Impact of preoperative clopidogrel in off pump coronary artery bypass surgery: A propensity score analysis

Guillermo N. Vaccarino, MD,[a] Jorge Thierer, MD,[b] Mariano Albertal, MD, PhD,[b] Mariano Vrancic, MD,[a] Fernando Piccinini, MD,[a] Mariano Benzadón, MD,[c] Hernán Raich, MD,[a] and Daniel O. Navia, MD[a]

Objective: The aim of our study was to evaluate the impact of recent clopidrogel use before off-pump coronary artery bypass grafting on the postoperative risk of bleeding.

Methods: During the period January 2003 to December 2006, 1104 consecutive patients underwent off-pump coronary artery bypass grafting. Patients were divided into two groups according to the recent use of clopidrogel (within 7 days). We performed a propensity score to further adjust for differences between the patients with and without recent use of clopidrogel.

Results: Mean age was 64 ± 14 years and 87% were male. The clopidrogel group had a greater incidence of patients in unstable condition, requiring emergency coronary bypass grafting, and with a high EuroSCORE. Propensity score analysis selected 88 patients with and 176 without recent use of clopidrogel. By propensity score, the clopidrogel group had higher requirements for fresh frozen plasma units (18.1% vs 8.5%; $P = .02$), reoperation owing to bleeding (5.6% vs 0.5%; $P = .009$), and higher need for postoperative mechanical ventilation (4% vs 10%; $P = .04$), whereas mortality and length of stay were similar between groups.

Conclusion: Recent use of clopidogrel before off-pump coronary artery bypass grafting is associated with greater risk for bleeding with similar mortality rate.

Currently, a percutaneous approach is preferred for patients with high-risk acute coronary syndromes. The percutaneous approach is favored particularly because of improvements in stent design and the possibility of exerting a strong platelet inhibition by dual antiplatelet therapy. During coronary angioplasty, oral administration of clopidogrel, a direct adenosine diphosphate receptor antagonist, has reduced the likelihood of in-stent thrombosis from 18% to 24% to values lower than 2%.[1,2] Thus, dual antiplatelet therapy (aspirin plus clopidogrel) is well tolerated and constitutes the standard oral prophylaxis for stent thrombosis.[3-6]

The multicenter randomized clinical trials CAPRIE* and CURE† have established the basis for standardization of clopidogrel administration to all patients with acute coronary syndromes.[7,8] Owing to the aforementioned reasons, many patients receive clopidogrel before cardiac catheterization.[4-9]

Several investigators have reported an increase in surgical bleeding risk owing to clopidogrel administration before coronary artery bypass grafting (CABG). Furthermore, the irreversible antiplatelet activity of clopidogrel combined with the known deleterious effects of extracorporeal circulation on the coagulation cascade further increases the likelihood of cardiac reoperation up to 10 times.[10-14]

Off-pump surgical revascularization (OPCABG) is a safe technique and reduces bleeding risk when compared with on-pump surgery.[15-21] Nevertheless, clopidogrel administration before OPCABG could potentially reduce its homeostatic advantage.[22-27]

Therefore, the aim of our study was to determine the impact of clopidogrel administration before OPCABG on the risk of bleeding and subsequent need for cardiac reoperation.

PATIENTS AND METHODS

From January 2003 to December 2006, we prospectively included 1104 consecutive patients who underwent OPCABG. Patients were excluded from the analysis if they had significant valvular heart disease, congenital heart disease, ascending aortic disease, or if surgery was combined with carotid revascularization. During the study period, only 46 (4%) patients underwent on-pump CABG. We divided the population into two groups according to the administration of clopidogrel within 7 days before cardiac surgery: (1) clopidogrel group and (2) control group. All patients from both groups received aspirin before the surgical procedure and an intraoperative intravenous bolus of unfractionated heparin dosage of 300 IU/kg with adjusted heparin doses to maintain activated clotting times greater than 450 seconds. During all procedures, heparin reversal was performed with protamine (activated clotting time goal < 110 seconds). It has been customary in our institution to refrain from administering hemostatic drugs such as aprotinin or aminocaproic acid. Several surgical studies have reported an enhanced risk of graft thrombosis with the use of aprotinin.

