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Clopidogrel Increases Blood Transfusion and Hemorrhagic Complications in Patients Undergoing Cardiac Surgery

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Background. Utilization of the irreversible antiplatelet agent clopidogrel is increasing in the treatment acute coronary syndrome patients. Consequently, more patients are presenting for urgent cardiac surgery with an irreversible defect in platelet function. The objective of this study was to determine whether recent clopidogrel administration predicts transfusion and hemorrhagic complication in cardiac surgery patients.

Methods. This retrospective study included all patients undergoing isolated coronary artery bypass graft surgery (CABG), isolated valve, or CABG plus valve at a single center between 2004 and 2008. The outcomes of interest were transfusion and hemorrhagic complication. Clopidogrel stop interval was defined as the time between last dose and presentation to the operating room, and was examined in daily increments from 0 to 5 days, more than 5 days, and not receiving clopidogrel preoperatively. By logistic regression, the association of clopidogrel stop

interval with transfusion and with hemorrhagic complication was examined after adjusting for other risk factors.

Results. Of 3,779 patients included in this study, 26.4% (999) received clopidogrel preoperatively. The overall rates of transfusion and hemorrhagic complication were 34.1% and 4.1%, respectively. Clopidogrel use within 24 hours was an independent predictor of transfusion (odds ratio 2.4; 95% confidence interval: 1.8 to 3.3) and of hemorrhagic complication (odds ratio 2.1; 95% confidence interval: 1.3 to 3.6).

Conclusions. Patients receiving clopidogrel within 24 hours of surgery are at increased risk for transfusion and hemorrhagic complication. Timing of surgery for patients receiving clopidogrel should take into account the interval from the last dose.

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The effectiveness of clopidogrel in acute coronary syndrome is well established, with level 1 evidence indicating reduction in death and major morbidity in ST-segment elevation myocardial infarction, non-ST-segment elevation MI, as well as a reduction in in-stent thrombosis after percutaneous coronary intervention (PCI) [1–6]. American Heart Association/American College of Surgery guidelines support the administration of clopidogrel in STEMI, NSTEMI, and before PCI [7–9]. As a consequence of these developments, more patients are presenting for urgent cardiac surgery having received clopidogrel.

Several studies suggest cardiac surgical patients are at increased risk of adverse outcomes, transfusion, and hemorrhagic complications when receiving clopidogrel

preoperatively [10, 11], although these results are inconsistent. Karabulut and colleagues demonstrated no increased risk for transfusions or hemorrhagic complications in cardiac surgical patients receiving clopidogrel [12], whereas others have shown an increase in transfusion of two to four units on average [10, 13], and still others, including Ley and coworkers [14] have shown a tenfold increase in reexploration for tamponade. The potential for increased bleeding complications with clopidogrel extends to off-pump surgery as well [15].

Cardiac surgery patients who experience significant postoperative bleeding or receive blood transfusions are at increased risk for other adverse outcomes. Blood transfusions have been associated with increased rates of clinically significant infections, ischemic, and 30-day mortality [16]. Return to the operating room for bleeding complications has been identified as an independent risk factor for operative mortality, and nonfatal adverse outcomes [17].

Given the adverse outcomes associated with blood

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transfusion and hemorrhagic complication after cardiac surgery we believed that further study of clopidogrel use in cardiac surgery patients was warranted. Additionally, the relationship between the interval from the last dose of clopidogrel to cardiac surgical intervention and hemorrhagic complications has not been well delineated. The purpose of this study was to study the relationship between clopidogrel use and the risk of blood transfusion and hemorrhagic complication.

Material and Methods

Approval for conducting this study was obtained by the Institutional Review Board of the Capital District Health Authority. We note that the need for individual patient consent for this study was waived by the Review Board.

Data Sources and Study Population

This retrospective study includes all consecutive patients undergoing isolated CABG, isolated valve, or CABG plus valve at the Queen Elizabeth II Health Sciences Center (QEII HSC) in Halifax, Nova Scotia, between June 2004 and August 2008. Data were obtained from the Maritime Heart Center (MHC) registry, a detailed clinical database containing preoperative, intraoperative, and postoperative data collected prospectively on all cardiac surgical cases performed at the QEII HSC from 1995 to the present.

