Antiplatelet agents used for early intervention in acute coronary syndrome: Myocardial salvage versus bleeding complications

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Supplemental material is available online.

Acute coronary syndrome (ACS) is a costly health care issue worldwide.¹ Numerous well-conducted clinical trials have demonstrated that early intervention is associated with the greatest long-term survival, better myocardial preservation, and improved quality of life. Consequently, inpatient cardiovascular procedures in the United States have increased over 4-fold since 1979.¹ Notably, the use of antiplatelet therapies has increased well beyond this number and has affected the management of the one-quarter million patients who undergo cardiac surgery each year. The use of antithrombotic agents carries a risk of minor and major bleeding, notably when patients undergo coronary artery bypass grafting (CABG) in the early phase of ACS, the time at which antithrombotic use is greatest and most effective. Concerns over excess bleeding in patients undergoing CABG may lead to withholding antiplatelet agents, perhaps sacrificing early benefit for some patients. The use of blood products, notably platelet transfusions, to treat bleeding has short- and long-term risks that have not yet been balanced against the risks of decreased myocardial survival associated with nonuse of antiplatelet therapy. A better understanding of the risks and benefits associated with early antiplatelet therapy is necessary to improve the outcomes of all patients with ACS, including those who undergo CABG.

VALUE OF EARLY INTERVENTION IN ACS

Numerous clinical trials conducted over 3 decades have rigorously evaluated management strategies for ACS. These studies have shown that early intervention combined with appropriate antiplatelet agent use results in significantly improved outcomes. The findings of these trials have been

used to generate the well-stated and widely used American College of Cardiology/American Heart Association (ACC/AHA) clinical guidelines for ACS management.^{2,3}

Results of trials such as FRISC-II (Fast Revascularization during Instability in Coronary artery disease-II),⁴ ISAR-COOL (Intracoronary Stenting with Antithrombotic Regimen COOLing off),⁵ and ACUTY (Acute Catheterization and Urgent Intervention Triage strategy)⁶ exemplify the value of antiplatelet drugs in early ACS treatment. However, the value of early coronary intervention accompanied by profound inhibition of platelet aggregation and thrombus formation incurs an increased risk of bleeding, which has its own attendant morbidity and mortality. Despite the additional risk of bleeding, the use of appropriate pharmacotherapy in patients with ACS is paramount. Recognition of both the benefit of early interventional therapy in patients with ACS with the simultaneous finding of benefit for antiplatelet therapies has led to critical issues in developing strategies that best combine these tactics while minimizing potential risk. Central to this discussion is the following paradox: cardiologists want intensive antiplatelet therapy, frequently with multiple agents, to avoid thrombosis whereas surgeons want to minimize antiplatelet therapy to avoid bleeding. Thus, there is tension in balancing the risks of bleeding and transfusion against improved long-term outcomes in a frequently used treatment pattern for patients with ACS consisting of early intervention and later CABG. Although significant evidence exists to address this concern, it is unclear whether the perception of bleeding risk with antiplatelet agents is aligned with actual evidence for the real risk-versus-benefit equation.

PLATELET INHIBITION AND THE RISK OF BLEEDING

A wealth of clinical trial data provides evidence for the benefit of antiplatelet therapy in preventing recurrent ischemia after ACS.^{7,8} This is a critical consideration in secondary prevention, particularly in the perioperative period when platelet activity is high and associated with significant risk for a second, potentially fatal ischemic event. It is therefore imperative that a timely antiplatelet strategy be implemented with due consideration for the potential and real risk of abruptly stopping such beneficial therapy because of bleeding concerns in patients undergoing CABG.

Intrinsic to any strategy for inhibiting platelet function is the increased risk for bleeding. Bleeding is usually classified according to clinical or laboratory criteria as major (life-threatening, severe) or minor.⁹ However, bleeding

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FIGURE 1. Differences in risk of bleeding in patients who underwent coronary artery bypass grafting in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial depending on the bleeding definition used. All *P* values > .05. GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI, Thrombolysis In Myocardial Infarction. Adapted with permission.¹⁰

definitions have not been uniformly applied, leading to as much as a 3-fold difference in the reported incidence of major bleeding (Figure 1).¹⁰ Points of discrepancy between criteria for major bleeding include a decrease in hemoglobin (from ≥ 3 g/dL to ≥ 5 g/dL), a requirement for transfusion (≥ 1 unit or ≥ 2 units), or a requirement for an overt source of bleeding.¹⁰

A growing body of evidence shows that, regardless of the classification system applied, bleeding is an independent predictor of adverse clinical outcomes. TIMI (Thrombolysis In Myocardial Infarction) major bleeding, GUSTO (Global Utilization of Strategies To Open occluded arteries) moderate or severe bleeding, and a drop in hemoglobin have all been associated with early mortality and/or other adverse cardiovascular events within 30 days¹⁰; whether such bleeding is also associated with mortality at 6 months or 1 year is currently unclear. Thus, the prevalence and risk for bleeding in patients with ACS with or without intervention, remains a significant concern requiring careful consideration to balance the risk of bleeding with the benefit of antiplatelet therapies.

ANTIPLATELET THERAPIES AND INTERVENTION

Based on the importance of antiplatelet therapy in treating ACS, evidence-based guidelines for their use have been prepared.^{2,3} Because aspirin and clopidogrel are the only antiplatelet therapies currently recommended at a class I level for both immediate and long-term use in patients with ACS they will be the main focus of the remaining discussion.