Operative Technique

All surgical procedures were performed by the same surgical team. OPCABG was performed through a standard median sternotomy, the

From the Department of Cardiac Surgery[a] and the Research Department,[b] Instituto Cardiovascular de Buenos Aires, Ciudad Autónoma de Buenos Aires and the Department of Cardiac Surgery, Cardiovascular Intensive Care Unit,[c] Instituto Cardiovascular de Buenos Aires, Ciudad Autonoma de Buenos Aires, Argentina.

Received for publication Jan 28, 2008; revisions received April 24, 2008; accepted for publication Aug 4, 2008.

Address for reprints: Guillermo N. Vaccarino, MD, Department of Cardiac Surgery, Instituto Cardiovascular de Buenos Aires, Blanco Encalada 1543, Ciudad Autónoma de Buenos Aires, Argentina (E-mail: gnvaccarino@icba-cardiovascular.com.ar).

J Thorac Cardiovasc Surg 2009;137:309-13
0022-5223/$36.00

doi:10.1016/j.jtcvs.2008.08.002

*CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events.
†CURE = Clopidogrel in Unstable angina to prevent Recurrent Events.

ACD

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
ITA = internal thoracic artery
OPCABG = off-pump coronary artery bypass grafting

pericardial cavity was opened wide, and deep pericardial sutures were placed for traction. The internal thoracic artery (ITA) was harvested by a skeletonized technique. The in situ left ITA was used for the left anterior descending coronary artery. Allen's test was routinely performed before harvesting the radial artery, and capillary refilling of the palm within 10 seconds was judged as negative. Whenever a saphenous vein graft was used, it was extracted with minimally invasive technique as previously described.[28]

Proximal free right ITA anastomosis and radial artery graft were performed according to the technique of Tector and Schmahl.[29] Right ITA, radial artery, and saphenous vein grafts were used for revascularization of the lateral and inferior myocardial territories. Distal anastomoses were performed while the heart was stabilized with an Octopus II/III stabilizer (Medtronic, Minneapolis, Minn). A cell salvage device was not used during the operation in any patients.

Indications for cardiac reoperation were as follows: (1) excessive bleeding and/or (2) cardiac tamponade. Excessive postoperative bleeding was defined as more than 300 mL during the first hour, more than 250 mL during the second hour, more than 200 mL during the third hour, or a total of 1000 mL or more during the first 6 hours.

Blood and blood products transfusions (red cells, platelets, plasma, and cryoprecipitate) were counted by units. Postoperative need for transfusion was defined by the following criteria: (1) reduction in hematocrit to 21% or less and (2) hematocrit between 21% and 30% in the context of active bleeding, hypovolemia, hypoxemia, or neurologic symptoms.

We analyzed the following baseline variables that have been previously reported as predictors of postoperative bleeding[19-23]: age, gender, presence of chronic systemic hypertension, diabetes mellitus, renal insufficiency, hematocrit and creatinine levels, EuroSCORE, prior acute myocardial infarction, CABG, presence of heart failure, current clinical presentation, left ventricular ejection fraction, carotid or peripheral vascular disease, and chronic pulmonary obstructive disease.

Major adverse cardiovascular events were defined as the occurrence of one of the following: death, stroke, or myocardial infarction.

Statistical Analysis

Continuous variables are expressed as mean values (± standard deviation) and compared by the Student *t* test. Categorical variables are expressed as percentages and compared by the χ^2 statistic or Fisher's exact test.

We performed two separate analyses regarding the relationship between clopidogrel use and bleeding complications. In the first analysis, we included the entire population (n = 1104) and compared both groups' clinical results. For the second analysis, in an attempt to control for baseline differences between the two groups, we performed a propensity score that would predict the use of clopidogrel. Only the variables that differed between the two unmatched groups (n = 1104) were included to generate a propensity score to predict perioperative clopidrogel administration by a logistic regression analysis. All patients, regardless of their clopidrogel status, received a propensity score. All scores were sorted numerically. Whenever possible, patients with similar scores were matched in a 1:2 clopidrogel/control fashion. We obtained 88 comparisons (n = 88 in the clopidrogel group and n = 166 in the control group).

