The Heart Surgery Forum #2007-1196
11 (3), 2008 [Epub June 2008]
doi: 10.1532/HSF98.20071196

Online address: http://cardenjennings.metapress.com

The Role of Clopidogrel and Acetylsalicylic Acid in the Prevention of Early-Phase Graft Occlusion Due to Reactive Thrombocytosis after Coronary Artery Bypass Operation

Ilyas Kayacioglu, MD,[1] Rafet Gunay, MD,[1] Huseyin Saskin, MD,[1] Mustafa Idiz, MD,[1] Yavuz Sensoz, MD,[1] Mehmet Ates, MD,[1] Burak Tangurek, MD,[2] Ahmet Taha Alper, MD,[2] Mahmut Murat Demirtas, MD,[1] Ibrahim Yekeler, MD[1]

[1]Cardiovascular Surgery and [2]Cardiology Departments, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center, Istanbul, Turkey

ABSTRACT

Background. Reactive thrombocytosis has been reported in 20% of patients after coronary artery bypass grafting (CABG), a frequency that might be related to the high incidence of thrombotic complications. The present study was planned to investigate the effect of combined treatment with clopidogrel and acetylsalicylic acid (ASA) on post-CABG reactive thrombocytosis.

Methods. Included in this prospective, randomized study were 60 patients who underwent CABG operation with a 6-month follow-up. Three study groups were defined: group 1 (n = 20), a control group of patients who have not developed reactive thrombocytosis after CABG surgery; group 2 (n = 20), patients who have developed reactive thrombocytosis and continue taking ASA (300 mg/day); and group 3 (n = 20), patients who have developed reactive thrombocytosis and continue taking ASA (300 mg/day) with the addition of clopidogrel (75 mg/day).

Results. The mean ages and sex distributions of the patient groups were similar. There were no significant differences between the groups regarding cardiovascular risk factors, baseline laboratory findings, or intraoperative characteristics. Thrombocytosis disappeared within the first month after the operation in both treatment groups. An evaluation of graft patency in the sixth postoperative month revealed that group 2 had significantly more patients with a "positive" result in the exercise test than group 3 and that group 3 had a lower incidence of graft occlusion than group 2 ($P < .01$).

Conclusions. Combination antiplatelet therapy with ASA and clopidogrel seems to be more effective than ASA alone for maintaining graft patency in patients with reactive thrombocytosis.

Received October 10, 2007; received in revised form January 31, 2008; accepted February 4, 2008.

Correspondence: Dr. Rafet Gunay, Haznedar Mah. Yıldız Sk. No: 3/3, Gungoren, 34590 Istanbul, Turkey; 90-212-5390344; fax: 90-216-4189649 (e-mail: rafetgunay@hotmail.com).

INTRODUCTION

The main limitation on grafting success is stenosis or occlusion of the grafts. Subsequent reoperations further reduce the clinical benefits and increase the risk of perioperative mortality and morbidity [FitzGibbon 1996].

Impaired platelet functions are observed after major cardiac surgical interventions. Decreases in platelet counts have been reported during cardiopulmonary bypass (CPB) and are due to several factors, such as hemodilution, platelet destruction, heparinization, platelet sequestration, and adhesion to the extracorporeal system [McKenzie 1969]. After the initial post-CPB decrease in platelet count, a prominent increase, called *reactive thrombocytosis*, may be observed not only in the platelet count, but also in platelet adhesion and aggregation [McKenzie 1969]. Reactive thrombocytosis (platelet count $>450 \times 10^3/mm^3$) has been reported in 20% of patients who undergo coronary artery bypass grafting (CABG) surgery. It seems likely that reactive thrombocytosis is related to the high incidence of thrombotic complications, such as early and delayed graft occlusion and myocardial infarction [Schmuziger 1995].

There is a tendency to use thienopyridines, especially clopidogrel, ticlopidine, and glycoprotein IIb/IIIa inhibitors, for antiplatelet therapy in patients with coronary artery disease. The effects of these agents on platelet functions are different from those of acetylsalicylic acid (ASA) [Quinn 1999]. Therefore, our aim in the present study was to compare the beneficial effects of combined treatment with clopidogrel plus ASA and treatment with ASA alone on post-CABG reactive thrombocytosis.

