

Comparison of postoperative bleeding in patients undergoing coronary artery bypass surgery in two groups taking aspirin and aspirin plus CLS clopidogrel

Ali Pooria (1)

Hassan Teimouri (2)

Mostafa Cheraghi (3)

Babak Baharvand Ahmadi (3)

Mehrdad Namdari (3)

Reza Alipoor (4)

(1) Assistant Professor, Department of General Surgery, Lorestan University of Medical Sciences, Khorramabad, Iran

(2) Associated Professor, Department of Anesthesiology, Lorestan University of Medical Sciences, Khorramabad, Iran

(3) Assistant Professor, Department of Cardiology, Lorestan University of Medical Sciences, Khorramabad, Iran

(4) Student research committee, Fasa University of medical sciences, Fasa, Iran

Correspondence:

Mostafa Cheraghi

Address: Department of clinical training, Shohada Ashayer hospital, Enqelab St, Khorramabad, Lorestan, Iran

Tel/ Fax: +98-6633203004

Abstract

Introduction: Coronary Artery Bypass Grafting (CABG) is a surgical procedure that aims to ease symptoms and reduce the risk of death in patients with coronary artery occlusion. In this surgery, healthy blood vessels from other parts of the body replace occluded coronary arteries. This surgery is done to improve blood supply to the heart. Because of its invasive nature, this procedure is associated with complications including postoperative bleeding.

Methods: The study included 68 subjects in each group. The inclusion criteria were age of 40-80 years, serum creatinine under 1.5 mg/dl, platelet count above 100 thousand per microliter, hemoglobin above 8 g per deciliter, and normal PT and PTT. The patients underwent the procedure through the on-pump method. The study population included the patients undergoing CABG in Khorramabad Heart Hospital. The convenience, consecutive sampling method was applied, based on the inclusion criteria of the study.

Results: The mean age of the patients treated with aspirin was 60.9 ± 11.05 , and the mean age of the patients treated with aspirin plus clopidogrel was

60.48 ± 9.8 years. The mean FFP intake in the aspirin plus clopidogrel group during hospitalization was significantly higher than the mean in the aspirin group (PV= 0.0009). The mean cell pack intake in the aspirin plus clopidogrel group during hospitalization was higher than the mean in the aspirin group, but this difference was not statistically significant (PV=0.068).

Discussion: The rate of postoperative bleeding in the clopidogrel plus aspirin group was higher than the rate in the aspirin group, but this difference was not significant (PV=0.067). The rate of Hb, HCT, and platelets in the aspirin plus clopidogrel group at discharge was higher than the rate in the aspirin group, which was due to excess bleeding in the aspirin plus clopidogrel group compared to the aspirin group. The rate of FFP intake in the aspirin plus clopidogrel group was significantly higher than the rate in the aspirin group, which was due to excess bleeding in the aspirin plus clopidogrel group (PV=0.0009).

Key words: coronary artery bypass grafting, aspirin, clopidogrel

Please cite this article as: Pooria, A, et al. Comparison of postoperative bleeding in patients undergoing coronary artery bypass surgery in two groups taking aspirin and aspirin plus CLS clopidogrel. *World Family Medicine*. 2017; 15(8):17-23. DOI 10.5742/MEWFM.2017.93050