The use of a propensity score attempts to reproduce the baseline similarities of a randomized population; however, it has inherent limitations.[30] The statistical analysis was performed with Stata 9.1 software (StataCorp, College Station, Tex).

RESULTS

From a total of 1104 patients included in the analysis, 123 (11%) patients received clopidogrel within 7 days before the procedure (clopidogrel group) and 981 did not (control group). Baseline demographics of both surgical groups are shown in Table I. Age and gender proportions were similar between the two groups. As expected, the percentage of patients undergoing cardiac catheterization during the index hospitalization was significantly higher in the clopidogrel group (73% vs 33%; $P < .0001$). In addition, clinical presentation with an acute coronary syndrome was more frequent than in the control group (73% vs 63.4%; $P < .05$). Lower hematocrit (40.9% ± 4.2% vs 38% ± 43%; $P = .0005$) and creatinine (1.11 ± 0.29 mg/dL vs 1.19 ± 0.40 mg/dL; $P = .02$) values were observed in the clopidogrel group.

Clinical outcome data are detailed in Table II. There was a trend toward more renal insufficiency (4% vs 1.7%; $P = .08$) and a nonsignificant difference in the need for hemodyalysis (1.6% vs 0.6%; $P = .2$) in the clopidogrel group. Furthermore, the clopidogrel group was also associated with greater need for assisted mechanical ventilation (11.3% vs 2.5%; $P = .0001$) and transfusion (57.7% vs 45.9%; $P = .02$) than the controls. The rates of reoperation (1.7% vs 1.4%; $P = .03$) and major adverse cardiac events (17.07% vs 7.24%; $P = .0001$) were higher in the clopidogrel group. The median hospitalization lengths of stay were 8 days (interquartile ratio 25–75: 5–10) and 5 days (interquartile ratio 25–75: 4–7) for the clopidogrel and control groups, respectively ($P = .0001$). Overall 30-day mortality rate was 2.9%; this rate was 4.8% (n = 6) in the clopidogrel group and 2.7% (n = 27) for the controls ($P = .1$).

Baseline demographics and clinical outcomes in the two matched groups are summarized in Tables III and IV. By propensity score, clinical results of the 2:1 matched patients revealed greater need for reoperation for bleeding in the clopidogrel group (5.6% vs 0.5%; P .009) and tendency toward more transfusion (61.1% vs 51.1%; $P = .1$). From all blood products, only fresh frozen plasma transfusion rates were significantly higher in the clopidogrel group ($P = .02$). Other blood products such as red blood cells, platelets, and cryoprecipitate were similar between the two matched groups (Figure 1). Median hospitalization lengths of stay were similar between matched groups.

Mortality by propensity analysis did not differ between the groups (4.5% in the clopidogrel group and 2.8% in the controls). However, there was a tendency toward more major adverse events in the clopidogrel group than in the control group: 15.9% versus 9.6% (odds ratio 1.792, 95% confidence interval 0.826–3.887; $P = .1$).

DISCUSSION

Data from several large randomized multicenter trials have recognized the clinical benefits of dual-antiplatelet

TABLE I. Baseline demographics in the two unmatched groups

	Overall population (n = 1104)	Control group (n = 981)	Clopidogrel group (n = 123)	*P* value
Age, y	64.3 ± 13.8	64.5 ± 12.9	63 ± 20	.3
Male sex	959 (86.7)	856 (87.2)	103 (83.7)	.1
Elective	678 (61.4)	649 (66.1)	29 (23.5)	.0001
EuroSCORE	4.02 ± 3.5	3.8 ± 3.3	5.1 ± 4.5	.008
Prior myocardial infarction	446 (40.4)	395 (40.2)	51 (41.4)	.7
Prior CABG	44 (3.9)	37 (3.7)	7 (5.7)	.3
History of PVD	44 (3.9)	37 (3.7)	7 (5.7)	.3
History of carotid disease	56 (5.1)	51 (5.2)	5 (4)	.5
History of COPD	34 (2.8)	30 (3.5)	4 (3.5)	.8
Hypertension	758 (68.5)	672 (68.5)	86 (69.9)	.7
Diabetes mellitus	267 (24.1)	236 (24)	31 (25)	.7
Stable angina	172 (18)	159 (18.7)	13 (12.5)	.1
Unstable angina	662 (60.5)	618 (63.4)	89 (73)	.05
History of heart failure	26 (2.3)	21 (2.1)	5 (4)	.1
Hematocrit, %	40.6 ± 4.3	40.9 ± 4.2	38 ± 3	.0005
Creatinine, mg/dl.	1.18 ± 0.4	1.19 ± 0.4	1.11 ± 0.29	.02
Renal failure	38 (3.4)	36 (3.6)	2 (1.6)	.2
Ejection fraction < 50%	310 (28)	272 (27.2)	38 (30.8)	.4
Total number of grafts	3.03 ± 0.8	3.02 ± 0.8	3.05 ± 0.9	.7
LITA	1044 (94.6)	926 (94.4)	117 (95.1)	.7
RITA	736 (66.7)	660 (67.3)	86 (69.9)	.5
RA	496 (29.5)	285 (29.1)	38 (30.8)	.6
SVG	169 (13.4)	138 (14.1)	14 (11.3)	.4

