patients in the DAPT group and 3 (4.3%) patients in the control group (P = 0.492). To adjust the association between the study intervention and graft occlusion for each of our 3 centers, we performed a multivariable logistic regression analysis (Table 4). The analysis showed that the study center did not influence the study outcomes (P > 0.05).

Table 4. Multivariable analysis for adjusting the findings for the centers

	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value
Dual antiplatelet therapy	0.86 (0.34 – 2.19)	1.49 (0.59 – 3.74)	0.397
Center of study			
1 (reference)		–	–
2		0.51 (0.11 – 2.40)	0.392
3		1.66 (0.54 – 5.10)	0.378

Adverse Events

The frequencies of adverse events according to the study groups are presented in Table 5 (in the study treatment group, n=140) and in Table 6 (in the randomized patients, n=216). Additionally, the frequencies of serious adverse events, compared between the study groups, are mentioned in Table 7.

Table 5. Frequency of adverse events in the study population until the end of 6 months after follow-up in the study treatment groups (N=140)

	Plavix-Aspirin (n=71)	Aspirin (n=69)
Transient Mild Thrombocytopnia	3	4
Transient Mild Azotemia	1	1
Transient Microscopic Hematuria	1	0
Subcutaneous Emphysema	0	1
Vasovagal Syndrome	1	1
Ventricular Tachycardia	0	1
Fever	1	0
Pneumonia	0	0
Mediastinitis	0	0
Tamponade	0	1
Pericardial Effusion	1	1
Pleural Effusion	4	3
Hematoma at the Site of Saphenectomy	0	1
Wound Infection	2	1
Pressure Ulcer	0	0
Retroperitoneal abscess	0	0
Exsessive Bleeding	0	1
LV Clot	0	1
Death Due to CVA (Out of Hospital)	0	0
Death Due to Cirrhosis (Out of Hospital)	0	0
Death Due to Mediastinitis (in Hospital)	0	0
Total AEs	14	17
Total Patients with AEs	11	14
Total Patients with AEs Leading to Discontinuation	1	0
Total Patients with SAEs	5	8

LV, Left ventricle; CVA, Cerebrovascular accident; SAE, Serious adverse event

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Table 6. Frequency of adverse events in the study population until the end of 6 months after follow-up in the randomized patients (n=216)

	Plavix-Aspirin (n=111)	Aspirin (n=105)
Transient Mild Thrombocytopnia	3	4
Transient Mild Azotemia	1	1
Transient Microscopic Hematuria	1	0
Subcutaneous Emphysema	0	1
Vasovagal Syndrome	1	1
Ventricular Tachycardia	0	1
Fever	1	0
Pneumonia	0	1
Mediastinitis	1	0
Tamponade	0	1
Pericardial Effusion	2	2
Pleural Effusion	6	4
Hematoma at the Site of Saphenectomy	0	1
Wound Infection	2	1
Pressure Ulcer	2	1
Retroperitoneal abscess	1	0
Exsessive Bleeding	0	1
LV Clot	0	1
Death Due to CVA (Out of Hospital)	0	1
Death Due to Cirrhosis (Out of Hospital)	0	1
Death Due to Mediastinitis (in Hospital)	1	1
Total AEs	22	24
Total Patients with AEs	21	19
Total Patients with SAEs	7	15

LV, Left ventricle; CVA, Cerebrovascular accident; SAE, Serious adverse event

Table 7. Frequency of serious adverse events (SAEs) according to the study groups

Serious Adverse Events	Randomized (n=216)			Analyzed (n=140)		
	Total	DAPT (n=111)	Aspirin (n=105)	Total	DAPT (n=71)	Aspirin (n=69)
Death	4	1	3	0	0	0
Requiring/Prolonging Hospitalization	16	5	11	11	4	7
Congenital Anomaly/ Birth Defect	0	0	0	0	0	0
Life-threatening	3	1	2	2	1	1
Persistent/Significant Disability/ Incapacity	0	0	0	0	0	0
Other Medically Important Events	0	0	0	0	0	0

DAPT, Dual antiplatelet therapy

DISCUSSION

In the present study, we compared the effect of DAPT (ie, aspirin and clopidogrel) with that of aspirin alone in patients having undergone elective CABG. Our study was an open-label multicenter controlled randomized trial with a parallel design, and our analysis showed no significant differences in terms of the primary outcome (ie, graft patency 6 months after surgery) between the 2 groups of study. Additionally, the 2 groups were similar according to bleeding complications.

