British Journal of Medicine & Medical Research
14(3): 1-10, 2016, Article no.BJMMR.24386
ISSN: 2231-0614, NLM ID: 101570965

SCIENCEDOMAIN *international*
www.sciencedomain.org

ASpirin and Plavix Following Coronary Artery Bypass Grafting (*ASAP-CABG*): A Randomized, Double-Blind, Placebo-Controlled Pilot Trial

Ahmad M. Slim[1*], Emilio Fentanes[1], Dustin M. Thomas[1], Jennifer N. Slim[2], Taylor Triana[1], Homayoun R. Ahmadian[1], Ryan J. McDonough[1], Jason Saucedo[1], Norma J. Suarez[1], Dorette Pearce-Moore[1], H. Lester Kirchner[3], Edward Hulten[4], Ricardo C. Cury[5] and Kelley Branch[6]

[1]Cardiology Service, San Antonio Military Medical Center, 3551 Roger Brooke Drive, San Antonio, Texas 78234-6200, USA.
[2]Louisiana State University, New Orleans, LA, USA.
[3]Geisinger Medical Center, Danville, PA, USA.
[4]Cardiology Service, Walter Reed National Military Medical Center, Bethesda, MD, USA.
[5]Department of Radiology, Miami Cardiac and Vascular Institute, Baptist Health South Florida, Miami, FL, USA.
[6]Division of Cardiology, University of Washington, Seattle, WA, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Author AMS designed the study, wrote the protocol and wrote the first draft of the manuscript and reviewed the final draft. Authors DMT, EF, JNS, TT, HRA, RJMD, JS, NJS, DPM assisted in write up of first draft, performed physical exams and collected data end points, analyzed data and wrote final manuscript. Authors HLK, RCC and KB performed complex statistical analysis as well as wrote and approved final published draft. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/24386
Editor(s):
(1) Vijayalakshmi I. Balekundri, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India.
(2) Nurhan Cucer, Erciyes University, Medical Biology Department, Turkey.
(3) Philippe E. Spiess, Department of Genitourinary Oncology, Moffitt Cancer Center, USA and Department of Urology and Department of Oncologic Sciences (Joint Appointment), College of Medicine, University of South Florida, Tampa, FL, USA.
Reviewers:
(1) Gerez Fernandes Martins, Institute of Rio de Janeiro, Brazil.
(2) Gibran Roder Feguri, General University Hospital, Brazil.
Complete Peer review History: http://sciencedomain.org/review-history/13503

Original Research Article

Received 18th January 2016
Accepted 19th February 2016
Published 2nd March 2016

**Corresponding author: E-mail: ahmad.slim@acishealth.org;*

ABSTRACT

Background: Vein graft thrombosis is the leading cause of acute graft failure within the first post-operative month. Several studies have shown the benefit of post-operative dual anti-platelet therapy (DAPT) in preventing acute graft thrombosis. The purpose of this study was to determine whether peri-operative initiation of DAPT will improve short and intermediate term graft patency.
Methods: This was a randomized, double-blind, placebo controlled trial of 20 patients undergoing CABG to compare DAPT versus aspirin monotherapy. The primary outcome was post-operative graft patency at 2 and 52 weeks determined by <50% bypass graft stenosis by cardiac computed tomography angiography (CCTA). The secondary outcomes were (1) major adverse cardiovascular events (MACE), defined as myocardial infarction, thrombotic events, and angina, and (2) safety end-points defined as TIMI major and minor bleeding events.
Results: The study population consisted predominately of men (19/20 patients). At 2 weeks, all LIMA grafts were patent although vein graft patency for the DAPT group was only 83.3% (20/24) compared to 89.5% (17/19) for placebo (p=0.597). At 52 weeks, the patency rate in the placebo group was 52.6% (10/19) as compared to a patency of 71.4% (15/24) in the dual anti-platelet therapy arm (p=0.244).
Conclusion: The addition of clopidogrel to aspirin post-bypass surgery did not significantly improve venous graft patency at 2 weeks but trended toward higher graft patency at 52 weeks.

Keywords: Aspirin; Plavix; CCTA; coronary artery bypass surgery; graft patency; major adverse cardiovascular events.

Clinical Trials.gov ID: NCT01158703.

