

PRACTICE INSIGHTS

Clopidogrel-Associated Bleeding and Related Complications in Patients Undergoing Coronary Artery Bypass Grafting

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Objective. To determine if clopidogrel use before coronary artery bypass grafting (CABG) is associated with an increase in major bleeding, hemorrhage-related complications, or transfusion requirements.

Methods. A structured literature search of English-language articles was conducted by using MEDLINE, EMBASE, and the Cochrane Collaboration Database for the period of January 1, 1990–April 30, 2007. Studies were included if they met the following criteria: randomized controlled trials, prospective observational trials, or retrospective trials; characteristics and outcomes of patients who were exposed to clopidogrel within 7 days before CABG were analyzed; at least 20 patients were enrolled; and reported outcomes were related to transfusion requirements, resource utilization, clinical events, or hemorrhage-related reoperation rates. Patients were considered exposed to clopidogrel if they discontinued the drug within a specified time frame that was designated in each study. The rates of the outcomes were compared between those patients exposed and those not exposed to clopidogrel.

Results. Twenty-three studies, with data on 3505 patients exposed to clopidogrel before CABG, met the selection criteria. Results suggested that clopidogrel exposure within 7 days before CABG increased the risk of major bleeding and related complications, such as reoperation and blood product transfusions. For other outcomes such as mortality, myocardial infarction, or stroke, the studies' designs lacked statistical power to detect significant differences. In five of the 23 studies, antifibrinolytic therapy with aprotinin was evaluated; in the other studies, aprotinin may have been administered, but it was not discussed in detail. In these studies, the clopidogrel-exposed patients typically had significantly higher chest tube output volumes, reoperation rates due to bleeding, and greater transfusion requirements. Although aprotinin appeared to mitigate hemorrhagic risk, the drug has been temporarily suspended from the market due to safety concerns.

Conclusion. Clopidogrel exposure within 7 days before CABG is associated with an increase in major bleeding, hemorrhage-related complications, and transfusion requirements, and leads to potentially greater consumption of health care resources. The overall risks and benefits for each patient should be considered before using the drug.

Key Words: acute coronary syndrome, adenosine diphosphate inhibitors, bleeding, hemorrhage, clopidogrel, coronary artery bypass graft, CABG, thienopyridines.

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Coronary artery bypass grafting (CABG) is an established revascularization procedure for the treatment of advanced atherothrombotic coronary artery disease.¹ The National Center for Health Statistics estimated that 427,000 procedures were performed on 249,000 patients in the United States in 2004.² Antiplatelet drugs, particularly aspirin, are considered a mainstay for both primary and secondary prevention in atherothrombotic coronary artery disease.³ However, newer agents, such as clopidogrel (one of two commercially marketed thienopyridine adenosine 5'-diphosphate [ADP]-receptor antagonists in the United States), when combined with aspirin are highly beneficial in clinical-pathologic states of heightened platelet activation and recommended strongly for use among patients with non-ST-segment elevation acute coronary syndrome (ACS).^{4,5} Clopidogrel recently received approval by the United States Food and Drug Administration for a labeling change to include patients with ST-segment elevation ACS.⁶

The benefits of clopidogrel in patients with ACS were first demonstrated in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.⁷ On the basis of these data, current American Heart Association–American College of Cardiology (AHA-ACC)⁸ and European Society of Cardiology (ESC)⁵ management guidelines recommend platelet-directed pharmacotherapy with aspirin and clopidogrel in patients with ACS treated medically or after percutaneous coronary intervention for a minimum of 1 month (level of evidence A) and up to 12 months (level of evidence B). A course

of therapy of at least 12 months has been recommended for patients who receive drug-eluting stents to minimize the risk for stent thrombosis.⁹

Although current practice guidelines for patients with ACS clearly reflect the ability of clopidogrel, combined with aspirin, to reduce cardiovascular events, they also emphasize caution in individuals who subsequently require CABG, given the potential risk of perioperative hemorrhagic complications. Specifically, published guidelines recommend that high-risk patients with ACS in whom CABG may be required should not receive an ADP-receptor antagonist until the coronary anatomy is defined and a decision has been made not to perform surgical revascularization.⁵ Further, among patients taking clopidogrel who are scheduled for elective CABG, drug cessation at least 5 days and preferably 7 days before surgery is recommended.⁸

Clopidogrel, like ticlopidine and the investigational agent prasugrel, is a nonreversible platelet antagonist. As a prodrug, clopidogrel is rapidly and extensively metabolized hepatically to a carboxylic acid derivative (its active metabolite), with a plasma elimination half-life of approximately 8 hours. Platelet exposure to the active metabolite causes prolonged (7–10 days) inhibition of ADP-mediated platelet activation and aggregation. Thus, from the time of drug discontinuation, restoration of normal hemostasis is dependent on the introduction of new platelets into the circulation from bone marrow and extramedullary sources. Because cardiothoracic surgery represents a major hemostatic challenge and is required in greater than 15% of patients admitted to the hospital with ACS, clinicians are confronted regularly with complex decisions concerning the acceptable risk of antithrombotic agents and must rapidly determine which patients are at high risk requiring urgent or emergency surgical revascularization.

To better understand the overall clinical impact and health care delivery implications associated with clopidogrel use before elective, isolated CABG, we conducted a comprehensive review of published studies reporting transfusion requirements, rates of major bleeding and related complications, resource utilization, and outcomes in patients exposed to clopidogrel before CABG. Our objective was to determine if clopidogrel use before CABG was associated with increases in bleeding and its complications, and if so, to use this information to improve clinical decision making and patient care.

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Table 1. Description of the 23 Studies That Met Selection Criteria

Study Design and Purpose	No. of Patients	
	Exposed ^a	Nonexposed
Prospective, observational		
To investigate the independent effect of preoperative exposure to aspirin, heparin, and clopidogrel on early clinical outcomes of inpatients undergoing initial CABG ¹³	91	Did not receive any anticoagulants ^b : 133 Received anticoagulants ^b : 246
To determine if the immediate preoperative use of clopidogrel is associated with increased occurrence of postoperative bleeding ¹⁵	0–4 days: 41 5–8 days: 39	> 8 days: 232
To evaluate the effect of preoperative clopidogrel on CABG outcomes ¹⁹	59 (+ aspirin)	165 (+ placebo)
To evaluate the effects of clopidogrel on bleeding and use of bleeding products after CABG ²¹	48	1580
To evaluate potential role of off-pump CABG in eliminating need to delay surgery and in decreasing postoperative bleeding in patients exposed to clopidogrel ²⁷	15	63
To explore the effects of clopidogrel on bleeding complications after CABG ²⁸	51	194
Retrospective		
To evaluate the effect of clopidogrel on bleeding in urgent or emergency CABG ¹⁸	64	64
To analyze the effect of clopidogrel on bleeding, transfusion requirements, and reoperation for CABG ³³	25 (+ aspirin) 40 (+ aspirin)	255 (+ aspirin)
To evaluate the effect of preoperative clopidogrel exposure in patients undergoing CABG ²⁰	415	1944
To evaluate the effect of preoperative clopidogrel in patients undergoing off-pump CABG ³²	281	1291
To assess complications in patients who received clopidogrel and underwent subsequent CABG ¹¹	Hospitalized group: 64 ^c	Discharged home group: 61 ^c
To review the effect of preoperative clopidogrel on clinical outcomes, bleeding complications, and resource utilization after CABG ²²	18 59 (+ aspirin)	523 (aspirin only) 210
To evaluate the impact of antiplatelet drugs on cardiac patients ²³	48	117
To characterize clopidogrel use before CABG and examine the impact on transfusion requirements in patients with non-ST-elevation ACS (ad hoc analysis from CRUSADE study) ³	739	113
To evaluate the risk associated with use of aspirin and clopidogrel ²⁵	11 46 (+ aspirin)	497 105 (aspirin only)
Prospective and retrospective		
To examine the effect of clopidogrel received ≤ 6 days before CABG on postoperative need for transfusions ¹⁴	Prospective: 45 Retrospective: 53	45 428
Randomized		
To examine the benefits and risks of clopidogrel in patients undergoing CABG (CURE subgroup analysis) ¹⁷	1011	1061
To report outcomes of CABG surgery (CLARITY-TIMI 28 subgroup analysis) ³⁰	66 (+ aspirin)	70 (placebo + aspirin)
Studies that also analyzed aprotinin		
Prospective, observational		
To evaluate the influence of clopidogrel on postoperative bleeding and transfusion requirements in patients with myocardial revascularization; all patients received aprotinin ¹⁶	36	369
To compare the effect of preoperative aspirin with or without clopidogrel on postoperative bleeding and transfusion requirements; all patients received aprotinin ²⁹	60 (+ aspirin)	157 (aspirin only)