MATERIALS AND METHODS

Patients

We included 60 patients who underwent CABG operation in this prospective randomized study. All patients underwent their operations and follow-up with the same team of surgeons and physicians.

Study Protocol

The patient's age, sex, medical history of smoking, hypertension, and diabetes mellitus, and preoperative ejection fraction values were recorded. Patients with one or more of the following were excluded from the study: a preoperative platelet count <100,000/mm^3 or >400,000/mm^3, development of infection after the surgery (eg, mediastinitis, infection of the saphenous vein graft site, and so forth), >2 days stay in the intensive care unit following surgery, known hypersensitivity to ASA and/or clopidogrel, and a history of gastrointestinal and/or cerebral bleeding.

ASA therapy was started in all groups on the first postoperative day. The platelet count was measured 1 hour after the operation and on the first, third, and seventh postoperative days. We randomized the patients on the seventh postoperative day if platelet counts had not exceeded 450 × 10^3/mm^3 during the previous days. Those who developed reactive thrombocytosis were randomized into group 2 or 3. Group 2 patients continued ASA treatment, and group 3 patients continued ASA treatment along with clopidogrel at the doses given below. We defined the following 3 study groups: group 1 (n = 20), control patients who have not developed reactive thrombocytosis; group 2 (n = 20), patients who have developed reactive thrombocytosis (platelet count >450 × 10^3/mm^3) and continue ASA treatment (300 mg/day, orally); and group 3 (n = 20), patients who have developed reactive thrombocytosis (platelet count >450 × 10^3/mm^3) and continue ASA treatment (300 mg/day, orally) with the addition of clopidogrel (75 mg/day, orally).

The study protocol was approved by the local ethics committee of the study site. The study was conducted in adherence with the International Conference of Harmonization/Good Clinical Practice and local regulations.

Laboratory Tests, Exercise Test, and Angiography

The following laboratory tests were performed in all groups at the preoperative baseline and 1 hour, 1 day, 3 days, 7 days, 1 month, 3 months, and 6 months after the operation: complete blood count, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate, serum C-reactive protein (CRP), fibrinogen, creatine kinase–MB (CK-MB), serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, lactate dehydrogenase, blood urea nitrogen, creatinine, glucose, total cholesterol, triglycerides, and low-density lipoprotein, high-density lipoprotein, and very-low-density lipoprotein cholesterol. Exercise stress tests were performed at the first-, third-, and sixth-month follow-up visits in accordance with the Bruce protocol [Bruce 1973]. Functional capacity was assessed according to the results of the metabolic equivalent test [Ainsworth 2000], and patients were classified according to the New York Heart Association classification of functional capacity. For patients with a low functional capacity and maximal "positive" results in the exercise test, coronary angiography was performed at postoperative month 6.

Statistical Analysis

The results are expressed as the mean ± SD. We used the Statistical Package for the Social Sciences (SPSS) for Windows 9.0 (SPSS, Chicago, IL, USA) for statistical analyses. Categorical variables were analyzed with the chi-square test. Unpaired parametric data were analyzed by 1-way analysis of variance (ANOVA) and the Tukey HSD test for post hoc between-group comparisons. Repeated measurements were analyzed by 1-way ANOVA for repeated measures, and paired samples were analyzed by the Student *t* test with the Bonferroni correction. A *P* value <.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The mean ages of the patients in groups 1, 2, and 3 were 56.4 ± 8.9 years, 58.1 ± 10.5 years, and 56.6 ± 8.8 years, respectively, and almost all of the patients were male (Table 1). There were no significant differences between the groups with respect to cardiovascular risk factors, including age, sex distribution, presence of hypertension, diabetes mellitus, or hyperlipidemia, and smoking. We used preoperative ejection fraction values to assess ventricular function, and the values for the 3 groups were 0.54 ± 0.07, 0.50 ± 0.09, and 0.55 ± 0.09, respectively; the differences in ejection fraction between the groups were not significant. Table 2 summarizes the patients' baseline laboratory findings, which revealed no significant differences between the groups except for platelet count and CRP and fibrinogen levels.