1. BACKGROUND

Coronary artery bypass graft surgery (CABG) is the treatment of choice for many patients with ischemic heart disease and depressed ejection fraction, extensive symptomatic ischemic burden, or diabetes mellitus. In 2010, an estimated 397,000-inpatient bypass procedures were performed in the United States [1]. Despite aggressive medical therapy, up to 15% of vein grafts occlude in the first year after CABG. Ten years post surgery, only 60% of grafts are patent and only 50% of patent vein grafts are free of significant stenosis [2]. Early graft thrombosis can occur at the time of surgery due to focal endothelial disruption [3,4] and reactive thrombocytosis [5].

In addition, literature suggests that there are significantly increased rates of occlusion of all graft types, particularly saphenous venous grafts, with off-pump coronary artery bypass when compared to on-pump coronary artery bypass [6]. While the use of aspirin for antiplatelet therapy in patients who undergo CABG remains the standard of care [7], the use of additional clopidogrel therapy is becoming more widespread.

We conducted a randomized, double blind, placebo controlled pilot trial in which we examined the effects of aspirin and placebo vs. aspirin and clopidogrel on the arterial and venous graft patency after bypass surgery using coronary CT angiography (CCTA) scan. This study also examined major cardiovascular events, including death, myocardial infarction, all thrombotic events, and recurrent angina.

2. METHODS

2.1 Study Protocol and Oversight

The ASpirin and Plavix following Coronary Artery Bypass Grafting (ASAP-CABG) protocol was reviewed and approved by the institutional review board at San Antonio Military Medical Center (SAMMC) where the trial was conducted. The study was partially funded by Bristol-Myers Squibb (New York, US) who provided trial active therapy and placebo only, ClinicalTrials.gov ID: NCT01158703.

2.2 Study Population

All patients provided written informed consent to participate in the study. Patients were eligible if they were ≥ 18 years of age and undergoing CABG with or without cardiopulmonary bypass. Patients were excluded if they had a left ventricular ejection fraction of less than 30%, underwent emergent surgery, valve surgery, redo

CABG, developed post-operative cardiogenic shock for more than 48 hours, post-operative bleeding or cardiac tamponade requiring reoperation, or required post-operative anticoagulation. Additional exclusion criteria include serum creatinine level > 1.4 mg/dL, inability to undergo CCTA, an allergy to aspirin or clopidogrel, inability to provide inform consent, and pregnant or breastfeeding females. This is described in Table 1.

Table 1. Pilot Study inclusion and exclusion criteria

Inclusion criteria:
1. Patients undergoing coronary artery bypass grafting with or without cardiopulmonary bypass.
2. Age greater than or equal to 18 years of age
Exclusion criteria:
1. Left ventricular ejection fraction <30%
2. Emergency surgery
3. Valve surgery
4. Redo CABG
5. Postoperative cardiogenic shock for more than 48hrs
6. Postoperative bleeding or cardiac tamponade
7. Requirement of postoperative anticoagulation
8. Serum Creatinine >1.4 mg/dL
9. Contraindication to use of postoperative coronary CT scan
10. Allergy or Contraindication to aspirin or clopidogrel
11. Inability to provide inform consent
12. Pregnant or breast feeding females

2.3 Study Design

This randomized, double-blind, placebo-controlled pilot study compared DAPT and ASA monotherapy with placebo for the incidence of short and intermediate term graft stenosis after CABG. Candidates who met the inclusion criteria and signed an informed written consent before surgery were enrolled. The drugs used in the trial are recognized and approved to use. The protocol was approved by the local institutional review board in their Medical Center, where the trial was conducted. Also, the trial has an ID: NCT01158703. After successful surgery, subjects were randomized to aspirin 81 mg daily plus placebo or aspirin 81 mg daily plus clopidogrel 75 mg daily. For all subjects, the first 30 days consisted of aspirin 325 mg daily, after which the dose was decreased to 81mg daily. Treatment was started 6 hours after surgery via nasogastric tube until the patient was extubated and able to swallow medications orally. All subjects received background therapy as recommended by the current American College of Cardiology / American Heart Association guidelines, which included beta blockers, angiotensin converting enzyme inhibitors, and lipid lowering medications as clinically indicated. At 2 weeks (end of phase I), CCTA was obtained to assess for graft patency and to establish a baseline for each subject. At 52 weeks, CCTA was repeated under the same conditions.