Table 1. (continued)

No. of Days Clopidogrel Discontinued Before Surgery	
Exposed Patients ^a	Nonexposed Patients
< 5 days	≥ 5 days
≤ 4 days	> 8 days
Within 5–8 days	
≤ 7 days	> 7 days or no exposure
≤ 2 days	NA
≤ 4 days	NA
≤ 5 days	NA
≤ 5 days	NA
≤ 3 days	No exposure or > 7 days
4–7 days	
≤ 7 days	> 7 days or no exposure
≤ 7 days	> 7 days
3–5 days	NA
NR	NR
NR	NR
≤ 7 days	No exposure
≤ 5 days	> 5 days
≤ 7 days	NA
≤ 7 days	NA
≤ 6 days	NA
NA	NA
At discretion of surgeon	At discretion of surgeon
≤ 5 days	No exposure
≤ 3 days	NA
≤ 5 days	No exposure

Methods

A structured literature search was conducted to identify studies that evaluated the association between clopidogrel exposure and bleeding-related outcomes in patients undergoing CABG. The search was limited to original studies published in English for the period of January 1, 1990–April 30, 2007, and was conducted by using MEDLINE and EMBASE. The Cochrane Database for Systematic Reviews was also used to identify relevant literature. Both Medical Index Subject Headings and free-text search terms were used to identify pertinent literature. Search terms included clopidogrel and CABG and bleeding or hemorrhage.

Titles and abstracts of articles identified were reviewed for possible inclusion. Each title and abstract was screened by reviewers (A.S.P., G.T.S., C.B.F.) using a standardized inclusion-exclusion form. Reviews, case reports, editorials, letters, or other non-original research articles were excluded. Articles that met the general inclusion criteria were retrieved for review of the full text. Studies were included if they met the following criteria: they were randomized controlled trials, prospective observational studies, or retrospective studies; they analyzed characteristics and outcomes of patients who were exposed to clopidogrel within 7 days before CABG; and they reported postoperative bleeding-related outcomes, including chest tube output, transfusion requirements, mortality, hospital length of stay, and reoperation. Studies were excluded if the number of patients exposed to clopidogrel was not reported, or if fewer than 20 patients were enrolled in the study.

A standardized data abstraction form was developed, piloted on several studies, and refined (the form is available on request). Data abstracted from each study included the study objective, study design, and demographic and clinical characteristics of exposed and nonexposed patients. Patients were considered exposed if they discontinued clopidogrel within a specified time frame up to 7 days before CABG that was designated in each study. Data also were collected regarding the exposure (i.e., number of days between clopidogrel discontinuation and CABG), and peri- and postoperative clinical and resource utilization outcomes in the exposed and nonexposed groups. The abstraction process also involved confirmation of the inclusion criteria,

Table 1. Description of the 23 Studies That Met Selection Criteria (continued)

Study Design and Purpose	No. of Patients	
	Exposed ^a	Nonexposed
Studies that also analyzed aprotinin (continued)		
Retrospective		
To investigate whether or not intraoperative use of aprotinin decreases bleeding and transfusion requirements after CABG in patients treated with clopidogrel < 5 days before surgery ²⁴	18	15
Randomized		
To compare two treatment strategies: clopidogrel discontinued within 5 days before surgery, and clopidogrel continued until surgery; patients administered aprotinin at surgeon discretion ¹²	25	24
To investigate if aprotinin decreases bleeding and transfusion requirements after urgent or emergency CABG in patients treated with clopidogrel < 5 days before surgery ²⁶	37 (given aprotinin)	8 (given placebo)

CABG = coronary artery bypass graft surgery; NR = not reported; NA = not applicable; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial; CLARITY-TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 trial; ACS = acute coronary syndrome; CRUSADE = Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines.

^aPatients were considered exposed if they discontinued clopidogrel within a specified time frame that was designated in each study.

^bAnticoagulants used in this study were aspirin and intravenous unfractionated heparin.

^cHospitalized group included patients who stopped clopidogrel and underwent CABG within 3–5 days of clopidogrel cessation; discharged home group included patients who stopped clopidogrel and went home but returned for CABG within 3–5 days of clopidogrel cessation.

and, if necessary, the exclusion of studies based on information that was more detailed. Decisions were made by consensus.

Mean differences (and confidence intervals [CIs] around mean differences) between clopidogrel-exposed and nonexposed patient groups were calculated from data in each study when provided. Volume of blood products transfused was reported either in units or milliliters; for consistency, these volumes were converted to units, assuming 220 ml/unit. For the figures and tables, only studies reporting our prespecified outcomes were included. Only studies that reported means were summarized in the figures. For the outcome of reoperation, absolute risk and 95% CIs were calculated for studies where sufficient data were reported.¹⁰

Results

The titles and abstracts of 376 articles were reviewed; 325 were excluded due to failure to meet inclusion criteria. Of the 51 articles that underwent full review, only 23 studies met the criteria for inclusion in our analysis.^{11–33} Only four studies (17%) were randomized trials.^{12, 17, 26, 30} Ten studies (43%) were retrospective, and eight (35%) used a prospective, observational design (Table 1). One study included analyses of both retrospectively and prospectively defined patient cohorts.¹⁴ Overall, the data from the studies included 13,475 patients, 3505 of whom had

been exposed to clopidogrel within 7 days before CABG.

The number of patients studied within the individual published reports ranged from 33–2359. The primary indication for clopidogrel administration was prevention of thrombotic events in patients with ACS. Most studies did not cite a source of funding. A small proportion of the 23 studies were sponsored by a pharmaceutical company (five studies), hospital (two), or foundation (one).