Intraoperative and Early Postoperative Characteristics

All patients underwent CABG surgery with CPB. There were no intergroup differences regarding CPB time, cross-clamping time during the operation, duration of intubation, drainage volume, development of arrhythmia, and 1-hour CK-MB levels during the early postoperative intensive care unit stays. The only significant difference was the development of postoperative electrocardiographic changes in 9 of the 20 patients in group 2, compared with only 1 patient in group 1 and 2 patients in group 3 (*P* = .003).

Postoperative Laboratory Findings

Platelet Counts There were no differences between the groups with respect to the patients' platelet counts at 1 hour after the operation and on postoperative days 1 and 3.

Table 1. Demographics and Basic Characteristics of the Patients*

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	*P*
Age, y	56.4 ± 8.9	58.1 ± 10.5	56.6 ± 8.8	.827
M/F sex, n	16/4	19/1	19/1	.189
Hypertension, n	11	13	9	.446
Diabetes mellitus, n	4	5	5	.911
Hyperlipidemia, n	5	11	11	.089
Cigarette smokers, n	13	18	15	.170
Ejection fraction	0.54 ± 0.07	0.50 ± 0.09	0.55 ± 0.09	.122

*Age and ejection fraction data are presented as the mean ± SD.

Table 2. Preoperative Laboratory Findings for the Patients*

	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	*P*
Hemoglobin, g/dL	15.17 ± 1.66	14.95 ± 0.96	14.92 ± 1.47	.825
Hematocrit, %	43.87 ± 4.86	43.32 ± 2.69	42.86 ± 3.73	.714
Platelet count, /mm^3	209,450 ± 49,068	256,350 ± 63,643	238,500 ± 46,442	.026†
Platelet volume, fL	8.14 ± 1.09	7.91 ± 0.76	8.27 ± 0.89	.438
Erythrocyte sedimentation rate, mm/h	25.55 ± 19.38	32.50 ± 20.61	24.00 ± 10.98	.271
CRP, mg/dL	4.55 ± 2.54	5.85 ± 3.47	3.05 ± 1.60	.006†
Fibrinogen, mg/dL	248.70 ± 64.34	304.20 ± 72.65	238.20 ± 60.91	.005†

*Data are presented as the mean ± SD.

†Indicates a statistically significant difference between the groups.

According to the study protocol described above, the patients who had platelet counts within the normal range were assigned to group 1, and the others who developed thrombocytosis were assigned to group 2 or 3. Platelet counts did not exceed the upper normal limit throughout the follow-up period in any of the patients in group 1. In both treatment groups, thrombocytosis disappeared within the first month (Figure 1). Because the mean pretreatment platelet count of the patients who received ASA plus clopidogrel (group 3) was significantly higher than the mean platelet count of ASA-only patients (group 2) on the seventh day after bypass surgery, the mean platelet count in group 3 remained higher than in the other groups throughout the follow-up period. However, the lack of a significant difference between the 2 treatment groups indicated the similar efficacies of the 2 treatments in returning high platelet counts to within the normal range. The differences in the values for serial measurements were significant in each group ($P < .01$).

Serum Fibrinogen Levels The levels of serum fibrinogen, which is known to trigger the development of coronary artery disease and atherosclerosis, were measured at the baseline and at postoperative day 7, month 1, month 3, and month 6. Unfortunately, the preoperative mean fibrinogen concentration in group 2, although within the normal range, was significantly higher than in the other groups and remained significantly higher throughout the follow-up period (Figure 2). No significant difference between groups 1 and 3 was observed. Differences in the values of serial measurements were significant in each group ($P < .01$).