Surgical Technique

For CABG surgery conducted with cardiopulmonary bypass (CPB), we utilized upper aortic cannulation and two-stage venous cannulation of the right atrium/inferior vena cava. During CPB, the target mean perfusion pressure was 60 mm Hg. Body temperature was allowed to drift to a minimum of 32°C. Intermittent cold blood cardioplegia (1:4 blood to crystalloid/max K⁺ concentration 22 mEq/L) was delivered antegrade through the aortic root unless otherwise indicated. A small proportion of patients were operated upon with non-CPB-based beating-heart techniques utilizing a commercially available tissue stabilizer (Octopus III system; Medtronic Inc, Minneapolis, MN). Distal anastomoses were carried out with continuous polypropylene suture (7-0 venous grafts, 8-0 arterial grafts). Choice of conduit (arterial versus venous), construction of grafts (sequential, composite, and so forth), choice of valve (tissue versus mechanical), surgical approach for valve replacement (Sondergaard's groove, transeptal, and so forth) were surgeon dependent. Heparin was given at a dose of 300 IU /kg to achieve a target activated clotting time of greater than 450 s (in the beating-heart group, a dose of 100 IU/kg was utilized). On completion of the procedure, heparin was reversed with protamine sulphate with a goal of normalizing the activated clotting time. No special blood conservation techniques were em-

Table 1. Clinical Characteristics Associated With Clopidogrel Stop Interval

	≤24 Hours (n = 324) % (n)	2 Days (n = 120) % (n)	3 Days (n = 90) % (n)	4 Days (n = 98) % (n)	5 Days (n = 110) % (n)	>5 Days (n = 257) % (n)	Not Receiving Clopidogrel (n = 2,780) % (n)	p Value
Female sex	23.2 (75)	26.7 (32)	26.7 (24)	27.6 (27)	28.2 (31)	22.6 (58)	25.2 (700)	0.8472
Age, years								
<60	25.9 (84)	29.2 (35)	23.3 (21)	22.4 (22)	30.9 (34)	26.5 (68)	28.4 (790)	
60 to 69	30.2 (98)	33.3 (40)	30.0 (27)	35.7 (35)	27.3 (30)	30.7 (79)	30.9 (860)	
70 to 79	34.9 (113)	25.0 (30)	33.3 (30)	32.6 (32)	30.0 (33)	32.3 (83)	29.8 (828)	
>80	9.0 (29)	12.5 (15)	13.3 (12)	9.2 (9)	11.8 (13)	10.5 (27)	10.9 (302)	0.8868
Diabetes mellitus	38.3 (124)	34.2 (41)	42.2 (38)	43.9 (43)	39.1 (43)	37.7 (97)	34.4 (955)	0.1885
Renal failure	9.0 (29)	6.7 (8)	11.1 (10)	7.1 (7)	2.7 (3)	7.8 (20)	5.5 (154)	0.0326
EF <40%	22.6 (72)	13.3 (16)	21.4 (19)	13.4 (13)	12.8 (14)	19.1 (49)	13.5 (374)	0.0002
CHF	25.6 (83)	19.2 (23)	21.1 (19)	13.3 (13)	18.2 (20)	23.0 (59)	20.9 (581)	0.1753
PVD/CVD	33.6 (109)	33.3 (40)	25.6 (23)	31.6 (31)	30.0 (33)	33.1 (85)	23.3 (648)	0.0001
COPD	19.8 (64)	16.7 (20)	10.0 (9)	14.3 (14)	15.4 (17)	14.4 (37)	15.3 (425)	0.3306
Low hemoglobin	34.3 (111)	24.2 (29)	34.4 (31)	28.6 (28)	22.7 (25)	23.4 (60)	20.4 (566)	0.0001
Urgency								
Elective	6.2 (20)	10.0 (12)	18.9 (17)	40.8 (40)	48.2 (53)	40.9 (105)	54.5 (1514)	
In-house	38.0 (123)	75.0 (90)	65.6 (59)	54.1 (53)	49.1 (54)	54.5 (140)	36.2 (1005)	
Urgent	38.6 (125)	13.3 (16)	14.4 (13)	4.1 (4)	2.7 (3)	4.3 (11)	7.3 (204)	
Emergent	17.3 (56)	1.7 (2)	1.1 (1)	1.0 (1)	0.0 (0)	0.4 (1)	2.0 (57)	0.0001
Procedure								
CABG	91.0 (295)	95.0 (114)	87.8 (79)	92.9 (91)	90.9 (100)	85.2 (219)	65.1 (1809)	
Valve	1.5 (5)	1.7 (2)	5.6 (5)	2.0 (2)	5.4 (6)	5.4 (14)	22.3 (621)	
CABG+valve	7.4 (24)	3.3 (4)	6.7 (6)	5.1 (5)	3.6 (4)	9.3 (24)	12.6 (350)	0.0001
Prior cardiac surgery	6.2 (20)	6.7 (8)	4.4 (4)	2.0 (2)	1.8 (2)	5.8 (15)	8.4 (234)	0.0149

CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; EF = ejection fraction; PVD = peripheral vascular disease.

Table 2. Unadjusted In-hospital Outcomes Associated With Clopidogrel Stop Interval

	≤24 Hours (n = 324) % (n)	2 Days (n = 120) % (n)	3 Days (n = 90) % (n)	4 Days (n = 98) % (n)	5 Days (n = 110) % (n)	>5 Days (n = 257) % (n)	Not Receiving Clopidogrel (n = 2,780) % (n)	p Value
Blood transfusion	59.9 (194)	43.3 (52)	40.0 (36)	43.9 (43)	29.1 (32)	30.7 (79)	30.7 (854)	0.0001
Hemorrhagic complication	8.0 (26)	2.5 (3)	4.4 (4)	3.1 (3)	2.7 (3)	3.9 (10)	3.8 (105)	0.0470
Mortality	8.3 (27)	0.8 (1)	8.9 (8)	4.1 (4)	4.6 (5)	4.3 (11)	4.0 (110)	0.0024
Sepsis/DSWI	5.2 (17)	5.0 (6)	5.6 (5)	3.1 (3)	3.6 (4)	3.1 (8)	3.2 (90)	0.4740
Ventilation >24 hours	34.9 (113)	21.7 (26)	22.2 (20)	15.3 (15)	10.0 (11)	13.6 (35)	14.1 (392)	0.0001

DSWI = deep sternal wound infection.

ployed other than nonhemic prime, retransfusion of all contents of the oxygenator/circuit at the end of CPB, and acceptance of normovolemic anemia. Postoperatively, nonhemic volume expanders were used routinely.

Variable Selection

The interval between the last dose of clopidogrel and cardiac surgical intervention (clopidogrel stop interval) was examined in daily increments from 0 to 5 days and greater than 5 days, and was compared with patients not receiving clopidogrel preoperatively. Preoperative patient characteristics of interest included age (less than 60 years old, 60 to 69, 70 to 79, and 80 years or more), sex, diabetes mellitus, renal failure (serum creatinine greater than 176 μmol/L), procedure (isolated CABG, isolated valve, CABG plus valve), low hemoglobin (less than 120 g/L), peripheral vascular or cerebrovascular disease, left ventricular dysfunction defined as ejection fraction (EF) less than 40%, prior cardiac surgery, and urgency status: elective cases (waiting at home), in-house cases (requiring hospitalization but able to wait more than 24 hours before surgery); and urgent (requiring a procedure within 24 hours to prevent further clinical deterioration), and emergent (requiring immediate surgery).

Primary postoperative outcomes were transfusion of any blood product, including packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate, received during the intraoperative or postoperative period; and hemorrhagic complication (tamponade or reexploration for bleeding). Other outcomes included mortality, sepsis, and deep sternal wound infection, and prolonged mechanical ventilation (longer than 24 hours).

Statistical Analysis

Preoperative, intraoperative, and postoperative characteristics were examined among the various clopidogrel stop intervals. The association of clinical characteristics with blood transfusion and with hemorrhagic complication was evaluated univariately. Continuous variables were compared using a two-tailed t test or Wilcoxon rank sum test, and categorical variables were analyzed by χ² or Fisher's exact test, as appropriate. Fully-adjusted logistic regression models were generated to examine the association of clopidogrel stop interval with blood transfusion and with hemorrhagic complication after adjusting for relevant prognostic variables. A receiver operating char-

acteristic curve was calculated as a measure of sensitivity and specificity for each logistic regression model. A bootstrap procedure was performed on 200 subsamples to confirm the independent predictors of each outcome; furthermore, the 95% confidence interval (CI) of the receiver operating characteristic curve was obtained from the 2.5 and 97.5 percentiles of the bootstrap distribution.