The time of clopidogrel discontinuation before CABG varied across studies (Table 1). Most studies defined patients as clopidogrel exposed when discontinuation occurred within 5 or 7 days before CABG. In four studies, clopidogrel was discontinued within 4 days before surgery.^{15, 16, 21, 27} In eight of the 23 studies, clopidogrel was discontinued within 5 days before surgery.^{13, 18, 24, 26, 28–31} In five studies, clopidogrel was discontinued within 7 days before surgery.^{19, 20, 23, 25, 32} In one study clopidogrel was discontinued within 6 days before surgery¹⁴; one study compared clopidogrel discontinuation within 4 days before surgery with discontinuation 5–8 days before surgery¹⁵; and one study compared clopidogrel discontinuation less than 4 days before surgery, 4–7 days before surgery, and more than 7 days before surgery.³³

The dosage of clopidogrel received in the qualifying studies varied. Ten of the studies did not describe the clopidogrel dosage,^{14–16, 18, 19, 23, 25,}

Table 1. (continued)

No. of Days Clopidogrel Discontinued Before Surgery	
Exposed Patients ^a	Nonexposed Patients
≤ 5 days	NA
0 days (same day as surgery)	≤ 5 days (placebo)
≤ 5 days	≤ 5 days

^{28, 29, 31} seven studies analyzed patients who had received a 300-mg loading dose followed by a 75-mg/day regimen,^{11, 13, 17, 24, 26, 30, 33} and the remaining six studies noted only that patients had received at least 75 mg/day in the period preceding the CABG.^{12, 20-22, 27, 32} None of the

studies analyzed the effect of a loading dose on their outcomes.

Patients exposed to clopidogrel also received aspirin in at least 15 of the 23 studies.^{12, 13, 17-22, 25, 27-30, 32, 33} However, only six studies described or included aspirin exposure in their analyses.^{19, 22, 25, 29, 30, 33} In five studies, antifibrinolytic therapy with aprotinin during CABG was evaluated in clopidogrel-exposed patients.^{12, 16, 24, 26, 29}

Tables 2 and 3 summarize the findings of the studies reporting differences in chest tube output, blood product transfusions, and reoperation due to bleeding. In four of seven comparisons, clopidogrel-exposed patients had significantly higher chest tube output based on 95% CIs (Figure 1). In the studies where aprotinin use was not specifically discussed, clopidogrel-exposed patients had significantly greater platelet transfusion requirements in all but one study (Figure 2). Similarly, in these studies, clopidogrel-exposed patients were associated with a trend toward higher reoperation rates due to uncontrolled bleeding and/or cardiac

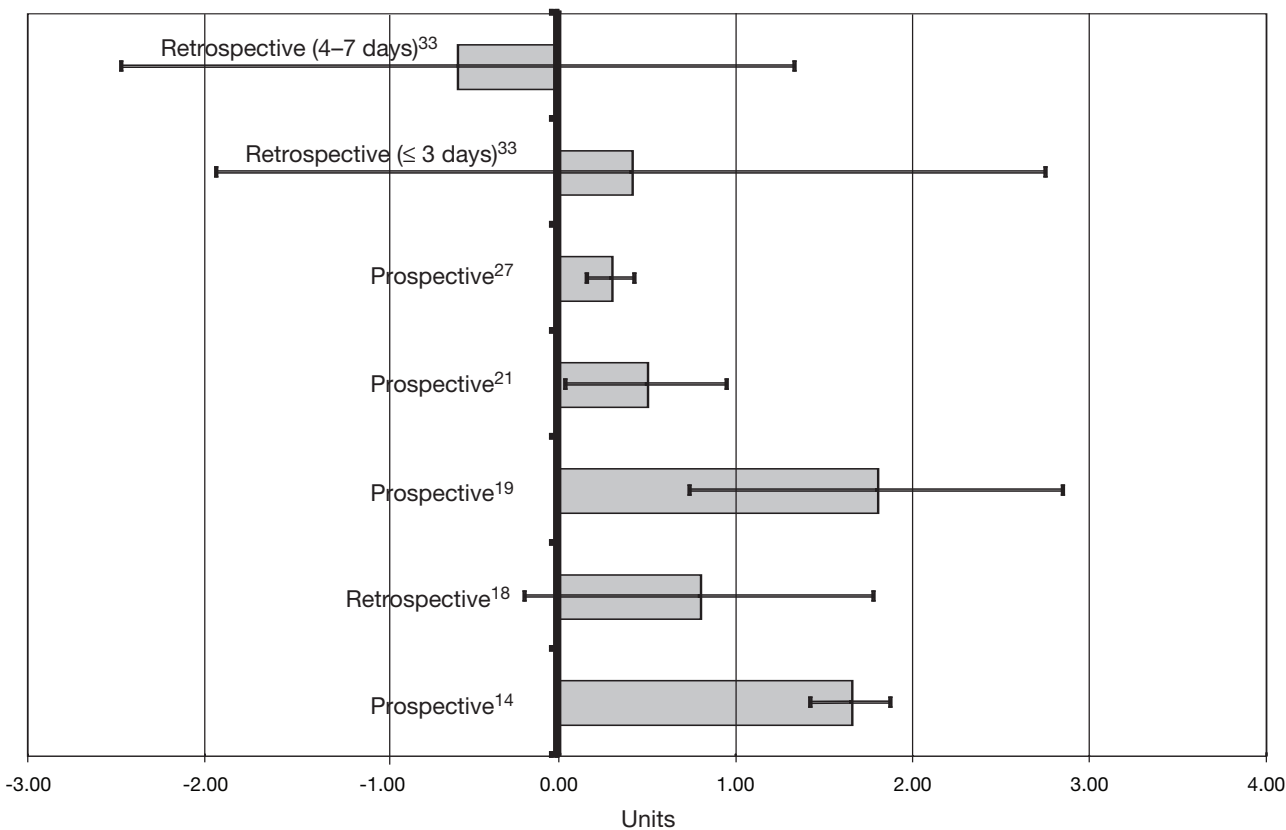


Figure 1. Mean difference (in units) in chest tube output. Bar segments represent mean difference over 24 hours for patients exposed to clopidogrel compared with nonexposed patients, with error bars representing 95% confidence intervals. A positive value indicates that mean chest tube output was greater in the exposed group.

Table 2. Chest Tube Output and Transfusion Requirements in Clopidogrel-Exposed and Nonexposed Patients