Introduction

Coronary artery bypass grafting (CABG) is a surgical procedure that aims to ease symptoms and reduce the risk of death in patients with coronary artery occlusion. In these patients, healthy vessels of other parts of the body are grafted to replace the occluded coronary arteries and this improves blood flow to the heart. Due to the aggressive and invasive nature of this surgery, it is associated with complications. From among the complications of this surgery, bleeding after CABG can be cited. The prevalence of this complication is so high that 17% of patients need blood transfusions after surgery and approximately 3 to 5 percent of patients require re-exploration (1). The amount of bleeding after surgery varies based on factors such as platelet count and pre-operative fibrinogen concentrations (1). Also, it should be noted that patients undergoing CABG often use antiplatelet and anticoagulant drugs due to heart disease and this issue affects the occurrence and severity of postoperative bleeding. It is expected that various antiplatelet drugs have different effects on post-operative bleeding. One of the drugs that nowadays is used as an antiplatelet drug is clopidogrel. This medication irreversibly inhibits platelet activation and aggregation (2). Various studies conducted on the effects of this drug on CABG post-operative bleeding have reported mixed results. Several studies have reported that the use of this drug has no effect on the amount of post-operative bleeding (3). In contrast, some studies have reported that the use of this drug increases the rate of postoperative bleeding (4-6). In addition, it has been reported that the preoperative use of clopidogrel with a loading dose of 600 mg increases the risk of bleeding in comparison with a loading dose of 300 mg (7). On the other hand, the use of clopidogrel in patients undergoing CABG shows benefits, which include a decline in the rates of cardiovascular events (5) and a reduction in the likelihood of replaced vessel occlusion (3).

In this study, considering the benefits that have been proposed for the use of clopidogrel plus aspirin in patients undergoing CABG, and also given the mixed results obtained from different studies, we decided to compare postoperative bleeding in patients undergoing coronary artery bypass surgery in two groups taking aspirin and aspirin plus clopidogrel.

Materials and Methods

In this study, the number of subjects in each group was 68 patients. The inclusion criteria included an age of between 40 and 80 years, serum creatinine levels less than 1.5 mg/dl, a platelet count of over 100 thousand per microliter, hemoglobin levels of more than 8 g per dl, and normal PT and PTT, and the use of the on-pump CABG for the patients. The studied population included patients who had undergone CABG in the Specialist Cardiac Hospital of Khorramabad, Iran. The convenience and consecutive sampling methods were used based on the inclusion criteria of the study.

In this study, candidate patients for angiography underwent coronary angiography by two groups of cardiologists. One group were specialists who were able to perform angioplasty and the other group was not able to perform this operation. Cardiologists who were not able to perform angioplasty prescribed aspirin (325 mg daily) for patients scheduled to undergo angiography. In contrast, given the fact that patients who are scheduled to undergo coronary angiography may need angioplasty too, cardiologists who were able to perform angioplasty prescribed clopidogrel (with a dose of 600mg per day) in addition to aspirin (with a dose of 325mg) for the patients to be ready to undergo angioplasty, if necessary. The advantage of this strategy is that it spares the patient from another procedure to perform angioplasty.

In both groups, if the findings of angiography showed that some patients needed to undergo CABG, cardiac surgeons subsequently operated on them. Therefore, some of the patients who underwent CABG had taken aspirin before surgery and others had used clopidogrel (600 mg daily) in addition to aspirin. In this study, patients were divided into two group based on the use or non-use of clopidogrel. Inclusion criteria were an age of between 40 and 80 years, serum creatinine levels of less than 1.5 mg/dl, a platelet count of more than 100,000 per microliter, hemoglobin more than 8 g/dl, and normal PT and PTT .

Exclusion criteria included a history of hereditary bleeding disorders, use of anticoagulant drugs in the previous month, having undergone CABG surgery in the past, the use of clopidogrel before the start of the current study, a history of taking clopidogrel in the aspirin group, a history of allergy to clopidogrel and aspirin, a history of cerebrovascular disease, a history of severe hepatic disease, cancer, severe bleeding or cardiac tamponade after surgery which needed surgical intervention, the need for anticoagulant drugs after surgery, and gastrointestinal bleeding after surgery.

Demographic variables, laboratory indicators, signs and symptoms of the patients, the amount of postoperative bleeding, and the amount of blood transfused (during the first 24 hours), duration of ICU and hospital stays, and duration of drain use in patients were recorded in the data collection form of the study. This form was completed by executive colleagues of the project. To describe the data, descriptive statistical methods (mean, standard deviation, and frequency percentages) and, to compare the examined variables, analytical statistical methods, including the independent t-test, chi-square, and analysis of variance were used.

