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Aspirin Plus Clopidogrel Therapy Increases Early Venous Graft Patency After Coronary Artery Bypass Surgery

A Single-Center, Randomized, Controlled Trial

Ge Gao, MD,* Zhe Zheng, MD,* Yi Pi, MD,* Bin Lu, MD,† Jinguo Lu, MD,† Shengshou Hu, MD*

Beijing, The People's Republic of China

Objectives We sought to evaluate the effect of aspirin plus clopidogrel versus aspirin alone on saphenous vein graft occlusion at 3 months after coronary artery bypass grafting (CABG).

Background Prevalence of graft occlusion is high after CABG. Aggressive antiplatelet therapy is expected to improve early post-operative graft patency.

Methods From December 2007 through December 2008, 249 consecutive patients undergoing elective CABG at Fuwai Hospital were randomly assigned to 2 groups: 124 received aspirin (100 mg) plus clopidogrel (75 mg) daily (AC group), and 125 received aspirin (100 mg) alone daily (A group). Antiplatelet therapies were initiated when post-operative chest tube drainage was ≤30 cc/h for 2 h. All participants were invited for clinical follow-up and 64-slice multislice computed tomography angiography (MSCTA) analysis at 3 months post-operatively. Generalized estimating equations analysis was used to determine predictors of graft patency.

Results One participant, from group A, died before 3-month follow-up. Of the remaining 248 patients, 224 (90.3%) underwent MSCTA. Participants had similar pre-operative and intraoperative characteristics at baseline. No significant differences were observed in intraoperative transit-time flow measurement findings or major adverse cardiac-related events. Three-month MSCTA follow-up revealed that saphenous vein graft patency was 91.6% (219 of 239) in the AC group versus 85.7% (198 of 231) in the A group ($p = 0.043$). In multivariate analysis, combined antiplatelet therapy independently increased venous graft patency ($p = 0.045$).

Conclusions Aspirin plus clopidogrel is more effective in venous graft patency than aspirin alone in the short term after CABG, but further, long-term study is needed. (The Clopidogrel and Aspirin After Surgery for Coronary Artery Disease; NCT00776477) (J Am Coll Cardiol 2010;56:1639–43) © 2010 by the American College of Cardiology Foundation

There is a high prevalence of venous graft closure within 3 months after coronary artery bypass grafting (CABG) surgery (1). The main mechanism at this stage is graft thrombosis, which sets the stage for graft stenosis and occlusion. Despite its established comprehensive clinical use and benefit in patients with coronary heart disease, aspirin therapy has limitations, including failure to arouse a complete antiplatelet response in 5% to 10% of patients (2). Clopidogrel is a promising antiplatelet agent; its clinical efficacy at reducing ischemic events and mortality in patients with coronary and vascular disease has been demonstrated in several large clinical trials (3,4). To date, however, no trial has prospectively evaluated the synergistic effects of aspirin plus clopidogrel on saphenous vein graft (SVG) disease after CABG. Therefore, we conducted a randomized controlled trial comparing aspirin plus clopidogrel with aspirin alone in CABG patients revascularized with at least 1 saphenous vein. The aim of this study was to evaluate the effect of combined antiplatelet therapy 3 months after CABG on SVG patency and also the major adverse cardiac-related events.

From the *Department of Surgery, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, The People's Republic of China; and the †Center of Imageology, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, The People's Republic of China. This study was supported by the Key Project in the National Science & Technology Pillar Program during the 11th 5-Year Plan Period (2006BAI01A09). The authors have reported that they have no relationships to disclose. The first 3 authors contributed equally to this work.

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Methods

Patients. The study was a prospective randomized controlled trial. All patients referred for isolated surgical coronary revascularization from December 2007 to December 2008

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting

MACE = major adverse cardiac events

MSCTA = multislice computed tomography angiography

SVG = saphenous vein graft

with at least 1 SVG at Fuwai Hospital were screened according to the inclusion criteria. This study was approved by the local ethical committee with patient informed consent.

Inclusion criteria. Patients undergoing primary isolated CABG, with or without cardiopulmonary bypass, were eligible for inclusion in the study.