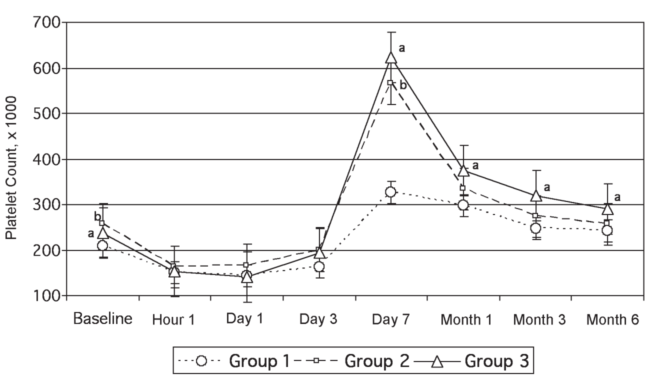

Figure 1. Changes in platelet counts: values at the baseline and during 6 months of postoperative follow-up. [a]$P < .05$, group 3 versus group 1. [b]$P < .05$, group 2 versus group 1.

CRP Levels We measured the concentrations of another cardiovascular risk factor, the acute-phase reactant CRP. A significant increase in CRP levels was observed on the seventh postoperative day in all groups (Figure 3). The CRP levels in group 2 remained significantly higher than those in the other 2 groups throughout the follow-up period. Despite this difference, the numbers of patients with CRP levels >1 mg/dL were similar in the 3 groups. Differences in the values of serial measurements were significant in each group ($P < .01$).

CK-MB Levels The CK-MB level is used as an indicator of acute myocardial infarction in patients with coronary artery disease and during post-CABG follow-up. Although CK-MB levels remained high for the first 3 postoperative days, there were no significant intergroup differences, except that the mean CK-MB level of the patients treated with ASA plus clopidogrel (group 3) was lower than that of the ASA-only patients (group 2) at the month 6 measurement (Figure 4). Differences in the values of serial measurements were significant in each group ($P < .01$).

Evaluation of Graft Patency at Postoperative Month 6: Exercise Test and Angiography Results

All patients in the study performed the exercise test in accordance with the Bruce protocol [Bruce 1973] at the follow-up visits at postoperative months 1, 3, and 6. One patient (5%) in group 1 and 7 patients (35%) in group 2 had positive results in the exercise test, whereas the results of the exercise tests were negative in all of the patients in group 3 ($P = .002$ for the intergroup difference). A significant difference was found between groups 2 and 3 in favor of group 3, regarding the positive results in the exercise test and the incidence of graft occlusion ($P < .01$).

The patient groups were significantly different with respect to New York Heart Association functional capacity class at the first and sixth postoperative months ($P = .026$, and $P = .017$, respectively), with higher proportions of group 3 patients in functional class I.

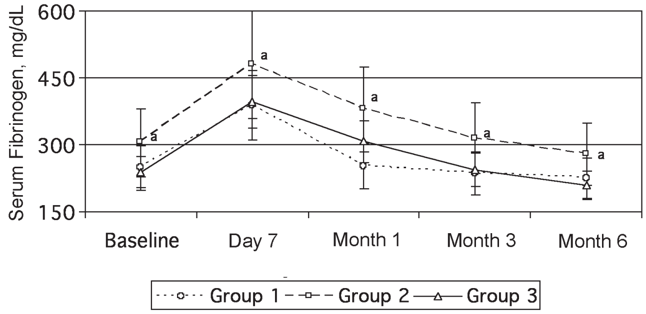

Figure 2. Serum fibrinogen levels at baseline and during 6 months of postoperative follow-up. [a]$P < .05$, group 2 versus groups 1 and 3.

Coronary and graft angiography evaluations were performed after the month 6 evaluation in the 8 patients with "positive" results in the exercise test. The only patient in group 1 had 80% stenosis of the native circumflex artery, which was not present before the CABG surgery. In group 2, 1 patient had occlusion of the left internal mammary artery, and 3 patients had occlusion of the venous graft. New stenosis of 70% to 80% was detected in the circumflex artery of 1 patient, and stenosis of 50% to 60% was detected in the right coronary artery of another patient; these stenoses were not present before the operation. The angiograms of the remaining 2 patients in group 2 who underwent this procedure had a normal appearance. The angiography results for groups 1 and 2 were significantly different with respect to the incidence of graft occlusion ($P = .018$).

COMMENT

CABG surgery is a common intervention performed all over the world. The main limitation on grafting success is stenosis or occlusion of the grafts, which affects mortality and morbidity. Thrombosis is the major impairment of vein graft patency in patients who undergo CABG surgery and develops because of hemostatic imbalance. The rate of graft occlusion is approximately 2% to 3% per year [Johnson 1989]. Approximately 10% to 15% of grafts are occluded in the acute postoperative phase (within a few hours or days) [Roberts 1981].