Results

The mean age of the patients treated with aspirin was 60.9 ± 11.05 , and the mean age of the patients treated with aspirin and clopidogrel was 60.48 ± 9.8 . According to t-test, the difference in age between the two groups was not statistically significant ($p=0.78$). In the aspirin group, 42.9% of the patients and, in the aspirin plus clopidogrel group, 45.7% of the patients were younger than 60 years old. The rest of the patients of the two groups were older than 60 years old. The difference in age distribution between the two groups was not statistically significant according to a chi-square test ($P=0.73$).

The mean BMI in the group treated with aspirin was 27.3 ± 4.2 and in the group treated with clopidogrel + aspirin, was 28.3 ± 10 . According to t-test, the difference in mean BMI was not statistically significant between the two groups ($p=0.46$). In the aspirin group, the mean EF of the patients was 46.5 ± 10.9 percent and, in the aspirin plus clopidogrel group, was 46.2 ± 9.2 percent, which difference was not found to be statistically significant ($p=0.86$). None of the patients in both groups were HIV positive or HCV positive.

Based on chi-square test, the difference in the need for blood transfusion in the studied groups during the first 24 hours after surgery was not statistically significant ($p=0.8$). (Table 1)

Table 1: The difference in the need for blood transfusion in the studied groups during the first 24 hours after surgery

		Need for blood transfusion during the first 24 hours after surgery		
		Has	Has not	Total
		N (%)	N (%)	N (%)
Groups	Aspirin	61 (87.1)	9 (12.9)	70 (100)
	Aspirin plus clopidogrel	60 (85.7)	10 (14.3)	70 (100)

* "N" represents the number of patients in each group

** Statistical test: Chi-Square test

Additionally, according to the above table, the difference in the need for blood transfusions during hospital stay was not statistically significant between the group receiving aspirin (91.4%) and the group receiving aspirin + clopidogrel (87.1%) ($p=0.41$) (Table 2).

Table 2: The difference in the need for blood transfusion in the studied groups during hospital stay

		Need for blood transfusion during hospital stay		
		Has	Has not	Total
		N (%)	N (%)	N (%)
Groups	Aspirin	64 (91.4)	6 (8.6)	70 (100)
	Aspirin plus clopidogrel	61 (87.1)	9 (12.9)	70 (100)

* "N" represents the number of patients in each group

** Statistical test: Chi-Square test

According to the results of a repeated measures, test differences in bleeding in each group over time was statistically significant (time effect). But the difference between the two groups was not statistically significant in any of the times (24 hours after surgery and until the removal of the drain) (group effect and the time-group interaction were not statistically significant either) ($p=0.9$). According to an independent t-test, the difference in the mean bleeding during the first 24 hours after surgery was not statistically significant in both groups receiving aspirin and clopidogrel + aspirin ($p=0.067$). Although the amount of bleeding in the group receiving aspirin + clopidogrel was more than the aspirin group, this difference was not statistically significant. Despite the fact that the group receiving aspirin + clopidogrel had more bleeding until the removal of the drain in comparison with the group receiving aspirin, this difference was not statistically significant as determined by a t-test ($p=0.27$).

The mean duration of ICU stay for the group receiving aspirin was 53.12 hours and in the group receiving aspirin + clopidogrel, it was 50.35 hours. This difference was not statistically significant ($p=0.51$).

The mean duration of drain use in the aspirin group was 106.2 hours and it was 107.4 hours in the group receiving aspirin + clopidogrel, but this difference was not statistically significant as determined by a t-test ($p>0.05$).