Subjects were followed on quarterly basis for secondary outcomes and safety outcomes. In the immediate postoperative period, complete blood counts were obtained to assess the hemoglobin level. During follow-up visits for routine postoperative cardiac care, pertinent laboratory evaluations and pill counts were performed.

2.4 Non-invasive Graft Analysis by Coronary CTA

All scans were analyzed by a cardiologist with level-III American College of Cardiology or American College of Radiology-certified imaging expertise in accordance with Society of Cardiovascular Computed Tomography (SCCT) guidelines. Scans were performed following SCCT guidelines [8]. Studies were obtained using a 128-slice dual-source scanner with a high-pitch single heart beat image acquisition capabilities (SOMATOM Definition Flash CT; Siemens, Erlagen, Germany). Patients were treated before scan acquisition with metoprolol tartrate 0-100 mg and nitroglycerin spray 0.4 to 0.8 mg within 2 minutes of scan acquisition based on an internal protocol. Fig. 1 summarizes the algorithm used for selection of image acquisition protocol settings based on a previously published article [9]. All scans used a triphasic iodixanol (GE Healthcare, Wakesau, WI) intravenous (IV) contrast injection protocol consisting of 75 mL of iodixanol followed by 40 mL of 50% contrast mixed with normal saline chased with normal saline at a flow rate of 5 mL/s. Total IV contrast volume ranged from 105 to 115 mL. Image reconstruction was performed using filter-back projection to reconstruct with oblique and multi-planar images of the bypass grafts. Quantitative vessel analysis was performed with Vitrea 6.3 Software (Vital Images, Inc, Minnetonka, Minnesota).

2.5 Study Endpoints

The primary endpoints were the incidence of ≥50% stenosis in any graft at 2 weeks and 52 weeks after surgery. The secondary endpoint was major adverse cardiovascular events at 6 months and 1 year. The primary safety end-point was the incidence of TIMI major and minor bleeding. Each endpoint compared ASA and placebo treatment with DAPT. The trial duration was planned for one year.

2.6 Statistical Analysis

In this pilot study, the independent variable was treatment (placebo or clopidogrel) and the dependent variable was the binary incidence of ≥ 50% postoperative stenosis. Data were tabulated for patient- and the graft-level analyses. The null hypothesis (H_o) states there was no significant difference in incidence of graft stenosis, major adverse events, or bleeding between treatments. The needed sample size was determined to be 75 subjects (160 grafts assumed to correlate with 60 subjects and extra 15 subjects to account from drop out) in each arm to reach statistical significance. The expected incidence in of stenosis in the ASA monotherapy group was 20% and the expected incidence in the DAPT group was 10%. According to this method, 157 grafts per group were needed to detect a decrease in probability from 20-10% with a level of confidence of 95% and a power of 80%. All analyses were performed as intention-to-treat. Comparisons between the arms were accomplished using the exact Wilcoxon Rank sum test for continuous variables and Fisher's exact test for categorical variables. Analysis of the primary outcome of graft status (patent vs. occluded) utilized all available grafts per enrolled participant. Comparison between treatment groups was accomplished using a Generalized Estimating Equations model for logistic regression to account for the multiple grafts per participant. The model assumed a robust independence covariance structure. Analysis of secondary outcomes was accomplished using Fisher's exact test. Flow through all grafts peri-operatively was recorded and was utilized as a possible surrogate indicator of two weeks graft patency and compared between groups using a Generalized Estimating Equations model for linear regression and a robust independence covariance structure. An interaction was then tested between velocity and treatment. Statistical analysis was performed with SPSS software with p-values < 0.05 considered significant.