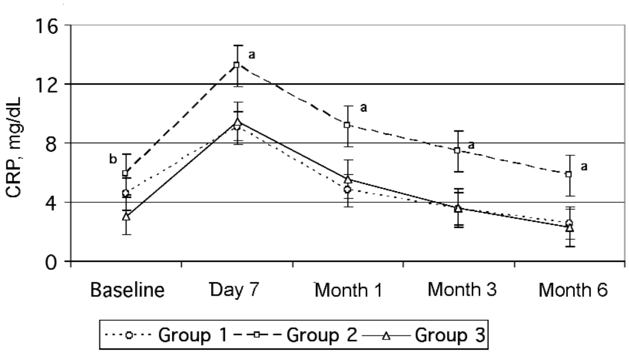

Figure 3. Serum levels of C-reactive protein (CRP). [a]$P < .05$, group 2 versus groups 1 and 3. [b]$P < .05$, group 2 versus group 3. Serial measurements were significantly different ($P < .001$) in all groups.

There are many causes of acute graft occlusion. The most evident cause is a small diameter of the native vessel associated with high resistance and low flow [Chesebro 1982]. Another cause is disturbed runoff due to discordance between the artery and graft diameters [FitzGibbon 1986]. Other important factors affecting graft patency are the surgical manipulations before anastomosis, the distal and proximal anastomosis diameters, the peripheral runoff of coronary vessels, atherosclerosis at the proximal part of the distal anastomosis, the aliveness of the perfused myocardial area, and postoperative antithrombotic therapy [Packham 1986]. According to most studies, the major determinants of graft patency are the ability of the graft to adapt to the coronary circulation, its tendency to develop proliferative atherosclerotic changes after implantation, and its antithrombotic properties [Motwani 1998].

Researchers have suggested that women are more prone than men for developing graft occlusion because the diameters of their vessels are smaller [Johnson 1989]. Atherosclerosis is seen more often in elderly patients, and graft occlusion usually develops after the first year in such patients [Lichtlen 1992]. However, we found no difference between the control and treatment groups in this study with respect to mean age and sex distribution.

Diabetes mellitus, hypertension, and smoking are well-known cardiovascular risk factors. For example, smokers develop coronary artery disease and graft occlusion after CABG surgery 3 times more often than nonsmokers, because nicotine causes platelet dysfunction [Schmuziger 1995]. Smoking and hyperlipidemia have also been suggested to cause postoperative reactive thrombocytosis and acute graft occlusion in patients who have undergone CABG surgery [Schmuziger 1995]. The groups in the present study were similar with respect to the distributions of patients with these risk factors. Although the preoperative cholesterol level has been found to be significantly higher in patients with reactive thrombocytosis [Christenson 1996], the cholesterol levels in the groups in our study did not differ during the follow-up. Extensive baseline laboratory screening revealed that the 3 groups were similar.

The success of CABG surgery depends on postoperative graft patency. The major predictor of long-term graft patency is the quality of the distal vessel into which the graft is placed, and graft patency may be improved with specific platelet-inhibitor therapy [Goldman 1988]. Clopidogrel is a thienopyridine derivative that blocks platelet aggregation by inhibiting the binding of adenosine diphosphate to its platelet receptors, which leads to direct inhibition of fibrinogen binding to the glycoprotein IIb/IIIa complex, thereby inhibiting platelet aggregation [Quinn 1999]. Clopidogrel was found to be more effective than ASA in inhibiting the ischemic processes occurring after CABG surgeries [Blatt 2001]. In the study of Lorenz et al [1984], a 100-mg daily dose of ASA or placebo was given to patients for 4 months, starting on the first