Study Design	No. of Patients		Chest Tube Output ^b (units)		Received Platelet Transfusion ^c	
	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed
Prospective, observational ^{13, d}						
No anticoagulant ^e	91	133	NR	NR	43 (48)	11 (8)
Received anticoagulant ^e	91	246	NR	NR	43 (48)	29 (12)
Prospective, observational ^{14, d}						
At 24 hrs	45	45	6.0 ± 0.7	4.4 ± 0.3	9.0 ± 1.7	1.2 ± 0.5
Prospective, observational ^{15, d}						
0–4 days	41	232 ^f	NR	NR	NR	NR
5–8 days	39	232 ^f	NR	NR	NR	NR
Prospective, observational ¹⁹	59 ^g	165 ^h				
At 8 hrs			3.5 ± 3.3	3.5 ± 1.8	30 (51)	30 (18)
At 24 hrs			5.6 ± 5.1	3.8 ± 2.8	0.9 ± 1.2	0.2 ± 0.9
Prospective, observational ²¹	48 ^f	1580 ⁱ	3.3 ± 1.2	2.8 ± 1.6	NR	NR
Prospective, observational ²⁷	15 ^g	63			0 (0)	0 (0)
At 8 hrs			1.8 ± 0.3	1.9 ± 0.1		
At 24 hrs			3.9 ± 0.5	3.6 ± 0.2		
Prospective, observational ²⁸	51	194	19.6% ^k	12.4% ^k	4.3 ± 10	1.7 ± 4.4
Retrospective ^{14, d}	53	428	NR	NR	12.5 ± 2.1	2.3 ± 0.3
Retrospective ¹⁸						
At 24 hrs	6 ^c	64	4.4 ± 2.9	3.6 ± 2.9	0.5 ± 0.9	0.3 ± 0.2
Retrospective ^{33, d}						
≤ 3 days	25 ^g	255 ⁱ	8.2 ± 5.6	7.9 ± 5.7	NR	NR
4–7 days	40 ^g		7.3 ± 5.6	NA	NR	NA
Retrospective ²⁰	415 ^g	1944 ⁱ	NR	NR	79 (19)	170 (9)
Retrospective ³²	281 ^g	1291 ⁱ	400 (100–2000)	400 (100–3400)		
Postoperative					55 (19.6)	118 (9.1)
Intraoperative					9 (3.2)	13 (1.0)
Retrospective ¹¹	Hospitalized group: 64 ^j	Discharged home group: 61 ^j	NR	NR	NR	NR
Retrospective ^{22, d}						
Clopidogrel vs aspirin	18	523 ⁱ	NR	NR	0 (0–1)	0 (0–6)
Clopidogrel + aspirin vs neither drug	59 ^g	210	NR	NR	0 (median)	0 (median)
Retrospective ²³	48	117			NR	NR
At 8 hrs			23.9	2.2		
At 24 hrs			6.3	3.6		
Retrospective ³¹	739	113	NR	NR	249 (33.7)	20 (17.7)
Retrospective ^{25, d}						
Clopidogrel vs no aspirin or clopidogrel	11	497	NR	NR	3.6 ± 6.0	1.0 ± 3.7
Clopidogrel + aspirin vs aspirin alone	46	105	NR	NR	3.7 ± 5.2	1.3 ± 3.1
Randomized ¹⁷	1011 ^g	1061	NR	NR	NR	NR
Randomized ³⁰	66 ^g	70 ⁱ	NR	NR	NR	NR
Studies that also analyzed aprotinin						
Prospective, observational ¹⁶	136	369	NR	NR	125 (92)	173 (47)
Prospective, observational ²⁹	60 ^g	157	24-hr: 1.7 (95% CI 0.8–4.0)	24-hr: 1.6 (95% CI 0.7–3.9)	2.6 ± 1.1 1 (1.7) 7.0 ± 0.0	0.2 ± 0.6 2 (1.3) 7.5 ± 3.5

Table 2. (continued)

Received Red Blood Cell Transfusion ^b	
Exposed ^a	Nonexposed
56 (62)	39 (30)
56 (62)	86 (36)
4.3 ± 0.6	2.3 ± 0.5
NR	NR
NR	NR
47 (80)	96 (58)
2.5 ± 2.1	1.7 ± 2.2
0.5 ± 0.9	0.4 ± 0.9
1.7 ± 0.5	1.6 ± 0.3
37 (73)	100 (52)
3 ± 3	1.6 ± 2.1
6.4 ± 0.8	2.3 ± 0.1
54 (84)	48 (75)
2.7 ± 1.9	1.9 ± 1.6
5.8 ± 9.4	3.4 ± 4.1
2.8 ± 3.5	NA
226 (55)	732 (38)
2.3 (1.1–19.3)	2.3 (1.1–28.4)
157 (55.9)	444 (34.4)
62 (22.1)	206 (16.0)
29 (45)	29 (46.8)
3.4 (1.1–14.8)	2.2 (1.1–4.5)
NR	NR
NR	NR
NR	NR
480 (65.0)	69 (61.1)
2 (0–4)	2 (0–4)
2.9 ± 3.4	1.4 ± 2.0
2.4 ± 2.3	1.9 ± 2.4
NR	NR
> 2 units: 12 (75)	> 2 units: 14 (71)
> 4 units: 6 (50)	> 4 units: 2 (14)
57 (42)	48 (13)
4.6 ± 2.3	1.5 ± 2.2
23 (38.3)	60 (38.2)
2.87 ± 1.45	2.45 ± 0.95

tamponade (Table 3; Figure 3).

In addition to the five studies where aprotinin use during CABG was evaluated, one study reported the administration of aprotinin in greater than 70% of patients in each cohort¹⁵; no additional data on aprotinin use were provided in that study. Concomitant administration of aprotinin appeared to reduce or obscure the association between bleeding-related outcomes and clopidogrel exposure (Tables 2 and 3; Figures 2–4).

No obvious trend was associated with clopidogrel exposure in studies that compared rates of mortality (17 studies), stroke (10 studies), and myocardial infarction (11 studies; Table 4).

In the studies that compared clopidogrel-exposed and nonexposed patients on the basis of duration of mechanical ventilation, total intubation time, postoperative intensive care unit stay, or postoperative hospital length of stay, no consistent pattern was discerned across studies (Table 5). One study applied multivariate analysis and found that clopidogrel exposure 0–4 days before surgery was an independent predictor of longer stay in the intensive care unit and overall hospital stay, adjusting for aprotinin dosage and other patient and clinical factors.¹⁵ However, most studies did not find a significant difference in resource utilization–related outcomes based on exposure or nonexposure to clopidogrel.

Discussion

Antithrombotic therapy represents a mainstay in the evidence-based management of patients with ACS. Although the potential benefit of clopidogrel in combination with aspirin in this setting is incontrovertible,⁷ our literature review underscores concerns among clinicians and surgeons alike about the increased risk for important outcomes, including major bleeding, blood product transfusions, and hemorrhage-related reoperation among patients exposed to clopidogrel within 7 days before nonemergency CABG. For other outcomes such as mortality, stroke, and myocardial infarction, study designs tended to lack statistical power to detect significant differences between the clopidogrel-exposed and nonexposed groups, even if a true difference existed, because these events tended to be rare.

There were threats to the internal validity of many of the studies reviewed. Most of the studies were retrospective analyses, which can be susceptible to biases such as selective reporting of events and confounding by indication. More

Table 2. Chest Tube Output and Transfusion Requirements in Clopidogrel-Exposed and Nonexposed Patients (continued)

Study Design	No. of Patients		Chest Tube Output ^b (units)		Received Platelet Transfusion ^c	
	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed
Studies that also analyzed aprotinin (continued)						
Retrospective ²⁴	18	15	5.7(5.0–6.4)	8.6 (7.0–10.1)	0.1 (0–0.3)	0.6 (0.2 –0.9)
Randomized ¹²						
At 8 hrs	25 ^g	24	1.2 ± 0.8	1.8 ± 1.2	0.3 ± 1	1 ± 2.3
Randomized ²⁶	37	38 ^h			4 (11)	16 (42)
					0.1 ± 0.4	0.8 ± 1.3

NR = not reported; NA = not applicable; CI = confidence interval.

^aPatients were considered exposed if they discontinued clopidogrel within a specified time frame that was designated in each study.

^bData are mean ± SD, median (range), or median (95% confidence interval).

^cData are number (%) of patients, mean ± SD number of units, or median (range).

^dStudy reported end points for more than one experimental group.

^eAnticoagulants were aspirin and intravenous unfractionated heparin.

^fThe nonexposed group did not receive clopidogrel for at least 8 days.

^gClopidogrel was given with aspirin.

^hNonexposed group was given placebo.

ⁱNonexposed group was given aspirin.

^jHospitalized group included patients who stopped clopidogrel and underwent CABG within 3–5 days of clopidogrel cessation; discharged home group included patients who stopped clopidogrel and went home but returned for CABG within 3–5 days of clopidogrel cessation.