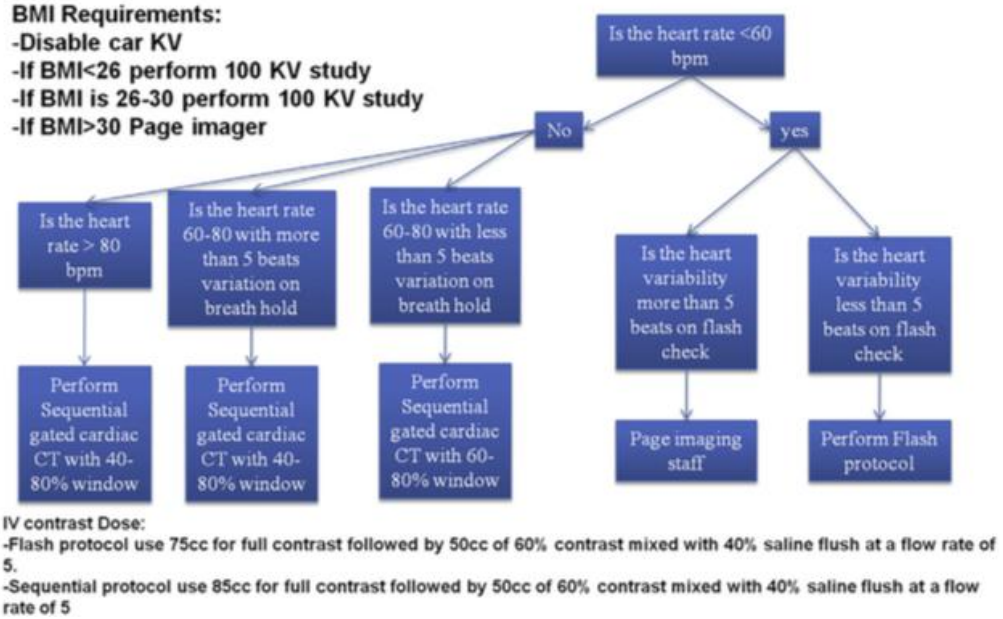

Fig. 1. Algorithm for selection of patient coronary CTA protocol based on body mass index (BMI), resting heart rate (HR) and HR variability. Flash protocol represents the use of high pitched, helical ECG-triggered image acquisition. CABG= coronary artery bypass grafting; IV= Intravenous; KV = tube voltage in kilo-voltage

3. RESULTS

Between July 7, 2010 and October 13, 2013 a total of 20 subjects were enrolled into the study due to the strict exclusion criteria (Table 1) and the limited number of subjects who agreed to participate in a single center. Of the 20 subjects who were enrolled, 8 were randomized to aspirin and placebo, and 12 were randomized to aspirin and clopidogrel. The 20 subjects contributed a total of 63 grafts. Ascertainment of end points was completed for all subjects in the study. The mean duration of therapy was 224 days for the aspirin and placebo group and 242.2 days for DAPT group. Adherence to treatment at 2 weeks was 100% for each arm and at 1 year was 50% in the DAPT arm and 62% in the aspirin and placebo arm, as described in Table 5.

The baseline characteristics of the patients who were enrolled in the study are shown in Table 2. After 2 weeks of therapy, a lower percentage of participants enrolled to DAPT had fewer patent grafts compared to aspirin monotherapy (88.9% vs. 92.6%) but did not reach statistically significance (odds ratio 1.56, 0.27-9.23 95% CI, p=0.492). At 52 weeks of therapy, the DAPT group demonstrated a higher proportion of patent grafts compared to Aspirin and placebo [(81.2% vs. 66.7%; odds ratio 0.46, 0.14-1.52 95% CI, p=0.205); Table 3]. When grafts were stratified by type (LIMA and SVG), all LIMA grafts were patent at 52 weeks and fewer SVG grafts were patent as shown in Table 3. The secondary outcomes, reported in Table 4, did not significantly vary by treatment arm. In addition, A treatment compliance analysis was performed restricting the treatment group to those that completed a full 12 months of therapy. Therefore, those participants randomized to Aspirin + Clopidogrel with less than 12 months of treatment duration were assigned to the Aspirin Alone group for this secondary analysis. This is referred to as a “per-protocol” analysis. The analysis of 52 week outcomes is presented in Tables 5 and 6 without statistically significant change in outcomes in the setting of being underpowered with low sample size.