Data are presented as numbers (percentages) or means ± standard deviation. *CABG,* Coronary artery bypass grafting; *PVD,* peripheral vascular disease; *COPD,* chronic obstructive pulmonary disease; *LITA,* left internal thoracic artery; *RITA,* right internal thoracic artery; *RA,* radial artery; *SVG,* saphenous vein graft.

therapy with aspirin and clopidogrel for patients with acute coronary syndromes.[7-9] Still, some patients require urgent surgical revascularization and need to be operated on while on the potent and irreversible platelet inhibition effect exerted by clopidogrel. Under such a scenario, CABG carries a dramatic increase in bleeding risk. Furthermore, several investigators have already demonstrated high transfusion and reoperation rates after on-pump CABG owing to recent clopidogrel use.[10-12,22,31,32]

OPCABG is a safe technique and reduces bleeding risk when compared with on-pump surgery.[20,22,24] However, limited data are available regarding the clopidogrel bleeding risk during OPCABG. In our study, total blood drainage was similar between groups. Although patients who received clopidogrel showed a transfusion rate similar to that of the control group (61.1% vs 51.1%; $P = .1$), there were more requirements for fresh frozen plasma units per patient (18% vs 8%; $P = .02$). It is possible that a low threshold for platelet transfusion may have prevented further bleeding in the clopidogrel group. Nevertheless, reoperation rates were higher in the clopidogrel group (5.6% vs 0.5%; $P = .009$). Although postoperative bleeding was similar between groups, intrathoracic blood and thrombus obtained during reoperation were not counted.

In concert with our results, a recent study reported experience in 224 consecutive surgical cases[11]; 54 of them received clopidogrel within 7 days before the procedure (clopidogrel group). In that study, the clopidogrel group had greater blood drainage during the postoperative days as well as an increased rate of blood transfusions and reoperations resulting from bleeding. Differences in study design between this latter study and ours may explain the differences in blood drainage.

TABLE II. Postoperative data in the two unmatched groups

	Overall population (n = 1104)	Control group (n = 981)	Clopidogrel group (n = 123)	*P* value
Renal dysfunction	22 (1.9)	17 (1.7)	5 (4)	.08
Dialysis	8 (0.7)	6 (0.6)	2 (1.6)	.2
Postoperative stroke	10 (0.9)	9 (0.9)	1 (0.8)	.9
AMV > 48 h	39 (3.5)	25 (2.5)	14 (11.3)	<.001
Perioperative MI	18 (1.6)	14 (1.4)	4 (3.2)	.1
Blood transfusion	518 (47.2)	441 (45.9)	70 (57.7)	.02
Bleeding re-exploration	19 (1.7)	14 (1.4)	5 (4)	.03
Postoperative blood loss, mL	846 ± 543	840 ± 537	892 ± 586	.3
Hospital stay, median, d	5 (4-8)	5 (4-7)	8 (5-10)	<.001
MACE	175 (15.85)	166 (17.07)	9 (7.24)	.0001
Mortality	33 (2.9)	27 (2.7)	6 (4.8)	.1

AMV, Assisted mechanical ventilation; *MI,* myocardial infarction; *MACE,* major adverse cardiovascular events.