^kStudy reported the percentage of patients who bled greater than 100 ml/hr for 2 consecutive hours.

recent studies^{29, 32} used risk-adjusted models in attempt to reduce the effect of preoperative variability between the clopidogrel-exposed and

nonexposed groups. Those studies found an increased risk of reoperation for bleeding and greater requirement for blood product trans-

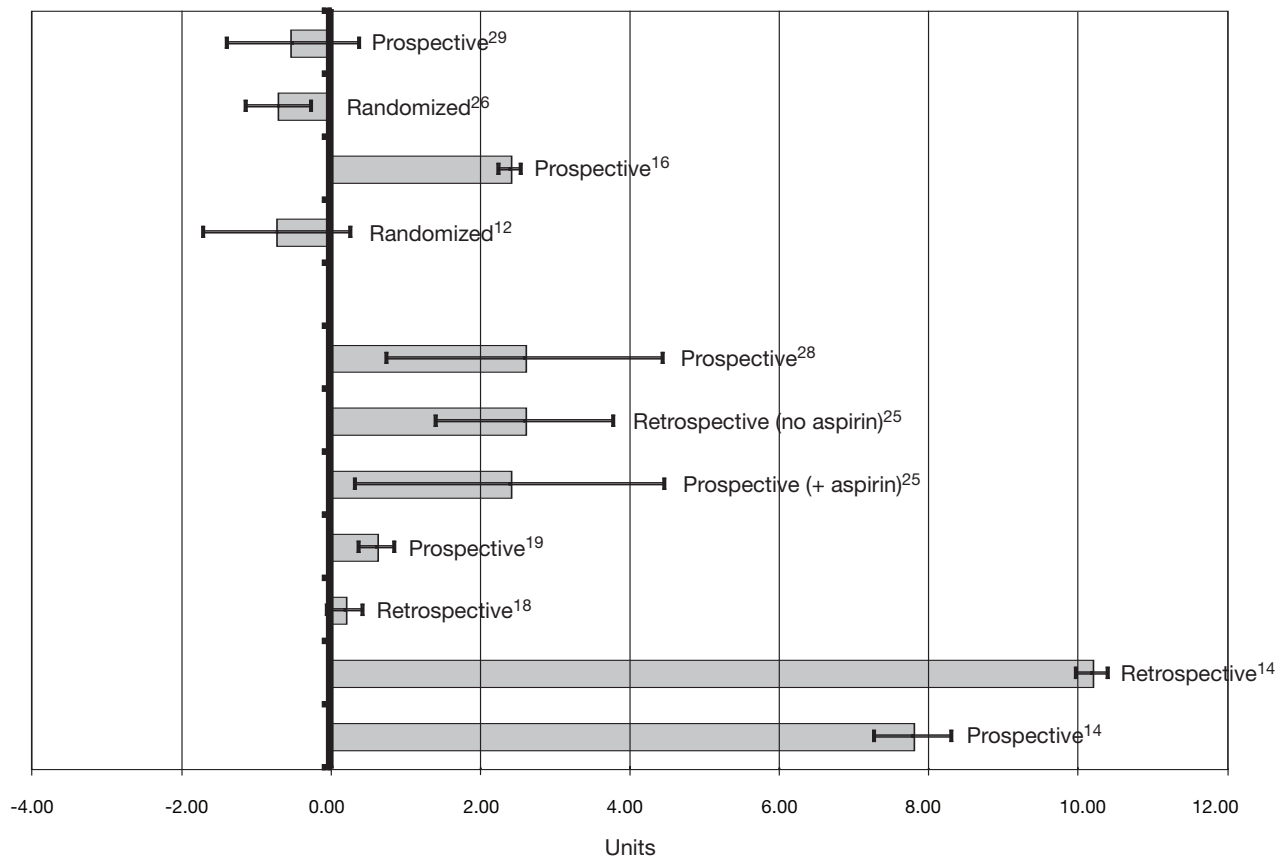


Figure 2. Mean difference in platelet transfusion requirements. Bar segments represent mean difference for patients exposed to clopidogrel compared with nonexposed patients, with error bars representing 95% confidence intervals. A positive value indicates that mean platelet transfusion requirements were greater in the exposed group.

Table 2. (continued)

Received Red Blood Cell Transfusion ^b	
Exposed ^a	Nonexposed
0.9 (0.1–1.7)	2.7 (1.7–4.1)
0.3 ± 1.2	1 ± 1.7
17 (47)	27 (71)
0.8 ± 1.3	1.6 ± 1.9

fusion with preoperative exposure to clopidogrel. The findings of our review are consistent with those generated from a post hoc analysis of data from the Organization to Assess Ischemic Syndromes (OASIS) and the CURE trials,³⁴ as well as a recent meta-analysis.³⁵

Implications for Clinical Practice

A decision to perform coronary angiography, percutaneous coronary intervention, or CABG in patients with ACS is based on several factors and derived from a wealth of clinical trial data (AHA-ACC, ESC).^{5, 8} Patients with high-risk coronary anatomy, recurrent myocardial ischemia, and hemodynamic compromise benefit from surgical revascularization that may be required during the initial hospitalization, whereas others may achieve sufficient clinical stability to undergo surgery on a more elective basis. Despite advances in pharmacologic therapy, recent results from the Global Registry of Acute Coronary Events (GRACE) indicate that more than 7% of patients hospitalized with ACS undergo CABG during the index hospitalization.³⁶ Although one might expect that surgery performed within several days of hospital admission is related to high-risk