Table 2. Descriptive analysis of baseline characteristics

Variable	Aspirin alone (n=8)	Aspirin+Clopidogrel (n=12)
	Mean (SD) / N (%)	Mean (SD) / N (%)
Systolic blood pressure	115.4 (12.34)	117.8 (10.7)
Diastolic blood pressure	65.1 (7.3)	69.5 (9.1)
Duration of therapy	224.0 (167.1)	242.2 (138.0)
Number of bypass grafts		
2	1 (12.5%)	3 (25.0%)
3	3 (37.5%)	6 (50.0%)
4	5 (50.0%)	3 (25.0%)
Hypertension	7 (87.5%)	12 (100.0%)
HLP	7 (87.5%)	12 (100.0)
Diabetes	5 (62.5%)	5 (41.7%)
Tobacco user	1 (12.5%)	0 (0.0%)

Table 3. Analysis of primary outcome

Outcome	Aspirin alone (n=27) N (%)	Aspirin + Clopidogrel (n=36) N (%)	P-value
Patent at 2 weeks	25 (92.6%)	32 (88.9%)	0.6332
Patent at 52 weeks	18 (66.7%)	26 (81.2%)*	0.1956
SVG Grafts	Aspirin alone (n=19) N (%)	Aspirin+Clopidogrel (n=24) N (%)	P-value
Patent at 2 weeks	17 (89.5%)	20 (83.3)	0.5966
Patent at 52 weeks	10 (52.6%)	15 (71.4%)**	0.2444

**n=32 in the Aspirin + Clopidogrel arm at 52 weeks, **n=21 in the Aspirin + Clopidogrel arm at 52 weeks*

Table 4. Analysis of secondary outcomes

Outcome	Aspirin alone (n=8) N (%)	Aspirin+Clopidogrel (n=12) N (%)	P-value
Myocardial infarction	1 (12.5%)	2 (16.7%)	0.6561
Angina	5 (62.5%)	7 (58.3%)	0.3521
Thrombotic event	0 (0.0%)	1 (9.1%)	0.5789

Table 5. Therapy compliance analysis of primary outcome – must be on Plavix for entire 12 months

Outcome	Aspirin alone (n=45) N (%)	Aspirin+Clopidogrel (n=18) N (%)	P-value
Patent at 2 weeks	41 (91.1%)	16 (88.9%)	0.8009
Patent at 52 weeks	32 (78.0%)	12 (66.7%)	0.3603
SVG Grafts	Aspirin alone (n=31) N (%)	Aspirin + Clopidogrel (n=12) N (%)	P-value
Patent at 2 weeks	27 (87.1%)	10 (83.3%)	0.7829
Patent at 52 weeks	19 (67.9%)**	6 (50.0%)	0.3244

**n=41 in the Aspirin Alone arm at 52 weeks, **n=29 in the Aspirin Alone arm at 52 weeks.*

Table 6. Therapy compliance analysis of secondary outcomes – must be on Plavix for entire 12 months

Outcome	Aspirin alone (n=14) N (%)	Aspirin+Clopidogrel (n=6) N (%)	P-value
Myocardial infarction	2 (14.3%)	1 (16.7%)	>0.99
Angina	8 (57.1%)	45 (66.7%)	>0.99
Thrombotic event	1 (7.1%)	0 (0%)	>0.99
MACE	9 (64.3%)	5 (83.3%)	0.6126

Comparison of graft flow (velocity) at the time of bypass surgery, all surgeries were on pump surgeries and none were performed off pump, was recorded to assess potential relation to graft patency at two weeks independent of DAPT. The average flow velocity per graft for the Aspirin+Clopidogrel group was 54.1 mL/min (SD=31.3 mL/min), and for Aspirin Alone it was 62.7 mL/min (SD=34.4 mL/min) without statistical impact on outcomes (p=0.3456). Lastly, the effect of velocity on treatment was estimated. This was performed by testing for an interaction between velocity and treatment. The interaction was not significant for the graft outcome at 2 weeks (patent vs. occluded) (p=0.0960) and also not significant at 52 weeks (p=0.0868). Thus, showing the effect of treatment was not dependent on velocity. There were no TIMI major and minor bleeding events reported throughout the trial.

4. DISCUSSION

Routine use of aspirin for antiplatelet therapy in patients who undergo coronary artery bypass grafting (CABG) remains the standard of care [7]. Utilizing aspirin and clopidogrel post-CABG is becoming more widely adopted, with national and international guidelines generally endorsing DAPT particularly after acute coronary syndrome [10].