TABLE III. Baseline demographics in the two matched groups

	Control group (n = 176)	Clopidogrel group (n = 88)	*P* value
Age, y	63.1 ± 19.8	63.2 ± 23.8	.9
Male sex	147 (83.5)	71 (80.6)	.5
Prior myocardial infarction	69 (39.2)	42 (47.7)	.1
EuroSCORE	4.09 ± 0.3	4.39 ± 0.5	.1
Prior CABG	9 (5.1)	6 (6.8)	.5
History of PVD	12 (6.8)	5 (5.6)	.7
History of carotid disease	8 (4.5)	5 (5.6)	.7
History of COPD	7 (3.9)	3 (3.4)	.8
Hypertension	119 (67.5)	62 (70.4)	.6
Diabetes mellitus	39 (22.1)	25 (28.4)	.2
Unstable angina	123 (69.8)	64 (72.7)	.6
History of heart failure	5 (2.8)	2 (2.2)	.7
Hematocrit, %	39.5 ± 4.3	39.4 ± 4.8	.8
Creatinine, mg/dL	1.14 ± 0.3	1.12 ± 0.3	.7
Renal failure	6 (3.4)	2 (2.2)	.6
EF < 50%	53 (30.1)	31 (35.2)	.4
Total number of grafts	3.02 ± 0.8	3.01 ± 0.9	.4
LITA	166 (94.7)	83 (94.5)	.7
RITA	117 (66.9)	58 (66.5)	.9
RA	51 (29.3)	26 (29.7)	.9
SVG	24 (13.7)	11 (13.2)	.7

Data are presented as numbers (percentages) or means ± standard deviation. *CABG,* Coronary artery bypass grafting; *PVD,* peripheral vascular disease; *COPD,* chronic obstructive pulmonary disease; *EF,* ejection fraction; *LITA,* left internal thoracic artery; *RITA,* right internal thoracic artery; *RA,* radial artery; *SVG,* saphenous vein graft.

Perioperative administration of clopidogrel clearly translates into greater postoperative bleeding after on-pump CABG and OPCABG. In a recent published study by Ascione and associates,[10] the authors demonstrated that administration of clopidogrel within 48 hours from CABG (62.8 % off-pump) carries a greater risk of death than receiving clopidogrel within 48 to 120 hours of the procedure. Thus, the shorter the interval between the last clopidogrel dose and the surgical procedure, the higher the bleeding risk.

TABLE IV. Postoperative data in the two matched groups

	Control group (n = 176)	Clopidogrel group (n = 88)	*P* value
Renal dysfunction	5 (2.8)	3 (3.4)	.8
Dialysis	3 (1.7)	2 (2.2)	.7
Postoperative stroke	4 (2.2)	1 (1.1)	.5
AMV > 48 h	7 (4)	9 (10)	.045
Perioperative MI	3 (1.7)	3 (3.4)	.3
Blood transfusion	88 (50)	53 (60.2)	.1
Bleeding re-exploration	1 (0.5)	5 (5.6)	.009
Postoperative blood loss, mL	845 ± 622	910 ± 325	.3
Hospital stay, median, d	7 (5-11)	8 (5-10)	.1
MACE	17 (9.6)	14 (15.9)	.1
Mortality	5 (2.8)	4 (4.5)	.4

AMV, Assisted mechanical ventilation; *MI,* myocardial infarction; *MACE,* major adverse cardiovascular events.

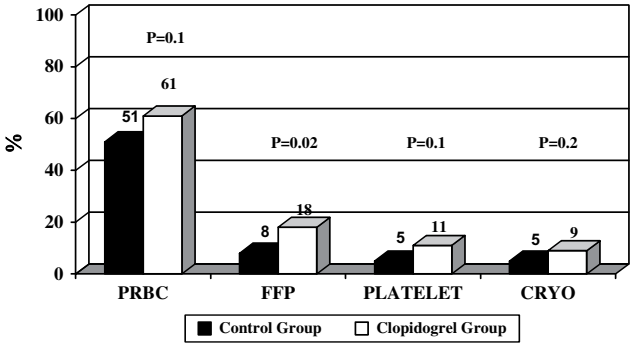

FIGURE 1. Blood products requirement in the two matched groups (percentage of patients with transfusion). *PRBC,* Packed red blood cells; *FFP,* fresh frozen plasma; *CRYO,* cryoprecipitates.