Exclusion criteria. Patients with an abnormal quantity of platelets before operation ($<100 \times 10^9$/l or $>300 \times 10^9$/l); previous CABG or other cardiac surgery; need for concomitant valve surgery or aneurysm resection; serum creatinine >130 μmol/l; left ventricular ejection fraction <30% on pre-operative ultrasound; liver disease; clopidogrel or aspirin intake within 7 days of operation; need for perioperative warfarin; active gastroduodenal ulcer or post-operative gastrointestinal bleeding; profuse post-operative pleural effusion (drainage >200 ml/h for 2 h or more); need for secondary thoracotomy to stop bleeding for cardiac tamponade; postoperative low cardiac output syndrome or requirement for high levels of hemodynamic support (more than 2 inotropes for more than 24 h and/or intra-aortic balloon pump); and clinical instability, such as perioperative myocardial infarction or malignant tumor, were excluded from the study.

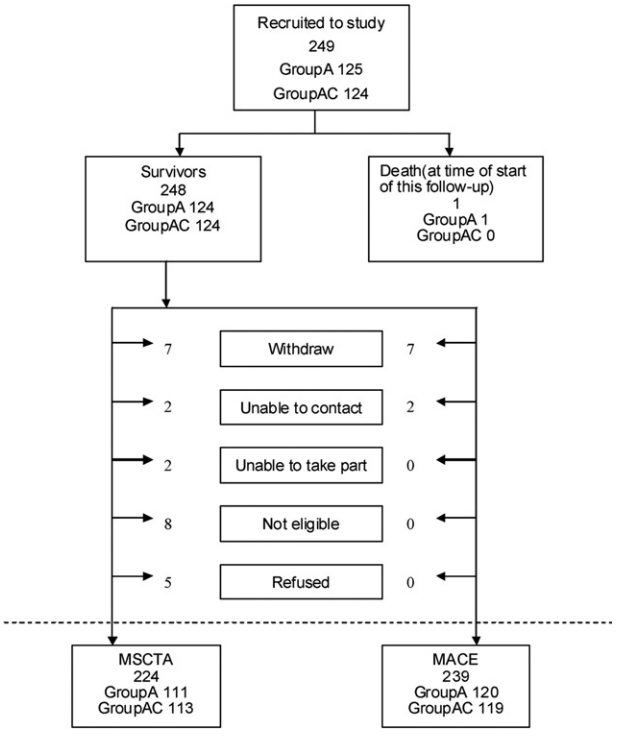

Figure 1 Flow Chart of the Study

Flow chart of the study, including deaths, numbers, and reasons for loss to follow-up and numbers contributing to analyses. GroupA = aspirin alone group; GroupAC = aspirin plus clopidogrel group; MACE = major adverse cardiac-related events; MSCTA = multislice computed tomography angiography.

Table 1 Pre-Operative Clinical Characteristics of the A and AC Groups

Characteristic	A Group (n = 111)	AC Group (n = 113)	p Value
Age (yrs)	59.8 ± 7.92	57.9 ± 8.25	0.096
Female	18 (16.2)	20 (17.7)	0.767
BMI (kg/m^2)	25.4 ± 3.60	25.9 ± 2.69	0.195
Hypertension	63 (56.8)	70 (61.9)	0.429
Diabetes	45 (40.5)	45 (39.8)	0.913
Hyperlipidemia	44 (39.6)	40 (35.4)	0.512
History of smoking	66 (59.5)	59 (52.2)	0.275
CHD family history	16 (14.4)	14 (12.4)	0.656
Previous PCI	18 (16.2)	12 (10.6)	0.219
Previous MI	49 (44.1)	56 (49.6)	0.417
Previous CVA	8 (7.2)	3 (2.7)	0.115
Pre-operative LVEF (%)	59.83 ± 7.87	60.64 ± 7.71	0.502
OPCAB	59 (53.2)	72 (63.7)	0.109

Values are mean ± SD or n (%).

A = aspirin alone; AC = aspirin plus clopidogrel; BMI = body mass index; CHD = coronary heart disease; CVA = cerebrovascular accident; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OPCAB = off-pump coronary artery bypass grafting; PCI = percutaneous coronary intervention.