Platelet activation, which occurs immediately after bypass surgery, is an important factor that appears to promote early thrombotic occlusion of vein grafts. During the first year after surgery, intimal hyperplasia forms a template for subsequent atherogenesis and thrombosis, which predominates following year one [11,12]. Antiplatelet agents may play a role in preventing the initial thrombus formation at the site of plaque and may minimize the impact of any embolization that does occur by preventing secondary thrombotic occlusion of the microvasculature [5,11,13-16].

Sub-analyses of DAPT treatments in patients' post-coronary bypass suggest improvement in cardiac outcomes. The CURE study demonstrated that the combination of DAPT with

aspirin and clopidogrel was more effective at reducing the primary outcome (cardiovascular death, nonfatal MI or stroke) compared to aspirin alone (clopidogrel and aspirin 9.3% vs. aspirin alone 11.4%, RRR 20%, $p < 0.001$) [17]. Studies have addressed the role of concomitant clopidogrel and aspirin for dual antiplatelet therapy after CABG [5,18-24]. However, studies are conflicting as to whether this is a result of bypass graft patency. Some studies support concomitant use of clopidogrel and aspirin for improved graft patency [5,20-22]; while other studies assert a lack of evidence or failed to demonstrate improved graft patency with dual antiplatelet therapy [19,24,25]. The PAPA (preoperative aspirin and postoperative antiplatelet) CABG study [21] randomized post-CABG patients to aspirin therapy versus aspirin and clopidogrel for 1 month. This trial revealed no differences between the two groups in the ratio of patients with occluded grafts and significant clinical outcomes, but concluded that the addition of clopidogrel to aspirin is feasible and safe and may be superior for prevention of graft failure in radial artery grafts. Gao and colleagues [22] showed significant improvement in graft patency based on coronary computed tomography angiography at 3 months post CABG in patients who received combination clopidogrel and aspirin versus aspirin alone post-CABG. The CASCADE [clopidogrel after surgery for coronary artery disease] study [24], which looked at saphenous vein graft intimal hyperplasia assessed by intravascular ultrasound at 1-year post CABG using aspirin and clopidogrel, conferred no benefit in reducing saphenous vein graft intimal hyperplasia. The CRYSSA (prevention of Coronary arteRY bypaSS occlusion After off-pump procedures) study by Mannacio and colleagues [20] showed decreased platelet resistance and significant improvement in venous graft patency in patients undergoing off-pump CABG who received combination clopidogrel and aspirin post-surgery versus aspirin alone based on 1-year angiographic data assessed by CCTA. Despite multiple trials, the combination of aspirin and clopidogrel as superior to aspirin alone on graft patency remains a point of debate.

Deo and colleagues [26] combined data from 25,728 patients and found that the use of dual anti-platelet therapy reduced early saphenous vein graft occlusion (RR =0.59 95% CI 0.43-0.82, $p=0.02$), in hospital or 30 day mortality when compared to aspirin alone (0.8% vs. 1.9%, $p<0.001$). Furthermore, when analyzing data from studies involving off pump CABG comparing DAPT versus aspirin alone, dual antiplatelet therapy reduced the risk of perioperative MI by 68% and saphenous venous graft occlusion by 55%. A meta-analysis by Nocerino et al. [27], which evaluated a total of 2,919 grafts with treatment up to 1 year after CABG, early occlusion occurred in a higher proportion of grafts treated with single therapy (OR for graft occlusion = 1.59 95% 1.16-2.17), as well as an increased graft loss rate (10.8%) when compared to DAPT.

While there is data suggesting a trend of improved graft patency with dual antiplatelet therapy, there is also data to support increased risk of bleeding. A combination of data from six different studies combining 18,090 patients found a trend towards higher risk of bleeding in patients treated with dual antiplatelet therapy after CABG (RR = 1.17, 95% CI 1.00–1.37, $p =0.05$) [26]. The CHARISMA (n=15603 patients) study did not report a significantly greater rate of severe bleeding with clopidogrel than with placebo [28]. Among UA/NSTEMI patients in the CRUSADE Registry [29] undergoing CABG, “early” CABG after clopidogrel was associated with an increase in any blood transfusion (OR 1.36, 95% CI 1.10 to 1.68) and the need for ≥ 4 units of blood (OR 1.70, 95% CI 1.32 to 2.1).

Multiple studies have advocated that graft patency is affected by multiple patient-specific and procedure-specific factors, and that the use of DAPT is only one such aspect [22,30-33]. Future studies are warranted to better define the role of such factors.