Table 3. Predictors of Intraoperative and Postoperative Blood Transfusion

	Adjusted Odds Ratio	95% Confidence Interval	p Value
Clopidogrel stop interval			
≤ 24 hours	2.4	1.8-3.3	0.0001
2 days	1.7	1.1-2.6	0.0271
3 days	1.1	0.6-1.8	0.8369
4 days	2.0	1.2-3.3	0.0066
5 days	1.0	0.6-1.6	0.9291
>5 days	0.9	0.7-1.3	0.6215
Not on clopidogrel	1.0	—	
Female sex	2.4	2.0-2.9	0.0001
Age, years			
>80	3.2	2.4-4.3	0.0001
70 to 79	2.3	1.9-2.9	0.0001
60 to 69	1.3	1.1-1.7	0.0129
<60	1.0	—	
Renal failure	2.2	1.6-3.2	0.0001
PVD/CVD	1.4	1.2-1.7	0.0002
Low hemoglobin	4.9	4.0-6.1	0.0001
Urgency			
Urgent/emergent	3.4	2.6-4.5	0.0001
In-house	1.8	1.5-2.1	0.0001
Elective	1.0	—	
Procedure			
CABG+valve	3.4	2.6-4.4	0.0001
Valve	1.1	0.8-1.4	0.5704
CABG	1.0	—	
Prior cardiac surgery	1.7	1.2-2.4	0.0014
Aprotinin therapy	1.0	0.8-1.3	0.9405

Logistic regression model receiver operating characteristic 83.4%, 95% confidence interval: 82.1% to 85.3%.

CABG = coronary artery bypass graft surgery; CVD = cardiovascular disease; PVD = peripheral vascular disease.

Statistical analysis was performed using SAS software version 9.1 (SAS, Cary, NC).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Patient Population

This study included 3,779 consecutive patients undergoing isolated CABG, isolated valve surgery, or CABG plus valve surgery. In the study, 26.4% of patients (999) received clopidogrel preoperatively and of those, 74.3% (742) presented to the operating room within 5 days of receiving clopidogrel. Compared with patients not prescribed clopidogrel, preoperative clopidogrel use was associated with higher transfusion (43.6% [436] versus 30.7% [854], $p = 0.0001$) and hemorrhagic complication (4.9% [49] versus 3.8% [105], $p = 0.12$). Examined by stop interval, 8.6% of patients (324) underwent surgery within 24 hours of receiving clopidogrel, 3.2% (120) discontinued clopidogrel 2 days before surgery, and 2.4% (90) discontinued 3 days before surgery, 2.6% (98) discontinued 4 days before surgery, and 2.9% (110) discontinued 5 days before surgery; 6.8% of patients (257) discontinued clopi-

Table 4. Predictors of Hemorrhagic Complication

	Adjusted Odds Ratio	95% Confidence Interval	<i>p</i> Value
Clopidogrel stop interval			
≤ 24 hours	2.1	1.3-3.6	0.0042
2 days	0.7	0.2-2.2	0.5201
3 days	1.2	0.4-3.3	0.7766
4 days	0.9	0.3-3.1	0.9261
5 days	0.8	0.3-2.7	0.7642
>5 days	1.1	0.5-2.1	0.8802
Not on clopidogrel	1.0	—	
Age, years			
>80	2.5	1.6-4.0	0.0001
70 to 79	1.5	1.0-2.1	0.0492
<70	1.0	—	
Renal failure	1.4	0.8-2.5	0.2650
PVD/CVD	1.4	1.0-2.0	0.0525
Hemoglobin <120 g/L	0.9	0.6-1.3	0.4273
Urgency			
Urgent/emergent	1.7	1.0-2.9	0.0708
In-house	1.5	1.0-2.3	0.0318
Elective	1.0	—	
Procedure			
CABG + valve	2.4	1.6-3.8	0.0001
Isolated valve	1.7	1.1-2.7	0.0202
Isolated CABG	1.0	—	

Logistic regression model receiver operating characteristic 68.6%, 95% confidence interval: 66.2% to 74.8%.