Nevertheless, Kapetanakis and associates[33] reported on 1572 patients undergoing only OPCABG. They found no mortality differences in patients taking clopidogrel preoperatively when compared with the controls, whereas morbidity was worse (prolonged assisted mechanical ventilation time, higher need for intra-aortic balloon pump use, and development of arrhythmias and stroke with no impact on myocardial infarction rate and renal dysfunction). In concordance with the aforementioned study, we did not observe differences between the two groups in terms of perioperative myocardial infarction, renal dysfunction, or mortality rates, whereas the clopidogrel group was associated with a greater need for postoperative mechanical ventilation. As also showed by Habib, Anoar, and Engoren,[34] we observed that transfusion rate was a predictor of prolonged mechanical ventilation (odds ratio 2.41; 95% confidence interval 1.48–3.94; $P < .0001$).

Study Limitations

Although most of the important clinical characteristics previously known to influence bleeding outcomes were adjusted by propensity score, the retrospective design of this single-center study and the small size of the study population raise the potential for errors. Nevertheless, data were gathered prospectively in our cardiac surgery database throughout the study period. It is also possible that subtle differences in patient care may exist between patients who recently received clopidogrel and those who did not. Platelets may have been administered more liberally to the clopidogrel group because of expected platelet dysfunction in these patients. This in turn may have affected bleeding risk and the amount of blood loss. We did not perform platelet function studies. Although propensity score helps adjust for differences between groups, it does not control for unmeasured differences in patient characteristics and clinical care. In our population, the use of propensity score may have been underpowered for the evaluation of differences in bleeding and transfusion rates between the two groups.

CONCLUSIONS

This study indicates that clopidogrel administration within 7 days of OPCABG surgery increases postoperative morbidity. Preoperative clopidogrel use was associated with higher rates of reoperation for bleeding, fresh frozen plasma transfusion, and need for assisted mechanical ventilation. There was a tendency toward greater mortality. Early platelet transfusion during surgery may prevent major postoperative bleeding. The decision to perform OPCABG within 7 days of administration of clopidogrel should be based on balancing the risk of delaying surgery versus the risk of increased bleeding and morbidity.