Different investigations have shown the important rate of graft (especially venous graft) failure early after CABG. Although different mechanisms including intimal

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hyperplasia, smooth muscle cell proliferation, and *de novo* atherosclerosis plaques have been suggested for the complication, thrombosis appears to play an important role in the early phase. Considering these mechanisms, it seems logical that potent platelet inhibition with DAPT may improve graft patency. This benefit should be weighed against the potential bleeding complication of the combined regimen. [6] The mentioned hypothesis was firstly tested in an acute coronary syndrome population. The CREDO [7] and CURE [8] trials analyzed the effect of DAPT vs aspirin alone in an acute coronary syndrome setting in which DAPT showed promising results toward decreasing the all-cause mortality without a significant increase in major bleeding.

Various studies have evaluated the value of DAPT in elective CABG patients. Graft patency, evaluated within 3 to 12 months following CABG, was their main outcome. In all of them, ASA and/or clopidogrel were re-administrated when chest tube drainage was no longer active. In our study, we chose to show the effect of DAPT on 6 months' graft patency.

Goa et al, [9] in their randomized controlled trial, investigated the value of the DAPT regimen vs aspirin monotherapy in elective CABG. Their primary outcome was graft failure 3 months after surgery. Graft failure was significantly lower in the DAPT group, in which a trend toward a decrease in all grafts failure was also detected. It should, however, be mentioned that bleeding complications were not elaborated separately in their analysis.

Mannacio et al, [10] in their CRYSSA trial, also studied the effect of DAPT on post-CABG graft patency and its relation with single or dual antiplatelet resistance. The study showed that the DAPT regimen had a beneficial effect compared with monotherapy. Their results also revealed that the combination of ASA and clopidogrel might overcome the single antiplatelet drug resistance and the synergistic activity of combined aspirin and clopidogrel was a strong predictor of saphenous vein graft (SVG) patency (RR: 5.1, 95% CI: 1.4 to 16.3; $P < 0.01$). Likewise, Gasparovic et al [11] compared specifically the 2 regimens on an aspirin-resistance population. There were no significant differences between the 2 groups regarding graft patency or bleeding complications. However, the subgroup analysis showed a benefit for the DAPT regimen in the obese population.

The CASCADE trial was also a randomized study with a genuine design. Their primary endpoint was the effect of clopidogrel on intimal hyperplasia 1 year after surgery. With the help of intravascular ultrasound, the SVGs were analyzed regarding intimal hyperplasia. Interestingly, clopidogrel had no impact on the primary outcome. [12]

Recently, van Diepen et al, [13] in their post hoc secondary analysis of the FREEDOM trial, showed that the DAPT regimen was not superior to ASA monotherapy in the post-CABG population. Their results were consistent in regard to primary graft patency, bleeding complications, and subgroup analysis in which important subgroups such as the ACS population and higher syntax scores were evaluated. Verma et al, [14] in their meta-analysis of studies investigating the role of the DAPT regimen compared with aspirin monotherapy in both ACS and elective populations, showed no additional benefit from adding clopidogrel to ASA in the post-CABG population.

Our study did not evaluate the possible effect of the DAPT regimen on the native coronary arteries. Previous research has shown that native coronary vessels are at risk of plaque rupture and other

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complications in which added clopidogrel might be beneficial. In a substudy of the CASCADE trial, Une et al [15] proved the efficacy of DAPT in reducing native coronary events compared with ASA monotherapy. The matter still needs further investigation.

A limitation of the current study was the considerable number of registered patients who chose not to undergo CT angiography (76 out of 216). As was shown in Table 3, this might not affect the internal validity of the study. However, from a sociological point of view, it may affect the generalizability of the results and may, thus, need to be considered in future studies.

In conclusion, there is still no consensus on the efficacy of the DAPT regimen in patients candidated for elective CABG. Our results showed a neutral effect of the DAPT regimen. Large multicenter randomized clinical trials are needed to definitely investigate the role of DAPT in patients with acute coronary syndrome after CABG and to clearly identify which patients will benefit the more.

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