In the group receiving aspirin, 3 patients (4.3%) and, in the group receiving aspirin + clopidogrel, 6 patients (8.6%) needed reoperation, but this difference was not statistically significant, according to Fisher's exact test ($p=0.24$). (Table 3)

Table 3: The difference in the need for need for reoperation in the studied groups

		Need for reoperation			P-Value
		Has	Has not	Total	
		N (%)	N (%)	N (%)	0.24
Groups	Aspirin	3 (4.3)	67 (95.7)	70 (100)	
	Aspirin plus clopidogrel	6 (8.6)	64 (91.4)	70 (100)	

* "N" represents the number of patients in each group

** Statistical test: Fisher's exact test †

In both groups, the average number of days of hospital stay was 6.5 days and the t-test showed no statistically significant difference in the number of days of hospitalization in the two groups. Based on the obtained results, the difference in the mean values of blood parameters before the surgery was not statistically significant ($p > 0.05$). Additionally, based on the results of an independent t-test, the differences in values of lipid profile, renal function and CRP indexes were not statistically significant in the two groups before the surgery ($p > 0.05$). (Table 4)

Table 4: The Comparison of mean and standard deviation of laboratory indices before the surgery in studied groups

Indicator type		Hb (g/dl)	RBC (μ l)	Hct (%)	WBC ($\times 10^3 \mu$ l)	Plt ($\times 10^3 \mu$ l)	PT (Sec)
		$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$
Groups	Aspirin	13.6 \pm 2.2	4.6 \pm 0.87	41.14 \pm 6.3	8.6 \pm 3.3	223757 \pm 65.6	12.99 \pm 1.08
	Aspirin plus clopidogrel	14 \pm 2.07	4.7 \pm 0.72	42.07 \pm 5.5	7.8 \pm 2.9	233314 \pm 64.9	12.90 \pm 1.85
T statistics		-1.19	-0.62	-0.92	1.55	-0.86	0.34
P Value		0.23	0.53	0.35	0.12	0.38	0.74

PTT (Sec)	TG	Cholesterol	BUN	Cr	CRP
$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$	$\mu \pm SD$
27.79 \pm 6.2	178.9 \pm 81.7	182.2 \pm 49.2	45.2 \pm 16.4	1.17 \pm 0.25	1.74 \pm 0.44
29.40 \pm 7.91	166.6 \pm 93.4	180.5 \pm 44	42.5 \pm 14.2	1.19 \pm 0.27	1.81.5 \pm 0.39
-1.33	0.82	0.22	1.03	-0.38	-1.01
0.18	0.4	0.82	0.3	0.7	0.31

Table 5- The Comparison of mean and standard deviation of laboratory indices in studied groups at discharge

Indicator type		Hb (g/dl)	Hct (%)	Plt ($\times 10^3 \mu\text{l}$)	BUN	Cr
		$\mu \pm \text{SD}$	$\mu \pm \text{SD}$	$\mu \pm \text{SD}$	$\mu \pm \text{SD}$	$\mu \pm \text{SD}$
Groups	Aspirin	11.1 \pm 9.7	32.9 \pm 5.2	235800 \pm 81.25	41.5 \pm 11	1 \pm 0.22
	Aspirin plus clopidogrel	9.72 \pm 1.3	29.9 \pm 4	209914 \pm 67.7	38 \pm 9	1.04 \pm 0.24
T statistics		4.15	3.90	2.04	2.03	-1.04
P Value		<0.0001	<0.0001	0.043	0.044	0.290

According to a t- test, the mean values of Hb, HCT, PLT and BUN was significantly higher at discharge in the group receiving aspirin than in the group receiving aspirin + clopidogrel. (Table 5).