CABG = coronary artery bypass graft surgery; CVD = cardiovascular disease; PVD = peripheral vascular disease.

Table 5. Rates of Blood Product Transfusion

	Preoperative Clopidogrel n = 999 n (%)	No Clopidogrel n = 2,780 n (%)	<i>p</i> Value
Red blood cells	406 (40.6)	805 (30.0)	<0.001
Fresh frozen plasma	148 (14.8)	299 (10.8)	0.0007
Platelets	127 (12.7)	228 (8.2)	<0.001

dogrel more than 5 days before surgery and 73.6% (2,780) were not taking clopidogrel. Preoperative clinical characteristics among the clopidogrel stop intervals are shown in Table 1. Patients receiving clopidogrel within 24 hours of surgery were more likely to be urgent or emergent, and have ejection fraction less than 40% and hemoglobin less than 120 g/L. Overall bilateral internal mammary artery use was 5.3% (163). Although bilateral internal mammary artery use had lower rates of blood product transfusion (21.5% [35] versus 34.7% [1,020], $p = 0.0005$), rates with its use did not differ in relation to whether the patient received preoperative clopidogrel (4.7% [45] versus 5.5% [118]; $p = 0.36$). Overall, 1.2% of patients (32) underwent isolated CABG with a beating-heart approach. Of the clopidogrel group, this represents 0.8% of patients (7), and in the nonclopidogrel group, this represents 1.4% (25), a nonsignificant difference ($p = 0.17$).

Unadjusted In-Hospital Outcomes

The overall rate of transfusion was 34.1% (1,290) in the study population, and annual rates did not change over the study period. Hemorrhagic complication occurred in 4.1% (154) of the study patients. Unadjusted postoperative outcomes occurring before hospital discharge are shown in Table 2. For patients receiving clopidogrel within 24 hours, the rate of transfusion was 59.9% (194 patients), and the rate of hemorrhagic complication was 8.0% (26 patients), considerably higher than the overall rates of these outcomes. In addition, patients receiving clopidogrel within 24 hours had a higher prevalence of mortality and prolonged mechanical ventilation.

Clopidogrel Stop Interval as Independent Predictor of Outcome

Predictors of blood product transfusion are shown in Table 3. Clopidogrel administration within 24 hours before surgery (odds ratio [OR] 2.4; 95% CI: 1.8 to 3.3) and 2 days before surgery (OR 1.7; 95% CI: 1.1 to 2.6) were independent predictors of transfusion. Risk of transfusion also increased with age, urgency and complexity of surgery. Other significant preoperative risk factors for transfusion included hemoglobin less than 120 g/L, renal failure, female sex, and prior cardiac surgery. Of note, overall, 10% of patients (384) received aprotinin. Although patients receiving aprotinin were more likely to undergo transfusion (transfusion rate 7.7% [191] without aprotinin; 15% [193] with aprotinin; $p < 0.0001$), in a fully adjusted model, aprotinin did not emerge as a significant factor (OR 1.01; 95% CI: 0.762 to 1.341; Table 3).

Clopidogrel administration within 24 hours before surgery was an independent predictor of hemorrhagic complication (tamponade or reexploration for bleeding [OR 2.1; 95% CI: 1.3 to 3.6; Table 4]). Risk of hemorrhagic complication also increased with age, urgency, and complexity of surgery. Clopidogrel use was also associated with an increase in transfusion rates for packed red blood cells, fresh frozen plasma, and platelets (Table 5).

Comment

The objective of this study was to determine the relationship between the outcomes of interest and the clopidogrel stop interval. We found that patients receiving clopidogrel within 24 hours of surgery experienced significantly higher transfusion rates and that transfusion rates decreased as the clopidogrel stop interval increased. Using logistic regression, we identified clopidogrel administration within 24 hours of surgery as an independent predictor of blood product transfusion (OR 2.4) and hemorrhagic complication (OR 2.1). In addition, the risk of both outcomes increased with age, urgency, and complexity of surgery.