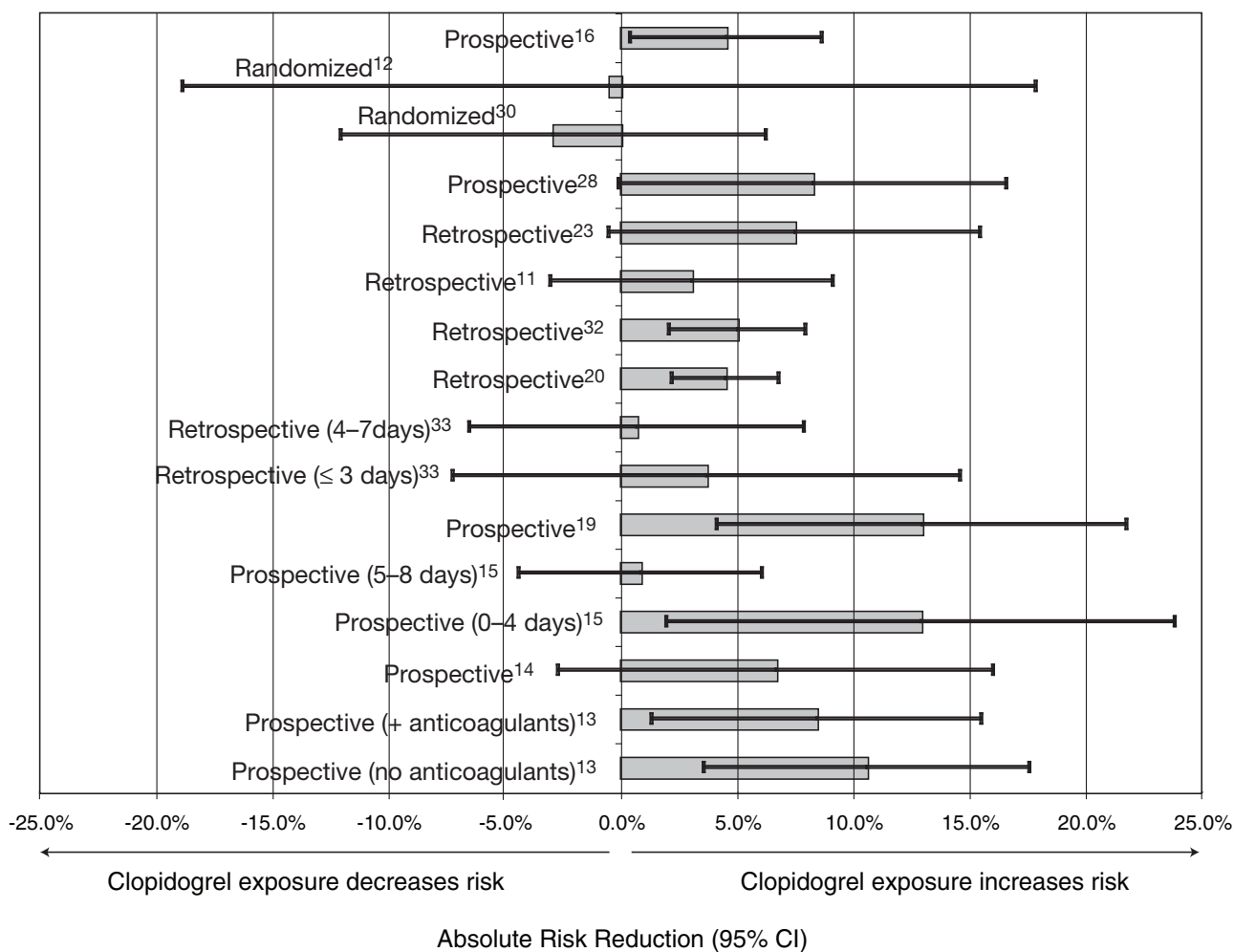


Figure 3. Absolute risk of reoperation associated with clopidogrel exposure. Bar segments represent mean difference in reoperation risk for patients exposed to clopidogrel compared with nonexposed patients, with error bars representing 95% confidence intervals.

Table 3. Reoperation Rates and Cryoprecipitate and Fresh Frozen Plasma Transfusion Requirements Among Clopidogrel-Exposed and Nonexposed Patients

Study Design	Received Cryoprecipitate Infusion ^a		Underwent Reoperation for Bleeding or Tamponade ^c		Received Fresh Frozen Plasma ^d	
	Exposed ^b	Nonexposed	Exposed ^b	Nonexposed	Exposed ^b	Nonexposed
Prospective, observational ^{13, e}						
No anticoagulant ^f	NR	NR	11 (12)	2 (1)	20 (22)	2 (1)
Received anticoagulant ^f	NR	NR	11 (12)	9 (4)	20 (22)	9 (4)
Prospective, observational ^{14, d}	NR	NR	4 (8.9)	1 (2.2)	1.0 ± 0.6	0.5 ± 0.3
Prospective, observational ^{15, e}						
0–4 days	NR	NR	6 (14.6)	4 (1.7)	NR	NR
5–8 days	NR	NR	1 (2.6)	4 (1.7)	NR	NR
Prospective, observational ¹⁹	0.2 ± 1.3	0.2 ± 1.2	8 (5.9)	1 (0.6)	0.7 ± 1.7	0.2 ± 0.9
Prospective, observational ²¹	NR	NR	0 (0)	1 (0.06)	1.1 ± 1.2	0.9 ± 1.1
Prospective, observational ²⁷	0	0	0	0	0	0
Prospective, observational ²⁸	2.4 ± 5.9	1.2 ± 4.6	5 (9.8)	3 (1.6)	1.1 ± 2.2	0.6 ± 1.8
Retrospective ^{14, e}	NR	NR	NR	NR	2.9 ± 1.0	1.0 ± 0.1
Retrospective ¹⁸	5 (7.8)	0 (0)	NR	NR	54 (84)	48 (75)
					0.5 ± 0.9	0.2 ± 1.0
Retrospective ^{33, e}						
≤ 3 days	NR	NR	2 (8)	11 (4.3)	NR	NR
4–7 days	NR	NR	2 (5)	NA	NR	NA
Retrospective ²⁰	NR	NR	24 (5.8)	25 (1.3)	54 (13)	150 (7.7)
Retrospective ³²	NR	NR	18 (6.4)	18 (1.4)	34 (12.1)	97 (7.5)
Retrospective ¹¹	NR	NR	3 (4.7) ^h	1 (1.6) ^h	NR	NR
Retrospective ^{22, e}						
Clopidogrel vs aspirin	NR	NR	0	1 (0.5)	0 (0–2)	0 (0–3)
Clopidogrel + aspirin vs neither drug	NR	NR	2 (3.4)	8 (1.5)	0 (0–4)	0 (0–4)
Retrospective ²³	NR	NR	4 (8.3)	1 (0.85)	NR	NR
Retrospective ^{25, e}						
Clopidogrel vs no aspirin or clopidogrel	1.8 ± 4.0	0.5 ± 3.2	NR	NR	2.5 ± 5.4	7.3 ± 4.4
Clopidogrel + aspirin vs aspirin alone	0.6 ± 3.3	0.6 ± 4.6	NR	NR	3.1 ± 5.4	1.6 ± 2.9
Randomized ^{17, g}	NR	NR	≤ 5 days: 18 (4.1)	11 (2.3)	NR	NR
Randomized ³⁰	NR	NR	6 (9)	10 (14.3)	NR	NR
Studies that also analyzed aprotinin						
Prospective, observational ¹⁶	NR	NR	8 (5.9)	5 (1.2)	97 (71)	33 (9)
					0.9 ± 1.4	0.3 ± 0.9
Prospective, observational ²⁹	NR	NR	0	2 (1)	1 (1.7)	2 (1.3)
					3.0 ± 0.0	3.0 ± 1.4
Retrospective ²⁴	NR	NR	0	3 (20)	0.1 (0–0.2)	0.5 (0–1.0)
Randomized ¹²	NR	NR	3 (12)	3 (12.5)	1.2 ± 4	1.3 ± 2.4
Randomized ²⁶	NR	NR	NR	NR	6 (17)	12 (32)
					0.4 ± 1.1	1.6 ± 1.9

NR = not reported; NA = not applicable.

^aData are number (%) of patients or mean ± SD number of units.^bPatients were considered exposed if they discontinued clopidogrel within a specified time frame that was designated in each study.^cData are number (%) of patients.^dData are number (%) of patients, mean ± SD number of units, or median (range).^eStudy reported end points for more than one experimental group.^fAnticoagulants were aspirin and intravenous unfractionated heparin.^gStudy contained an additional table listing number of days of clopidogrel exposure before coronary artery bypass graft surgery and number of major bleeds within 7 days of surgery.^hExposed subjects were considered the hospitalized group, which included patients who stopped clopidogrel and underwent CABG within 3–5 days of clopidogrel cessation; nonexposed patients were considered the discharged home group, which included patients who stopped clopidogrel and went home but returned for CABG within 3–5 days of clopidogrel cessation.