Based on a t-test, there was no significant difference between the mean injected platelet units for the studied groups during hospital stay ($p=0.47$). The mean FFP received during hospital stay was significantly higher in the group receiving aspirin + clopidogrel than in the group receiving aspirin ($p=0.0009$). Additionally, the mean amounts of the packed cells received during hospitalization was higher in the group receiving aspirin + clopidogrel than in the aspirin group. But this difference was not statistically significant ($p=0.068$). 75.7% of the patients receiving aspirin and 80% of the patients receiving aspirin + clopidogrel needed to receive FFP during hospitalization. According to a chi-square test, this difference was not statistically significant ($p=0.54$). None of the patients in either group needed receiving whole blood during hospitalization. The mean postoperative bleeding at various times after surgery and Hb and HCT amounts did not show any significant difference in the aspirin-receiving group in various age groups ($p > 0.05$). The need for blood transfusions in younger than 60 patients in the aspirin group was 83.4% and in the older than 60 patients was 97.5% and according to Fisher's exact test, this difference was statistically significant ($p=0.036$). Moreover, the difference in the amount of postoperative bleeding, hemoglobin and hematocrit in patients receiving aspirin + clopidogrel was not statistically significant in terms of age groups (under 60 and 60 years and older). 81.3% of the patients younger than 60 years and 92.1% of the patients 60 years and older who received aspirin + clopidogrel needed post-operative blood transfusions. Fisher's exact test did not show a significant difference between these groups ($p=0.17$).

Differences in the frequency distribution of the number of grafts in both groups was statistically significant ($p=0.022$), but the mean number of grafts was not statistically significant ($p=0.07$).

Discussion

Studies published in 1990 and 1991 indicated that the administration of aspirin preoperatively leads to further surgeries due to increased postoperative bleeding (6.6 vs. 1.7% and 6.3 vs. 2.4% in two studies) (8, 9). In subsequent studies, however, no increase in bleeding was observed. The administration of aspirin could even decrease mortalities in hospitals (10-12). In the past, concerns about bleeding lead physicians to advise patients undergoing CABG to discontinue taking aspirin three to five days before surgery. However, this general view is not recommended any more. ACCF/AHA2011 instructions recommend continuing to take aspirin or starting it before CABG surgery (13). Anemia is an independent risk factor predisposing complications and mortality after CABG. As a result, the transfer of red blood cells (RBC) is common. Blood transfusion rates have been reported to be between 40% and 90% (14). In the present study, this amount was 91.4% vs. 87.1% which was lower in the aspirin + clopidogrel group, but the difference was not statistically significant. As reported in 2010, among more than 82,000 patients from hospitals in the United States who had undergone CABG surgery with cardiopulmonary bypass in 2008, the rate of blood transfusions during surgery

was 56.1% (15). In addition, the bleeding which requires re-surgery was associated with a strong need for blood transfusions, and longer ICU and hospital stays. The re-surgery rates ranged from 4% to 6% (16). However, a study has shown that during 1995-1997, there has been a reduction in the rates of re-operation down to 2% (17). In the present study too, the need for repeated OR in the aspirin receiving group was less than half of the group receiving aspirin + clopidogrel. However, this difference was not statistically significant (3.4%vs. 6.8%).

Previous randomized trials have examined dual antiplatelet therapy with aspirin + clopidogrel in cardiovascular patients. There has been observed no clinical benefits in two studies that investigated combined antiplatelet treatment as compared with aspirin alone for patients with risk factors for atherosclerosis, cerebral, cardiac or peripheral vascular disease (18, 19). On the contrary, the combination of clopidogrel and aspirin as compared with aspirin alone has demonstrated significant improvements in the outcome of patients undergoing percutaneous vascular intervention (20), and in patients with acute coronary syndrome (21-23). In our study too, no benefits were observed in the group receiving aspirin + clopidogrel. Moreover, the aspirin group showed significantly lower