Sample size. According to previous studies, single-aspirin protocol has a venous graft occlusion rate of 15% 3 months after surgery. As for dual antiplatelet protocol, the rate is 10%. We found that a 5% difference between 2 arms can be reliably detected under a power of 80%, if we have 270 venous grafts in each arm (significance level = 0.05).

Surgical procedures. All patients underwent either off-pump or on-pump CABG, according to surgeon discretion on the basis of anatomic and clinical findings. Before chest closure, mean flow values and pulsatile index were obtained with transit-time flow measurement (Medi-stim Butterfly flowmeter, Medi-stim AS, Oslo, Norway). If mean flow values were <10 ml/min, pulsatile index was >5.0, or any possible graft kinking or compression needed to be detected, the anastomosis was redone. Patients were excluded from the study if remeasurement results remained unsatisfactory.

Administration of antiplatelet agents. Patients with successful CABG surgery were randomly assigned to 2 groups: group A, receiving aspirin 100 mg daily; group AC, receiving aspirin 100 mg plus clopidogrel 75 mg daily. Antiplatelet agents were given orally when clinical stability was ensured and chest tube output was <30 ml/h for at least 2 h. Both antiplatelet therapies should be administered within 48 h. All patients received antiplatelet therapy for 3 months after operation.

Primary and secondary end point. The primary objective was to determine the effect of dual antiplatelet therapy on the incidence of graft occlusion at 3 months after bypass surgery, as assessed by multislice computed tomography angiography (MSCTA). A secondary objective was to assess the effect of treatment on the occurrence of major adverse

Table 2 Graft Characteristics of Patients

Parameters	Group A (n = 111)	Group AC (n = 113)	p Value
Distal anastomosis (n)	416	427	
LAD	110	112	NS
Diagonal	56	61	NS
LCx system	131	133	NS
RCA system	119	121	NS
Per person	3.75 (416/111)	3.78 (427/113)	NS
Graft type (n)	345	359	
LIMA	109	112	NS
RA	3	5	NS
SVG	233	242	NS
Sequential bypass	70	68	NS
Number of grafts (n)	111	113	
2	6	5	NS
3	87	83	NS
4	18	25	NS
Grafts/patients	3.11 (345/111)	3.18 (359/113)	NS

A = aspirin alone; AC = aspirin plus clopidogrel; DA = diagonal artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LIMA = left internal mammary artery; RA = radial artery; RCA = right coronary artery; SVG = saphenous vein graft.

cardiac events (MACE), defined as follows: 1) cardiogenic death; 2) myocardial infarction (hospital visit for myocardial infarction reported by patient or hospital admission for myocardial infarction reported by cardiologist); and 3) the need for revascularization (repeat operation or angioplasty reported by patient or cardiologist) through 3 months after CABG.

Graft patency by 64-slice MSCTA. All patients were scheduled for a systematic MSCTA at 3 months after surgery with the 64-slice MSCTA scanner (GE Healthcare, Milwaukee, Wisconsin). The images were transferred to a stand-alone workstation (Deep Blue, ADW4.3, GE Healthcare) and evaluated with dedicated analysis software. The results of MSCTA were independently reviewed by 2 radiologists blinded to randomized allocation. Each graft was classified as patent (flow visible), occluded, or not analyzable (e.g., because the graft was obscured by a metal ligature clip or because the image quality was poor). When a conduit did not fill with contrast at all, it was considered occluded and was included with string sign found in any segment (including proximal anastomotic site, distal anastomotic site, and main trunk). Both of these latter findings were considered together and referred to as occlusion in the analysis. Discrepancies in patency definition were reviewed by a third investigator and resolved by consensus.

Statistical analysis. Clinical baseline characteristics and post-operative outcomes were compared statistically. The Student *t* test and chi-square test were used to analyze continuous and categorical variables, respectively. A non-parametric test was used to compare graft flow and pulsation indexes of the 2 groups. In univariate analyses, means and SDs were used for continuous variables, and frequencies and percentages were used for categorical variables. Multivariable generalized estimating equations analysis was used to examine independent risk factors related to vein graft patency. In all cases, a p value <0.05 was considered as statistically significant. All analyses were performed with SPSS statistical software version 11.0 (SPSS, Inc., Chicago, Illinois).