With a combined total of 63 grafts in this study, we aimed to help clarify whether combination aspirin and clopidogrel favorably impacts graft patency with lower incidence of major adverse cardiovascular events. Since there were no significant differences between treatment groups in terms of graft patency or adverse outcomes, this study suggests that the addition of clopidogrel to aspirin may not translate to improved 1-year graft patency or lower incidences of adverse cardiovascular events. Although this study neither supports nor disproves the concomitant use of clopidogrel and aspirin as superior to the use of aspirin alone, it cannot be dismissed as a reasonable adjunct to aspirin therapy. It does warrant future studies to better define the role of DAPT compared with the current standard aspirin therapy post-CABG and its impact on graft patency and clinical outcomes in order to make definitive recommendations.

Several limitations of the current study should be considered. The study did not recruit enough subjects due to strict exclusion criteria and low number of consenting patients. In excluding critically ill patients, the study may not accurately represent patients who will potentially benefit from DAPT, as patients with low cardiac output and low flow states usually encounter higher rates of thrombosis and major adverse cardiac events.

5. CONCLUSION

In conclusion, the results from our study showed a trend favoring venous graft patency at 52 weeks with dual anti-platelet therapy; however, it was not statistically significant difference or was it associated with lower incidence of adverse cardiovascular events due to the limitation of small sample size.

ETHICAL APPROVAL

All authors 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.

DISCLOSURE

The views and opinions expressed in this publication are those of the author(s) and do not reflect the official policy or the position of the Department of the Army, Department of Defense, or the US Government.

ACKNOWLEDGEMENT

The authors wanted to acknowledge the life work of Dorette Pearce-Moore who ensured the trial was conducted to the highest caliber of patient care and mourn her passing as a loss for all mankind.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Mozzafarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres J-P, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Munter P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein K, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. On behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics- 2015 update: A report from the American Heart Association. Circulation. 2015;131:e1-e294.
2. Lingaas PS, Hol PK, Lundblad R, et al. Clincal and angiographic outcome of coronary surgery with or without cardiopulmonary bypass: A prospective randomized trial. Heart Surg Forum. 2004; 7:37-41.
3. Helgason CM, Bolin KM, Hoff JA, Winkler SR, Mangat A, Tortorice KL, Brace LD. Development of aspirin resistance in persons with previous ischemic stroke. Stroke. 1994;25:2331-2336.
4. Gum PA, Kottke-Marchant K, Welsh PA, White J, Topol EJ. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol. 2003;41:961-965.
5. Kayacioglu I, Gunay R, Saskin H, Idiz M, et al. The role of clopidogrel and acetylsalicylic acid in the prevention of early-phase graft occlusion due to reactive thrombocytosis after coronary artery bypass operation. Heart Surg Forum. 2008;11:e152-e157.
6. Busheng Z, Jingxin Z, Haiqing L, Zixiong, et al. Comparison of graft patency between off-pump and on-pump coronary artery bypass grafting: an updated meta-analysis. Ann Thorac Surg. 2014;97:1335-1342.
7. Stein PD, Schunemann HJ, Dalen JE, Gutterman D. Antithrombotic therapy in patients with saphenous vein and internal mammary artery bypass grafts: The Seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest. 2004;126:600s–608s.
8. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: A report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2009;3:190-204.
9. Jones RL, Clark RA, Rubal BJ, et al. Temporal trends in radiation exposure and

utilization of coronary CT angiography, SPECT and invasive coronary angiography. Br J Med Med Res. 2014;4:3384-3392.