postoperative bleeding (834.67±595.81 vs. 662±506.39). Also, in the group receiving aspirin the mean values of Hb, HCT, BUN, and blood platelets at discharge were significantly higher than the group receiving aspirin + clopidogrel. Additionally, the mean amount of received FFP and the need for injections were lower in the aspirin group patients than the group receiving aspirin + clopidogrel (97.5 vs. 83.13%, $p=0.0009$). If the above criteria be considered as indicating a good prognosis, the group receiving aspirin had a better prognosis. Often surgeons prescribe clopidogrel commonly after CABG, believing that it prevents graft occlusion, and possibly improves clinical outcomes (24, 25). Although prospective randomized controlled trial data in this area is inadequate (24), previous studies cited in cardiac surgery literature have suggested that clopidogrel may improve postoperative outcomes (25-27). In a study of off-pump CABG patients, Ebrahimi et al demonstrated that adding clopidogrel to aspirin was accompanied with a tendency toward improvements in SVG remaining open up to 6 months after surgery (26). Recently, Gao et al have reported the results of a non-randomized trial in which 197 patients received 75 mg clopidogrel plus 100 mg aspirin the day after surgery based on a weekly replacement therapy. Within 7 days, the risk of life-threatening events or major bleeding after CABG surgery did not show a significant increase in patients receiving clopidogrel 5 days prior to CABG (9.6% vs 6.3% with placebo), but the same was not true for patients who had discontinued clopidogrel five days or more before CABG (4.4% vs. 5.3%) (29). These findings are supported by several other observational studies (30-37). In our study too, adding aspirin to clopidogrel did not lead to significant differences in life-threatening events, which confirms the cited studies. However, in a study by Wang et al, there was observed a good response to adding clopidogrel to aspirin after CABG (38).

Conclusion

Given the obtained results in the present study, the following conclusions can be drawn:

1. The amount of postoperative bleeding in the clopidogrel + aspirin was more than the aspirin group. However, its P Value is not significant, but it approaches the significance level ($p=0.067$).
2. The platelet, Hb, and HCT is lower at discharge in the clopidogrel + aspirin group than in the aspirin group, the cause of which is higher blood loss in the aspirin + clopidogrel group in comparison with the aspirin group.
3. FFP use in the aspirin + clopidogrel group was more than in the aspirin group which is due to increased blood loss in the first group ($p=0.000$).
4. To get more accurate results, further research is recommended with larger sample numbers.
5. Considering the importance of the drugs aspirin and clopidogrel in the prevention of heart attacks and their importance in the health system, it is recommended that the benefits of these drugs be not overlooked in comparison with their possible disadvantages.

References

1. Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. *Transfusion*. 2008; 48 (10):2152-8.
2. Angiolillo DJ, Guzman LA, Bass TA. Current antiplatelet therapies: benefits and limitations. *Am Heart J*. 2008; 156 (Suppl 2): S3-9.
3. Sun JC, Teoh KH, Lamy A, Sheth T, Ellins ML, Jung H, Yusuf S, Anand S, Connolly S, Whitlock RP, Eikelboom JW. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: the Preoperative Aspirin and Postoperative Anti-platelets in Coronary Artery Bypass Grafting study. *Am Heart J*. 2010; 160 (6): 1178-84.
4. Miceli A, Duggan SM, Aresu G, de Siena PM, Romeo F, Glauber M, Caputo M, Angelini GD. Combined clopidogrel and aspirin treatment up to surgery increases the risk of postoperative myocardial infarction, blood loss and reoperation for bleeding in patients undergoing coronary artery bypass grafting. *Eur J Cardiothorac Surg*. 2012 Jun 24. [Epub ahead of print].
5. Zhou YH, Wei X, Lu J, Ye XF, Wu MJ, Xu JF, Qin YY, He J. Effects of combined aspirin and clopidogrel therapy on cardiovascular outcomes: a systematic review and meta-analysis. *PLoS One*. 2012; 7 (2): e31642. Epub 2012 Feb 13.
6. Liu PS, Chen X, Shi KH, Xu M, Jiang YS. Impact of preoperative clopidogrel in coronary artery bypass grafting. *Zhonghua Wai Ke Za Zhi*. 2008; 46 (4): 252-5.
7. Cruden NL, Morch K, Wong DR, Klinke WP, Ofiesh J, Hilton JD. Clopidogrel loading dose and bleeding outcomes in patients undergoing urgent coronary artery bypass grafting. *Am Heart J*. 2011; 161 (2): 404-10.
8. Goldman S, Copeland J, Moritz T, et al. Starting aspirin therapy after operation. Effects on early graft patency. Department of Veterans Affairs Cooperative Study Group. *Circulation* 1991; 84:520.
9. Sethi GK, Copeland JG, Goldman S, et al. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. *J Am Coll Cardiol* 1990; 15: 15.
10. Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. *Circulation* 2005; 112: 1286.
11. Dacey LJ, Munoz JJ, Johnson ER, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. *Ann Thorac Surg* 2000; 70: 1986.
12. Mangano DT, Multicenter Study of Perioperative Ischemia Research Group. Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002; 347: 1309.
13. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; 124: 2610.

14. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* 2010; 304: 1559.†
15. Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010; 304: 1568.†
16. Sellman M, Intonti MA, Ivert T. Reoperations for bleeding after coronary artery bypass procedures during 25 years. *Eur J Cardiothorac Surg* 1997; 11: 521.†
17. Munoz JJ, Birkmeyer NJ, Dacey LJ, 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.†
18. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet*. 2004; 364: 331–337.†
19. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006; 354: 1706–1717.†
20. Steinhubl SR, Berger PB, Mann JT III, Fry ET, DeLago A, Wilmer C, Topol EJ. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002; 288: 2411–2420.†
21. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001; 345: 494–502.†
22. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet*. 2005; 366: 1607–1621.†
23. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, McCabe CH, Braunwald E. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005; 352: 1179–118†
24. Kulik A, Chan V, Ruel M. Antiplatelet therapy and coronary artery bypass graft surgery: perioperative safety and efficacy. *Expert Opin Drug Saf*. 2009; 8: 169–182.†
25. Kim DH, Daskalakis C, Silvestry SC, Sheth MP, Lee AN, Adams S, Hohmann S, Medvedev S, Whellan DJ. 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.†
26. Ibrahim K, Tjomslund O, Halvorsen D, Wiseth R, Wahba A, Karevold A, Haaverstad R. Effect of clopidogrel on midterm graft patency following off-pump coronary revascularization surgery. *Heart Surg Forum*. 2006; 9: E581–E586.†
27. Gurbuz AT, Zia AA, Vuran AC, 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: 190–195.†
28. 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.†
29. Fox KA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in unstable angina to prevent recurrent ischemic Events (CURE) Trial. *Circulation* 2004; 110:1202.†
30. Chu MW, Wilson SR, Novick RJ, et al. Does clopidogrel increase blood loss following coronary artery bypass surgery? *Ann Thorac Surg* 2004; 78:1536.†
31. 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.†
32. Berger JS, Frye CB, Harshaw Q, et al. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol* 2008; 52: 1693.†
33. Kim JH, Newby LK, Clare RM, et al. Clopidogrel use and bleeding after coronary artery bypass graft surgery. *Am Heart J* 2008; 156: 886.†
34. Bavry AA, Lincoff AM. Is clopidogrel cardiovascular medicine's double-edged sword? *Circulation* 2006; 113: 1638.†
35. Ebrahimi R, Dyke C, Mehran R, et al. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *J Am Coll Cardiol* 2009; 53: 1965.†
36. Nijjer SS, Watson G, Athanasiou T, Malik IS. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. *Eur Heart J* 2011; 32: 2970.†
37. Vito Antonio Mannacio¹, Luigi Di Tommaso, Anita Antignan, Vincenzo De Amicis, Carlo Vosa. 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. *Coronary revascularization*. 2012; (online)†
38. Wang X, Gong X, Zhu T, Zhang Q, Zhang Y, Wang, et al. Clopidogrel improves aspirin response after off-pump coronary artery bypass surgery. *J Biomed Res*. 2014; 28 (2): 108-13.†