Results

Two-hundred forty-nine cardiac surgery candidates were randomized to group A (n = 125) or group AC (n = 124). Of the 249 participants, 1 (0.4%) (from group A) died at 6 weeks after CABG surgery. Of the remaining 248 patients, 239 (96.4%) completed a 3-month follow-up, and 224 (90.3%) underwent MSCTA. Deaths, numbers and reasons for loss to follow-up, and numbers contributing to analyses are shown in Figure 1. The patient demographic, disease entity, and comorbidity data were collected prospectively and are summarized in Table 1. Participants had characteristics at baseline similar to the entire randomized cohort. No significant difference was found between the 2 groups in terms of MACE. Graft characteristics including number of distal anastomosis at different sites, number of different graft types, number of grafts and grafts/patients were compared; no significant difference was found (Table 2). Intraoperative transit-time flow measurement findings were also similar in both groups (Table 3).

At 3-month MSCTA follow-up, patency was studied in 704 grafts of 224 patients; 11 (1.6%) grafts were deemed nondiagnostic by 2 radiologists. Overall, 58 (8.4%) of 693 grafts were classified as occluded after disagreements were reconciled—23 (6.5%) in the AC group versus 35 (10.3%)

Table 3 Mean Graft Flow and Pulsation Index by Intraoperative TTFM in A and AC Groups

Graft Position	Graft Number		Graft Flow (ml/min)			Pulsation Index		
	A Group	AC Group	A Group 25th, 50th, 75th Percentiles	AC Group 25th, 50th, 75th Percentiles	p Value	A Group 25th, 50th, 75th Percentiles	AC Group 25th, 50th, 75th Percentiles	p Value
LIMA: anterior wall	109	112	21, 32, 33.5	18.5, 29, 32.75	0.054	1.7, 2.0, 2.2	1.625, 2.15, 2.375	0.176
Aorta: anterior wall	26	30	22, 34, 37	20, 29, 31.75	0.256	1.5, 1.9, 2.2	1.85, 2.0, 2.175	0.261
Aorta: lateral wall	97	102	30, 39, 49.5	27.75, 39.5, 50	0.573	1.5, 1.9, 2.1	1.6, 1.9, 2.2	0.577
Aorta: inferior wall	110	110	24, 37.5, 49.25	24, 36.5, 49	0.702	1.4, 2.0, 2.5	1.4, 1.9, 2.125	0.153

TTFM = transit-time flow measurement; other abbreviations as in Tables 1 and 2.

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Table 4 Prevalence of Graft Occlusion in A and AC Groups

	A Group		AC Group			
Type	Total/Evaluable	Occluded n (%)	Total/Evaluable	Occluded n (%)	p Value	Relative Risk (95% CI)
LIMA	109/106	1 (0.9)	112/110	2 (1.8)	0.583	0.519 (0.048–5.638)
RA	3/3	1 (33.3)	5/4	1 (25)	0.809	1.333 (0.129–13.743)
SVG	233/231	33 (14.3)	242/239	20 (8.4)	0.043	1.707 (1.010–2.886)
Total	345/340	35 (10.3)	359/353	23 (6.5)	0.073	1.580 (0.954–2.617)

CI = confidence interval; other abbreviations as in Tables 1 and 2.

in the A group. Graft patency for SVGs was 91.6% (219 of 239) in the AC group versus 85.7% (198 of 231) in the A group (relative risk: 1.707; 95% confidence interval: 1.010 to 2.886; p = 0.043) (Table 4). In the multivariate analysis, combined antiplatelet therapy independently increased venous graft patency (relative risk: 1.996; 95% confidence interval: 1.015 to 3.922; p = 0.045). Other strong predictors of higher venous graft patency rate were larger distal runoff, higher mean graft flow, and lower pulsatile index (Table 5).