Table 4. Postoperative Outcomes of Clopidogrel-Exposed and Nonexposed Patients

Study Design	No. (%) of Patients					
	Death		Stroke		Myocardial Infarction	
	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed	Exposed ^a	Nonexposed
Prospective, observational ^{13, b}						
No anticoagulant ^c	7 (8)	2 (1)	4 (4)	2 (1)	Perioperative ^d : 2 (2)	Perioperative ^d : 2 (1)
Received anticoagulant ^c	7 (8)	2 (0.8)	4 (4)	0	Perioperative ^d : 2 (2)	Perioperative ^d : 4 (2)
Prospective, observational ^{14, b}	1 (2.2)	0	NR	NR	NR	NR
Prospective, observational ^{15, b}						
0–4 days	1 (2.4)	10 (4.5)	4 (9.8)	7 (3)	2 (4.9)	9 (3.9)
5–8 days	0	10 (4.5)	2 (5.1)	7 (3)	0	9 (3.9)
Prospective, observational ¹⁹	1 (1.7)	6 (3.6)	2 (3.4)	8 (4.8)	0 (0)	6 (3.6)
Prospective, observational ²⁷	0	0	NR	NR	0	1
Prospective, observational ²⁸	2 (3.9)	7 (3.6)	NR	NR	NR	NR
Retrospective ^{33, b}						
≤ 3 days	2 (8)	8 (3.1)	NR	NR	NR	NR
4–7 days	0	NA	NR	NA	NR	NA
Retrospective ²⁰	7 (1.7)	28 (1.4)	12 (2.9)	32 (1.7)	9 (2.2)	14 (0.7)
Retrospective ³²	4 (1.4)	18 (1.4)	6 (2.1)	20 (1.6)	4 (1.4)	8 (0.6)
Retrospective ¹¹	≤ 30 days: 2 (3.1) ^e	≤ 30 days: 1 (1.6) ^e	1 (1.6) ^e	1 (1.6) ^e	1 (1.6) ^e	2 (3.2) ^e
Retrospective ²²	≤ 30 days: 1 (1.3)	≤ 30 days: 6 (0.8)	NR	NR	Perioperative ^d : 1 (1.3)	Perioperative ^d : 21 (2.8)
Retrospective ³¹	26 (3.5)	6 (5.3)	12 (1.6)	2 (1.8)	NR	NR
Randomized ¹⁷ (composite events)	65 (13.4)	87 (16.4)	65 (13.4)	87 (16.4)	65 (13.4)	87 (16.4)
Randomized ³⁰	CV death: 3 (4.5)	CV death: 3 (4.3)	Recurrent: 1 (1.5)	Recurrent: 0 (0.0)	Recurrent: 3 (4.5)	Recurrent: 2 (2.9)
Studies that also analyzed aprotinin						
Prospective, observational ¹⁶	2 (1.4)	3 (0.8)	NR	NR	4.30%	3.10%
Retrospective ²⁴	0	0	0	2 (13.3)	NR	NR
Randomized ¹²	2 (8)	0	NR	NR	0	0
Randomized ²⁶	1 (2.7)	3 (7.9)	NR	NR	NR	NR

NR = not reported; NA = not applicable; CV = cardiovascular.

^aPatients were considered exposed if they discontinued clopidogrel within a specified time frame that was designated in each study.

^bStudy reported end points for more than one experimental group.

^cAnticoagulants were aspirin and intravenous unfractionated heparin.

^dPerioperative included the preoperative through postoperative periods; the study did not break this down into hours.

^eExposed subjects were considered the hospitalized group, which included patients who stopped clopidogrel and underwent CABG within 3–5 days of clopidogrel cessation; nonexposed patients were considered the discharged home group, which included patients who stopped clopidogrel and went home but returned for CABG within 3–5 days of clopidogrel cessation.

features, data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry³¹ do not support this conclusion. In addition, the CRUSADE study, which included 2855 patients with non-ST-segment elevation ACS, showed considerable variance from the existing ACC-AHA guidelines, with 30% of patients (852/2855) receiving

clopidogrel within 24 hours of hospital admission and 87% (739/852) of those patients undergoing CABG within 5 days of clopidogrel exposure. Consistent with the findings of our structured review, exposure to clopidogrel was associated with a significant increase in blood product transfusions, including a 70% increase in the requirement for more than 4 units of packed red blood cells. In the CURE trial,¹⁷ patients undergoing CABG who were exposed to

Table 5. Resource Utilization Associated with Clopidogrel Exposure

Study Design	Intubation Time ^a (hrs)		Duration of Mechanical Ventilation ^a (hrs)	
	Exposed ^b	Nonexposed	Exposed ^b	Nonexposed
Prospective, observational ^{13, c}				
No anticoagulant ^d	9 (6–16)	7 (6–12)	NR	NR
Received anticoagulant ^d	9 (6–16)	7 (5–11)	NR	NR
Prospective, observational ¹⁴	NR	NR	16.9 ± 1.5	12.8 ± 0.9
Prospective, observational ¹⁵	NR	NR	NR	NR
Prospective, observational ¹⁹	Intubated ≤ 8 hrs: 54.2% (n=31)	Intubated ≤ 8 hrs: 75.8% (n=125)	NR	NR
Prospective, observational ²¹	NR	NR	NR	NR
Prospective, observational ²⁷	Intubated ≤ 8 hrs: 73% (n=11)	Intubated ≤ 8 hrs: 71% (n=45)	NR	NR
Prospective, observational ²⁸	NR	NR	24.1	22
Retrospective ¹⁸	NR	NR	11.9 ± 9.7	9.6 ± 5.9
Retrospective ³³				
≤ 3 days	19.1 ± 43.6	19.5 ± 64.8	NR	NR
4–7 days	10.6 ± 16.5	NA	NR	NA
Retrospective ²⁰	NR	NR	3.9% (n=16) ^e	3.6% (n=70) ^e
Retrospective ³²	NR	NR	3.2% (n=9) ^e	3.2% (n=41) ^e
Retrospective ¹¹	NR	NR	NR	NR
Retrospective ^{22, c}				
Clopidogrel vs no clopidogrel or aspirin	NR	NR	10.9 (1.6–453)	11.3 (2.8–693)
Clopidogrel + aspirin vs aspirin alone	NR	NR	10.9 (1.6–453)	11.3 (2.8–693)
Retrospective ²³	15.5 (mean) 8.0 (median) Intubated ≤ 8 hrs: 52% (n=25)	8.3 (mean) 6.0 (median) Intubated ≤ 8 hrs: 78.4% (n=91)	NR	NR
Retrospective ³¹	NR	NR	NR	NR
Studies that also analyzed aprotinin				
Prospective, observational ¹⁶	NR	NR	NR	NR
Prospective, observational ²⁹	NR	NR	> 10 hrs: 20%	> 10 hrs: 26%
Retrospective ²⁴	7 (4.9–9.1)	10 (6.9–13.1)	NR	NR
Randomized ¹²	NR	NR	NR	NR
Randomized ²⁶	NR	NR	NR	NR

NR = not reported; NA = not applicable; ICU = intensive care unit; OR = odds ratio.

^aData are mean ± SD or median (range).

^bPatients were considered exposed if they discontinued clopidogrel within a specified time frame that was designated in each study.

^cStudy reported end points for more than one experimental group.

^dAnticoagulants were aspirin and intravenous unfractionated heparin.

^eStudy did not report hours of ventilation, only reported the “need for prolonged ventilation.”

^fExposed subjects were considered the hospitalized group, which was patients who stopped clopidogrel and underwent CABG within 3–5 days of clopidogrel cessation; nonexposed patients were considered the discharged home group, which was patients who stopped clopidogrel and went home but returned for CABG within 3–5 days of clopidogrel cessation.

clopidogrel within 5 days of surgery experienced a 2.8% absolute increase of life-threatening hemorrhagic complications. In contrast, aspirin administration within 5 days of CABG is associated with a lower risk of postoperative mortality without a concomitant risk of reoperation

for bleeding or need for blood product transfusion.³⁷ Ongoing randomized trials of ADP-receptor antagonists represent a valuable opportunity to investigate fundamental mechanisms of perioperative hemostasis and optimal periprocedural antithrombotic therapy.