References

1. Leon M, Popma J, Gordon P, Cutlip D, Ho K, Giambartolomei A, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339: 1665-71.
2. Steinhubl S, Berger P, Man J. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-20.
3. Moussa I, Oetgen M, Roubin G, Colombo A, Wang X, Iyer S, et al. Effectiveness of clopidogrel and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation*. 1999;99:2364-6.
4. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intra-coronary stent implantation in a broad patient population. *Circulation*. 2001;104:539-43.
5. Stone G, Ellis S, Colombo A, Dawkins K, Cutlip D, Friedman M, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. *Circulation*. 2007;115:2842-7.
6. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, et al. TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation*. 2005;112:3306-13.
7. Harker L, Boissel J, Pilgrim A, Gent M. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. *Drug Saf*. 1999;21:325-35.
8. Mehta SR, Yusuf S. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J*. 2000;21:2033-41.
9. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patient Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelets glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non–Q-wave myocardial infarction. *N Engl J Med*. 1998;338:1488-97.
10. Ascione R, Ghosh A, Roger A, Cohen A, Monk C, Angelini G. In hospital patients exposed to clopidogrel before coronary artery bypass graft surgery: a word of caution. *Ann Thorac Surg*. 2005;79:1210-6.
11. Hongo R, Ley J, Dick S, Yee R. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass surgery. *J Am Coll Cardiol*. 2002;40:231-7.
12. Chu M, Wilson S, Novick R, Stitt L, Quantaz M. Does clopidogrel increase blood loss following coronary artery bypass surgery? *Ann Thorac Surg*. 2004;78: 1536-41.
13. Harper LA. Bleeding after cardiopulmonary bypass. *N Engl J Med*. 1986;314: 1446-7.
14. Levy JH. Platelet inhibitors and bleeding in cardiac surgical patients. *Ann Thorac Surg*. 2000;70:S9-11.
15. Mack M, Bachand D, Acuff T, Edgerton J, Prince S, Dewey T, et al. Improved outcomes in coronary artery bypass grafting with beating heart techniques. *J Thorac Cardiovasc Surg*. 2002;124:598-607.
16. Calafiore AM, Angelini GD, Bergsland J, Salerno TA. Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg*. 1996;62:1545-8.
17. Nuttall GA, Erchul DT, Haight TA. A comparison of bleeding and transfusion in patients who undergo coronary artery bypass grafting via sternotomy with and without cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2003;17: 447-51.
18. Puskas JD, Williams WH, Duke PG, Staples JR, Glas KE, Marshall JJ, et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;125:797-808.
19. Subramanian VA. Less invasive arterial CABG on a beating heart. *Ann Thorac Surg*. 1997;63:68-71.
20. Vedin J, Antovic A, Ericsson A, Vaage J. Hemostasis in off-pump compared to on-pump coronary artery bypass grafting: a prospective, randomized study. *Ann Thorac Surg*. 2005;80:586-93.
21. Yokoyama T, Baumgartner FJ, Gheissari A, Capouya ER, Panagiotides GP, Declusin RJ. Off-pump versus on-pump coronary bypass in high-risk subgroups. *Ann Thorac Surg*. 2000;70:1546-50.
22. Englberger L, Faeh B, Berdat PA, Eberli F, Meier B, Carrel T. Impact of clopidogrel in coronary artery bypass grafting. *Eur J Cardiothoracic Surg*. 2004;26: 96-101.
23. Muñoz JJ, Birkmeyer NJ, Dacey LJ, Birkmeyer JD, Charlesworth DC, Johnson ER, et al. Trends in rates of reexploration for hemorrhage after coronary artery bypass surgery. Northern New England Cardiovascular Disease Study Group. *Ann Thorac Surg*. 1999;68:1321-5.
24. Ascione R, Williams S, Lloyd CT, Sundaramoorthi T, Pitsis AA, Angelini GD. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2001;121:689-96.
25. Shennib H, Endo M, Benhameid O. A feasibility study of the safety and efficacy of a combined clopidogrel and aspirin regimen following off-pump coronary artery bypass grafting. *Heart Surg Forum*. 2003;6:288-91.
26. D'Ancona G, Donias HW, Karamanoukian RL, Bergsland J, Karamanoukian HL. OPCAB therapy survey: off-pump clopidogrel, aspirin or both therapy survey. *Heart Surg Forum*. 2001;4:354-8.
27. Gansera B, Schimdtler F, Spiliopoulos K, Angelis I, Neumaier-Prauser P, Kenkes BM. Urgent or emergent coronary revascularization using bilateral internal thoracic artery after previous clopidogrel antiplatelet therapy. *Thorac Cardiovasc Surg*. 2003;51:185-9.
28. Vrancic JM, Piccinini F, Vaccarino GN, Iparraguirre E, Albertal J, Navia D. Endoscopic saphenous vein harvesting: initial experience and learning curve. *Ann Thorac Surg*. 2000;70:1086-9.
29. Tector AJ, Schmahl TM. Techniques for multiple internal mammary artery bypass grafts. *Ann Thorac Surg*. 1984;38:281-6.
30. Austin PC. Propensity-score matching in the cardiovascular surgery literature from 2004 to 2006: a systematic review and suggestions for improvement. *J Thorac Cardiovasc Surg*. 2007;134:1128-35.
31. Gurbuz A, Zia A, Vuran A, Cui H, Aytac A. Postoperative clopidogrel improves mid-term outcome after off-pump coronary artery bypass graft surgery: a prospective study. *Eur J Cardiothorac Surg*. 2006;29:190-5.
32. Chen L, Bracey A, Radovanecevic R, Cooper J, Collard C, Vaughn W, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2004;128:425-31.
33. Kapetanakis E, Medlam D, Petro K, Haile E, Hill P, Dullum M, et al. Effect of clopidogrel premedication in off-pump cardiac surgery. Are we forfeiting the benefits of reduced hemorrhagic sequelae? *Circulation*. 2006;113:1667-74.
34. Habib R, Anoar Z, Engoren M. Determinants of prolonged mechanical ventilation after coronary artery bypass grafting. *Ann Thorac Surg*. 1996;62:1164-71.