Table 5 Multivariate Analysis of Relative Risk Factors for Venous Graft Patency at 3 Months After CABG

Risk Factor	Odds Ratio	95% CI	p Value
Sex			
Male	Reference		
Female	0.6	0.187–1.921	0.390
Hyperlipidemia			
Yes	Reference		
No	1.096	0.511–2.353	0.814
Diabetes			
Yes	Reference		
No	0.729	0.375–1.418	0.352
History of smoking			
Yes	Reference		
No	1.032	0.420–2.540	0.945
Antiplatelet therapy			
Aspirin alone	Reference		
Aspirin + clopidogrel	1.996	1.015–3.922	0.045
Anastomotic position of SVG			
RCA	Reference		
LCx	1.505	0.683–3.316	0.311
LAD	0.836	0.293–2.382	0.737
Sequential anastomosis			
Yes	Reference		
No	1.092	0.423–2.817	0.856
CABG procedure			
On-pump	Reference		
Off-pump	1.076	0.509–2.275	0.849
Age	1.026	0.985–1.069	0.213
BMI	1.038	0.942–1.143	0.452
Mean graft flow	1.045	1.005–1.088	0.029
Pulsation index	0.438	0.309–0.622	<0.001
Runoff	24.159	3.685–158.395	0.001
Proximal stenosis of target vessels	6.104	0.191–195.495	0.306

CABG = coronary artery bypass grafting; other abbreviations as in Tables 1 and 2.

Discussion

The primary reason for graft stenosis and occlusion after CABG is formation of thrombus, which is related to anastomotic technique, graft quality, and coagulation function in the perioperative period (5). Platelets play a fundamental role in this process. Even with standard aspirin therapy, a significant proportion of patients present post-operatively with graft stenosis or occlusion, especially with vein material, and seem to be at increased risk for developing adverse vascular events (6). Many people are affected by aspirin resistance, defined as undetectable platelet inhibition after 1 week of therapy (7). Clopidogrel is a thienopyridine antiplatelet agent that inhibits adenosine diphosphate-dependent platelet activation and aggregation, unlike aspirin, which mainly selectively depresses platelet cycloxygenase-1 and interrupts the formation of thromboxane A2. They work on different stages of thrombosis, and therefore theoretically the combination of aspirin and clopidogrel should lead to superior potent synergistic antithrombotic effects compared with either therapy alone (8).

The benefit of aspirin plus clopidogrel on the outcome of CABG has been demonstrated in several trials (3,9,10); whether the combination of aspirin and clopidogrel is superior to aspirin alone on graft patency is not yet resolved. Our study is the first randomized controlled trial to examine graft patency as the primary end point, providing definitive clinical data on the efficacy of combined antiplatelet therapy on SVG patency. The result of generalized estimating equation analysis demonstrates that SVG patency is affected by multiple patient-specific and procedure-specific features, and use of dual antiplatelet therapy is only 1 such factor. The positive aspect of this study is the exploration of an ideal antiplatelet protocol that can significantly improve venous graft patency.

Study limitations. It is important to remember that the current trials were carried out in a single center without placebo control, which is the main limitation of this study. In addition to the MSCTA observers, the investigator and patients were not blinded to the randomized allocation. However, the objective results of MSCTA would be hardly impaired by this shortcoming. Furthermore, we did not evaluate platelet function; consequently, individual variability in the antiplatelet therapy was not taken into account. In

the current study, there was no significant difference between the 2 groups on the end points of MACE, most probably due to our relatively small sample size and short follow-up period. Longer follow-up and larger sample size might be warranted to reveal the effectiveness of dual antiplatelet therapy on the end point of clinical outcome.

Conclusions

This study shows that the combination of aspirin plus clopidogrel significantly increased venous graft patency at 3 months after CABG compared with aspirin alone. Combined antiplatelet therapy, larger runoff, and higher mean graft flow are independently correlated with elevated venous graft patency, whereas pulsatile index is an independent risk predictor. No significant differences in MACE between the 2 groups were observed.

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Reprint requests and correspondence: Dr. Shengshou Hu, Department of Surgery, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 167A Beilishilu, Beijing 100037, The People's Republic of China. E-mail: shengshouhu@yahoo.com.

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Key Words: antiplatelet therapy ■ clopidogrel ■ coronary artery bypass grafting ■ graft patency ■ multislice computed tomography angiography.