10. Patel JH, Stoner JA, Owora A, Mathew ST, Thadani U. Evidence for using clopidogrel alone or in addition to aspirin in post coronary artery bypass surgery patients. The American Journal of Cardiology 2009;103:1687–1693.
11. Bhatt DL, Topol EJ. Antiplatelet and anticoagulant therapy in the secondary prevention of ischemic heart disease. Med Clin North Am. 2000;84:163-179.
12. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation. 1998;97:916-931.
13. Buchanan MR, Brister SJ. Individual variation in the effects of ASA on platelet function: Implications for the use of ASA clinically. Can J Cardiol. 1995;11:221–227.
14. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. Circulation. 2000;101:2823-2828.
15. Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation. 2001;103:363–368.
16. Zimmermann N, Wenk A, Kim U, Kienzle P, Weber AA, Gams E, Schror K, Hohlfeld T. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. Circulation. 2003;108:542–547.
17. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: Lessons from the caprie and cure studies. Arch Intern Med. 2004;164:2106–2110.
18. Saw J, Topol EJ, Steinhubl SR, Brennan D, Berger PB, Moliterno DJ. Comparison of long-term usefulness of clopidogrel therapy after the first percutaneous coronary intervention or coronary artery bypass grafting versus that after the second or repeat intervention. Am J Cardiol. 2004;94:623-625.
19. Williams JB, Lopes RD, Hafley GE, Ferguson Tb Jr, Mack MJ, Michael Gibson C, Harrington RA, Peterson ED, Smith PK, Mehta RH, Alexander JH. Relationship between postoperative clopidogrel use and subsequent angiographic and clinical outcomes following coronary artery bypass grafting. J Thromb Thrombolysis. 2013; 36:384-393.
20. Mannacio VA, Di Tommaso L, Antignan A, De Amicis V, Vosa C. Aspirin plus clopidogrel for optimal platelet inhibition following off-pump coronary artery bypass surgery: Results from the CRYSSA (prevention of Coronary artery bypass occlusion After off-pump procedures) randomized study. Heart. 2012:98;1710-1715.
21. Sun JC, Teoh KH, Lamy A, et al. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: The preoperative aspirin and postoperative antiplatelets in coronary artery bypass grafting study. Am Heart J. 2010;160:1178– 1184.
22. Gao G, Zheng Z, Pi Y, et al. Aspirin plus clopidogrel therapy increases early venous graft patency after coronary artery bypass surgery a single-center, randomized, controlled trial. J Am Coll Cardiol. 2010;56:1639– 1643.
23. Gao C, Ren C, Li D, Li L. Clopidogrel and aspirin versus clopidogrel alone on graft patency after coronary artery bypass grafting. Ann Thorac Surg. 2009;88:59-62.
24. Kulik A, Le May MR, Voisine P, et al: Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: The clopidogrel after surgery for coronary artery disease (CASCADE) Trial. Circulation. 2010;122:2680–2687.
25. Ebrahimi R, Bakaeen FG, Uberoi A, Ardehali A, Baltz JH, Hattler B, Almassi GH, Wagner TH, Collins JF, Grover FL, Shroyer AL. Effect of clopidogrel use post coronary artery bypass surgery on graft patency. Ann Thorac Surg. 2014;97:15-21
26. Deo SV, Dunlay SM, Shah IK, Altarabsheh SE, et al. Dual anti-platelet therapy after coronary artery bypass grafting: Is there any benefit? A systematic review and meta-analysis. J Card Surg. 2013;28:109-16.
27. Nocerino AG, Achenbach S, Routledge T, Edmonds L, Altman DG, Large S. Meta analysis of effect of single versus dual antiplatelet therapy on early patency of bypass conduits after coronary artey bypass grafting. Am J Cardiol. 2013. 112:1576-1579.

28. Bhatt DL, Fox KA, Hackle W, Berger PB, Black HR, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. NEJM. 2006; 354:1706-1717.
29. Mehta RH, Roe MT, Mulgund J, et al. Acute clopidogrel use and outcomes in patients with non-ST-segment elevation acute coronary syndromes undergoing coronary artery bypass surgery. J Am Coll Cardiol. 2006;48:281-286.
30. Mujanovic E, Nurkic M, Caluk J, et al. The effect of combined clopidogrel and aspirin therapy after off-pump coronary surgery: A pilot study. Innovations (Phila). 2009;4:265–268.
31. Gurbuz AT, Zia AA, Vuran AC, et al. Postoperative clopidogrel improves mid-term outcome after off-pump coronary artery bypass graft surgery: A prospective study. Eur J Cardiothorac Surg. 2006;29:190–195.
32. Chan V, Kulik A, Bourke ME, et al. Clopidogrel is safe early after on- and off-pump coronary artery bypass surgery. J Card Surg. 2007;22:493–497.
33. Kim DH, Daskalakis C, Silvestry SC, et al. Aspirin and clopidogrel use in the early postoperative period following on-pump and off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2009;138:1377–1384.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/13503