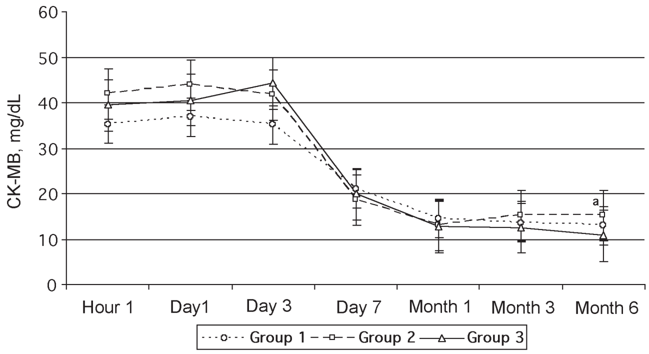

Figure 4. Serum creatine kinase–MB (CK-MB) levels during 6 months of postoperative follow-up. [a]$P < .05$, group 3 versus group 2, in favor of group 3.

day of the postoperative period; the frequency of graft patency was 90% in the ASA group and 68% in the placebo group.

The results of the CAPRIE trial [1996] suggest that long-term treatment with clopidogrel is more effective than aspirin in patients with a history of acute myocardial infarction, ischemic stroke, or peripheral arterial disease in reducing the cumulative risk of ischemic stroke, acute myocardial infarction, and cardiovascular death without significantly increasing the risk of serious adverse events. In the CURE study [2001], the percentages of patients with in-hospital refractory or severe ischemia, heart failure, and revascularization procedures were also significantly lower with clopidogrel plus ASA than with ASA alone. The antiplatelet agent clopidogrel has beneficial effects in patients with acute coronary syndromes without ST-segment elevation. Clopidogrel is a reasonable alternative to aspirin, especially if aspirin is not tolerated or is otherwise contraindicated [Quinn 1999].

On the other hand, platelet adhesion and aggregation evidently increase following the decline in the platelet count after CPB [McKenzie 1969]. A postoperative increase in platelet count (to $>450 \times 10^3/mm^3$, reactive thrombocytosis) was noted in 20% of CABG patients [Schmuziger 1995], and this reactive thrombocytosis was found to be related to an increased incidence of thrombotic complications, such as vein graft occlusion and myocardial infarction [Schmuziger 1995]. Therefore, thrombocytosis is accepted as one of the risk factors in patients who undergo CABG surgery.

Little is known about the effect of reactive thrombocytosis on acute graft occlusion in patients who undergo CABG surgery and have a platelet count $>450 \times 10^3/mm^3$. In clinical practice, the combination of aspirin and clopidogrel is recommended for patients with postoperative thrombocytosis [Motwani 1998]. In this study, we observed no significant difference between the group treated with ASA alone (group 2) and the group treated with ASA plus clopidogrel (group 3) in terms of returning high platelet counts to within the normal range. This finding indicates the similar efficacies of the 2 treatments.

Nevertheless, several statistically significant differences suggest the better performance of the combination therapy. For example, changes in electrocardiograms occurred postoperatively in 9 of the 20 patients in group 2, but only 1 patient in group 1 and 2 patients in group 3 developed such changes. CK-MB levels remained high for the first 3 postoperative days, and there were no significant intergroup differences, except for a lower mean CK-MB level in patients treated with ASA and clopidogrel (group 3) at the sixth month, compared with the patients treated with ASA alone (group 2). In the exercise and angiographic evaluations of graft patency at postoperative month 6, one (5%) of the patients in group 1 and 7 (35%) of the patients in group 2 had positive results in the exercise test, whereas the exercise test results were negative for all of the patients in group 3. These results indicate that none of the patients who received the combination therapy developed graft occlusion by 6 months after surgery, unlike those treated with ASA alone.

This study had several limitations. First, the sample size was small, but such prospective randomized studies can yield valuable scientific results even with a small sample size. A large series is necessary for evaluating patients who have reactive thrombocytosis; however, we encountered such patients in only approximately 5% of CABG operations. Second, we cannot state precise details on graft outcomes because we did not routinely perform postoperative coronary angiographic evaluations in our series. Performance of postoperative angiography in all of the patients would have provided more reliable results but was not feasible because of the costs. We performed coronary angiographic evaluations for patients who had positive results in the exercise test and on the basis of the patients' functional status. The third limitation is that group 2 patients had higher CRP and fibrinogen levels, which may indicate that patients in this group had a greater propensity to develop inflammation or hypercoagulability; however, Messinezy et al [1994] found that acute-phase markers, such as the erythrocyte sedimentation rate, CRP levels, fibrinogen concentrations, factor VIII procoagulant activities, and von Willebrand antigen values, are significantly elevated in patients with reactive thrombocytosis, whereas these indicators were within the normal ranges in patients with primary thrombocytosis. Therefore, it is not surprising that these factors were found to increase.