In light of the adverse outcomes associated with postoperative transfusion and hemorrhagic complication, the AHA/ACC guidelines recommend that clopidogrel be discontinued for at least 5 days and preferably for 7 days before CABG [7]. This is not always possible, however, when patients are presenting acutely for surgical intervention. In this study, 74.3% of patients receiving preoperative clopidogrel presented to the operating room within 5 days of discontinuing the drug. Similarly, Mehta and colleagues [13] found that 87% of patients receiving preoperative clopidogrel presented to the operating room within 5 days of their last dose. Surgeons are now faced with patients presenting with traditional urgent/emergent surgical indications (eg, tight left main disease, acute ischemia with myocardial dysfunction, or severe aortic stenosis with hemodynamic compromise) who have recently received clopidogrel. Some cases are being delayed, at times for several days, to avoid the negative outcomes associated with bleeding complications. Alternatively, surgeons are compelled to take patients with recent clopidogrel treatment to the operating room and deal with potential resultant coagulopathy.

Our study suggests that delaying surgery by at least 24 hours decreases the risk of transfusion and hemorrhagic complication. This is a far more feasible delay interval than 5 to 7 days for patients with relatively urgent indications for surgical intervention, although the safety of such an approach with patients with urgent indications for cardiac surgery remains to be demonstrated. Our findings are in substantial agreement with those of Ascione and associates [18] who found clopidogrel administration within 48 hours was associated with increased transfusion and adverse outcomes.

Alternative approaches include delaying clopidogrel administration until appropriate diagnostic studies or images are obtained, especially for patients with clinical indications of cardiovascular disease that is likely to be

best treated by surgical intervention. These could reasonably include patients with systolic murmurs and clinical signs of either significant mitral regurgitation or aortic stenosis, patients with prior noninvasive testing suggestive of left main disease or its equivalent, or patients with advanced diabetes who may have diffuse disease not amenable to PCI. Recent evidence from administrative data indicates that as many as 50% of patients receiving clopidogrel did not have documented indications for its use [19]. A more conservative approach to clopidogrel use in patients with strong potential for emergency cardiac surgery may be beneficial to overall outcomes in light of our results.

It is worth noting that the recent publications of a randomized trial as well as several retrospective studies have effectively removed aprotinin, an effective antifibrinolytic agent in relatively common use in cardiac surgery, from the market. While legitimate concerns were raised about the safety of this agent, aprotinin was demonstrated effective in decreasing the primary end point of massive transfusion set in the randomized trial [20], and its removal from the market reduces the ability of surgeons to offset the hemorrhagic risk of clopidogrel. We were unable to demonstrate a risk-adjusted effect of aprotinin administration on transfusion rates. Whether off-label aprotinin use is safe or effective in the subset of patients with recent clopidogrel use remains an area of potential interest and deserving of further study.

A recent multicenter retrospective study demonstrates a rapidly increasing utilization of recombinant activated factor VII as a rescue therapy in bleeding cardiac surgical patients [21]. This agent promotes systemic activation of the clotting system and is associated with high mortality (32%). Forty-six percent of nonsurvivors in that study had received antiplatelet agents other than aspirin. Indeed, in our own center, the utilization rate of recombinant activated factor VII has increased over time, and the percentage of these cases receiving clopidogrel at the time of surgery has risen from 11% in 2006 to 56% in 2008 (data not shown). Taken together, these data indicate that the use of nonaspirin antiplatelet agents is associated with the requirement for rescue therapy with a systemic procoagulant agent associated with high mortality.

We acknowledge several limitations to this study. Firstly, it is retrospective in nature and, as such, subject to bias by unmeasured confounders, particularly with regard to patient factors that lead to earlier surgical intervention even after clopidogrel administration. Secondly, although this is a relatively large cohort of patients, there may still be limitations in statistical power to detect significant differences in bleeding risk among the various stop intervals.

In conclusion, we recommend that if the clinical situation allows, for patients receiving clopidogrel, undergoing cardiac surgery should be delayed at least 24 hours. Also, for cardiac surgery patients, clopidogrel administration should be restricted to those with clear-cut indications for its use. For patients with a high likelihood of surgical intervention, consideration should be given to delaying clopidogrel loading until relevant diagnostic

studies can be obtained that will determine the role for urgent cardiac surgical intervention.

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