Table 5. (continued)

Postoperative ICU Stay ^a (hrs)		Postoperative Hospital Stay ^a (hrs)	
Exposed ^b	Nonexposed	Exposed ^b	Nonexposed
NR	NR	7 (6–11)	6 (5–8)
NR	NR	7 (6–11)	6 (5–8)
NR	NR	8.3 ± 1.1	6.6 ± 0.3
NR	NR	0–4 days: 7 (median) 5–8 days: 9 (median)	7 (median)
NR	NR	≤ 5 days: 33.9% (20 patients)	≤ 5 days: 46.7% (77 patients)
20.1 ± 2.9	21.9 ± 13.5	5.5 ± 1.7	5.4 ± 2.1
NR	NR	≤ 5 days: 87% (n=13)	≤ 5 days: 84% (n=53)
3.3 days	3.6 days	11.3	12.1
NR	NR	NR	NR
49.5 ± 63.5	52.1 ± 77.9	NR	NR
43.6 ± 39.3	NA	NR	NA
1 (1–28)	1 (0–50)	NR	NR
1 (1–28)	1 (0–30)	5 (1–62)	4 (1–79)
1 (1–33) ^f	1 (1–17) ^f	4.5 (3–57) ^f	5 (1–29) ^f
25.5 (5–129)	23.5 (5–864)	6 (3–50)	6 (3–50)
25 (6–453)	24 (2–1002)	6 (5–11)	6 (0–50)
46.9 (mean) 26 (median)	45.3 (mean) 26 (median)	8.3 (mean) 6.5 (median)	6.5 (mean) 5 (median)
NR	≤ 5 days: 25% (n=12) NR	≤ 5 days: 55.1% (n=64) 6 (median)	6 (median)
1.9 ± 1.3	1.1 ± 0.7	9.6 ± 2.1	7.9 ± 2.0
> 72 hrs: 10%	> 72 hrs: 9%	NR	NR
19 (17–21)	44 (9–79)	5.8 (5.5–6.2)	7.6 (6.0–9.3)
32.4 ± 24.7	46.2 ± 55	7.3 ± 3.5	10.9 ± 12.8
NR	NR	6.4 ± 1.5	7.2 ± 3.9

Impact on Blood Product Transfusion and Clinical Outcomes

Although the balance of evidence across studies indicated an association of clopidogrel exposure before CABG with perioperative bleeding and an increased requirement for blood product transfusion, the effect of concomitant use of other anticoagulants on outcomes was less clear. One group noted that patients who received clopidogrel and underwent CABG in less than 5 days from clopidogrel loading were also more likely to receive glycoprotein IIb-IIIa

antagonists than those not exposed to clopidogrel.³¹ To clarify the impact of glycoprotein IIb-IIIa antagonists on bleeding-related outcomes, patients receiving this particular class of potent platelet antagonists were excluded from the analysis; the relationship between clopidogrel exposure and bleeding was directionally and proportionally the same.

Our summation of clinical events across studies revealed that selective outcomes were consistently reported (such as red blood cell transfusions), whereas other end points (such as mortality) were inconsistently reported in the

final article. The relatively small number of studies reporting mortality, a brief follow-up period, and a widely recognized challenge of diagnosing perioperative myocardial infarction limited our ability to discern differences in these highly relevant clinical outcomes. However, the potential impact of blood product transfusion on both the short- and long-term outcomes after CABG should not be underestimated.

For instance, data collected on 8004 patients undergoing isolated CABG in Northern New England from 1996–2004 showed that having a lower risk-adjusted hematocrit was associated with an increased risk of developing low-output heart failure, and the risk was increased further when patients received red blood cell transfusions.³⁸ In a separate investigation, risk-adjusted probability of in-hospital mortality and morbidity was modeled as a function of red blood cell and collective blood product transfusion by using a logistic regression analysis.³⁹ The investigators in that study concluded that perioperative red blood cell transfusion was the most powerful independent predictor of postoperative morbid events after isolated CABG. These investigators subsequently evaluated the association between perioperative red blood cell transfusion and long-term survival among 10,289 patients who underwent isolated CABG.⁴⁰ Survival among transfused patients was significantly reduced, compared with nontransfused patients. Considered collectively, red blood cell transfusion was associated with risk-adjusted reductions in survival for both the early and late phases after CABG. Similarly, another group analyzed outcomes for 3024 consecutive patients who underwent isolated CABG and reported that the adjusted 30-day mortality rate for patients transfused with red blood cells was 1.9% compared with a mortality rate of 1.1% in patients not transfused.⁴¹

Therapeutic Options and Approaches to Patient Care

Optimal care for patients with ACS is the goal for all practicing clinicians and health care providers. Clearly, the intent is not to withhold drugs of potential benefit, but to individualize care based on carefully considered therapeutic options. Initially, calculation of a simple risk score at the time of hospital admission can be used to estimate the likelihood of CABG. A recently published risk score, based on clinical and laboratory variables, predicted CABG during the index hospitalization with considerable

accuracy (c-statistic 0.72, $p < 0.0001$).⁴² Among patients with a low likelihood of undergoing early CABG, clopidogrel administration may provide optimal benefit.

Patients with ACS who undergo CABG should be considered for clopidogrel (and aspirin) therapy after surgery, once hemostasis has been achieved. This approach has been taken by several surgical groups, with reported safety⁴³ and favorable outcomes,⁴⁴ particularly after off-pump surgery. Data derived from the CRUSADE registry suggest that nearly 25% of patients with non-ST-segment elevation ACS who undergo CABG during the index hospitalization receive clopidogrel at the time of hospital discharge.⁴⁵

Limitations

All systematic reviews synthesize data from existing research. Our review is subject to the reporting biases that occur when statistically significant, positive studies are more likely to be submitted and published, be published in English, and be published rapidly and cited more often than negative studies (i.e., publication bias). It is not possible to evaluate unpublished studies, thus there is no easy method to overcome this bias. The Egger test¹⁰ was applied in this review where sufficient data were reported.

A systematic review is also subject to the variability of end points reported, populations studied, and analytic techniques used by the individual studies and included in the article. Since data included in this article were significantly heterogeneous, a pooled summary estimate was less meaningful. Many studies chose to report the median as a measure of central tendency, which is a statistic that does not lend itself to aggregation. Instead, we chose to present the results in a disaggregated format, describing, when possible, the number of days between clopidogrel discontinuation and CABG, concomitant use of aspirin, and use of aprotinin. Finally, we were not able to assess the impact of clopidogrel loading doses on outcomes or conditions influencing decisions to continue clopidogrel up to the time of surgery, nor were we able to assess the potential protective benefit of clopidogrel in patients undergoing CABG as described in the CURE study.¹⁷

Conclusion

Results from this review of the literature suggest that clopidogrel exposure within 7 days

before CABG increases the risk for major bleeding and related complications, including reoperation and blood product transfusions. However, most of the evidence came from small single-site studies conducted within a wide variety of surgical practices, and confounding circumstances. As a result, the impact of clopidogrel-related bleeding on mortality and risk of postoperative myocardial infarction could not be determined. Antifibrinolytic therapy with aprotinin in patients exposed to clopidogrel appeared to mitigate hemorrhagic risk, but aprotinin has been temporarily suspended from marketing due to safety concerns.

Although the decision to use clopidogrel must consider the overall balance of risks and benefits on an individualized basis, the available evidence assessed in this review is congruent with current AHA-ACC and ESC guidelines, which recommend clopidogrel cessation at least 5 days before elective CABG to reduce perioperative bleeding, health care resource utilization, and the risk associated with blood product transfusion. Data from both the GRACE and CRUSADE registries indicate that these recommendations are not consistently followed.

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