In conclusion, the small size of our study population precludes providing an absolute recommendation, but our study has shown that serial measurements of platelet counts are important for detecting reactive thrombocytosis following CABG surgery. Antiplatelet therapy with the combination of ASA and clopidogrel seems to be more appropriate than ASA alone for maintaining graft patency when reactive thrombocytosis develops.

REFERENCES

Ainsworth BE, Haskell WL, Whitt MC, et al. 2000. Compendium of physical activities and update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498-504.

Blatt DL, Chew DP, Hirsh AT, Ringleb PA, Hacke W, Topol EJ. 2001. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. Circulation 103:363-8.

Bruce RA, Kussumi F, Hosmere D. 1973. Maximal oxygen intake and normographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 85:546-62.

CAPRIE Steering Committee. 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 348:1329-39.

Chesebro JH, Clements IP, Fuster V, et al. 1982. A platelet-inhibitor-drug trial in coronary-artery bypass operations: benefit of perioperative dipyridamole and aspirin therapy on early postoperative vein-graft patency. N Engl J Med 307:73-8.

Christenson JT, Gras PA, Grosclaude A, Simonet F, Schmuziger M. 1996. Reactive thrombocytosis following coronary artery bypass surgery: a possible link to a lipid dysfunction. J Cardiovasc Surg (Torino) 37:491-8.

CURE Trial Investigators. 2001. Effects of clopidogrel addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494-502.

FitzGibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. 1996. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 28:616-26.

FitzGibbon GM, Leach AJ, Keon WJ, Burton JR, Kafka HP. 1986. Coronary bypass graft fate: angiographic study of 1,179 vein grafts early, one year, and five years after operation. J Thorac Cardiovasc Surg 91:773-8.

Goldman S, Copeland J, Moritz MI, et al. 1988. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 77:1324-32.

Johnson WD, Brenowitz JB, Kayser KL. 1989. Factors influencing long-term (10-year to 15-year) survival after a successful coronary artery bypass operation. Ann Thorac Surg 48:19-25.

Lichtlen PR, Nikutta P, Jost S, Deckers J, Wiese B, Rafflenbeul W. 1992. Anatomical progression of coronary artery disease in humans as seen by prospective, repeated quantitated coronary angiography: relation to clinical events and risk factors. The INTACT Study Group. Circulation 86:828-38.

Lorenz RL, Scharky CV, Weber M, et al. 1984. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily): effects on platelet aggregation and thromboxane formation. Lancet 1:1261-4.

McKenzie FN, Dhall DP, Arfors KE, Nordlung S, Matheson NA. 1969. Blood platelet behaviour during and after open-heart surgery. Br Med J 2:795-8.

Messinezy M, Westwood N, Sawyer B, et al. 1994. Primary thrombocythaemia: a composite approach to diagnosis. Clin Lab Haematol 16:139-48.

Motwani JG, Topol EJ. 1998. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation 97:916-31.

Packham MA, Mustard JF. 1986. The role of platelets in the development and complications of atherosclerosis. Semin Hematol 23:8-26.

Quinn MJ, Fitzgerald DJ. 1999. Ticlopidine and clopidogrel. Circulation 100:1667-72.

Roberts AJ, Spies SM, Sanders JH, et al. 1981. Serial assessment of left ventricular performance following coronary artery bypass grafting: early postoperative results with myocardial protection afforded by multidose hypothermic potassium crystalloid cardioplegia. J Thorac Cardiovasc Surg 81:69-84.

Schmuziger M, Christenson JT, Maurice J, Simonet F, Velebit V. 1995. Reactive thrombocytosis after coronary bypass surgery: an important risk factor. Eur J Cardiothorac Surg 9:393-8.