Historically, the benefits of early aspirin use in the treatment of patients with ACS have been well established.¹¹ For patients undergoing CABG preoperative aspirin use has been associated with improved graft patency and reduces the risk of perioperative myocardial infarction (MI),

in-hospital mortality, and other adverse postoperative outcomes (Table E1).

Older aspirin studies sparked debate around aspirin use in CABG inasmuch as they showed that preoperative aspirin use was associated with increased blood loss, greater transfusion rates, and higher re-exploration rates (Table E2). However, numerous subsequent studies have described no significant increase in bleeding complications in patients undergoing CABG receiving aspirin in the 7 days before surgery (Tables E2 and E3). Thus, aspirin is not a significant risk factor for bleeding or transfusion.

The efficacy of dual antiplatelet therapy with aspirin and clopidogrel has been compared with aspirin monotherapy in patients with ACS and those undergoing percutaneous coronary intervention (PCI). The results of these large, prospective, randomized trials show that adding clopidogrel to aspirin consistently reduces the risk of adverse events, in most cases, without significantly increasing the risk of bleeding (Table E4). Overall, there is a clear, consistent benefit associated with clopidogrel pretreatment before PCI, and the reduction in cardiovascular events before PCI suggests that clopidogrel pretreatment should be initiated as soon as possible. Although the risk of bleeding may be greater with dual antiplatelet therapy, the excess risk is not enough to outweigh the benefits.

Data also suggest that aspirin and clopidogrel improve clinical outcomes without being associated with increased bleeding after CABG.^{12,13} Among the 1013 patients in the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study who received CABG during their index hospitalization, dual antiplatelet therapy reduced the relative risk of cardiovascular death, MI, and stroke by 19% compared with patients who received aspirin alone (relative risk, 0.81; 95% confidence interval [CI], 0.59–1.12); the bulk of this benefit was due to an 18% reduction in the relative risk of events occurring before surgery (relative risk, 0.82; 95% CI, 0.58–1.16).¹² Among the 136 CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) patients who underwent CABG, dual therapy with aspirin and clopidogrel reduced the risk of cardiovascular death, MI, and recurrent ischemia by 34% compared with those who received aspirin (odds ratio, 0.66; 95% CI, 0.27–1.63), a benefit due entirely to a reduction in MI and recurrent ischemia before surgery (odds ratio, 0.46; 95% CI, 0.16–1.36).¹³ Results of other studies disagree with those of CURE and CLARITY inasmuch as they show an increased risk of procedural bleeding, re-exploration, blood product usage, and chest drain blood loss in patients undergoing CABG receiving clopidogrel and aspirin, particularly within 5 to 7 days of the operation (Tables E2 and E3).

THE CABG CONUNDRUM

Only 7% to 12% of patients with non-ST-elevation MI and 4% of patients with ST-elevation MI undergo

CABG.^{14,15} Further, fewer than 1% of all CABG operations are done on an emergency basis (immediately after failed PCI).¹⁶ Given that CABG is performed in only a minority of patients, is effective antiplatelet treatment being withheld from the majority for the benefit of the minority?

The preponderance of evidence indicates that clopidogrel exposure within 5 to 7 days of CABG is associated with excess bleeding (Tables E2 and E3); thus, current guidelines recommend a clopidogrel washout period of 5 to 7 days before planned CABG.^{2,3} However, it is not clear how clopidogrel-associated excess bleeding has affected CABG clinical practice. Although transfusion rates are driven by institutional and practitioner preferences, they do provide some estimation of bleeding after CABG surgery. Thus, one way to loosely assess the effect of escalated platelet inhibition on CABG clinical practice is to examine the transfusion requirements reported for different antiplatelet regimens (Tables E2 and E3). Caveats to such comparisons include the potential masking effect of advancing surgical techniques,¹⁷ the varying transfusion thresholds among hospitals,¹⁸ the nonhomogeneous use of antiplatelet regimens perioperatively,¹⁹ and physician biases toward prophylactic, and perhaps unnecessary, transfusion of plasma and platelets in clopidogrel-treated patients.¹⁸ Given these caveats, observational data suggest that transfusion rates for patients undergoing CABG have remained relatively unchanged in the dual antiplatelet therapy era. In the early days of CABG, almost all patients received a transfusion.²⁰ With the advent of hemodilution and concerns over the quality of the blood supply, efforts were made to reduce blood transfusions throughout the 1980s and beyond. Examination of the data shows that although the amount of blood loss has increased anywhere from 30% to 100% along with escalated platelet inhibition, the percentage of patients receiving transfusions (between 20% and 60% depending on the study) and the amount of blood transfused per patient (mean of 2 to 3 units) has remained approximately the same (Tables E2 and E3). For this issue to be addressed more effectively, however, there is a need for prospective collection of post-CABG bleeding and transfusion rates in all clinical trials of antiplatelet agents.

The percentage of patients who have an adverse myocardial event while waiting for clopidogrel washout is not known. Although data from some studies support the CURE and CLARITY findings that fewer clopidogrel-exposed patients have adverse outcomes, data from other studies suggest the opposite.^{19,21} It is possible to extrapolate data from PCI-CURE, in which the time to PCI was 6 days and the incidence of an MI while waiting for intervention was 5.1% in the placebo group and 3.6% in the clopidogrel group ($P = .04$; number needed to treat = 66 to prevent an MI before PCI). Such an extrapolation suggests that the reduction in blood loss, risk of re-exploration, and blood product usage that accompanies cessation of clopidogrel

for 5 to 7 days before CABG comes at the expense of approximately a 1% increase in the risk of MI while waiting for surgery.²² This rate may be highest in the period immediately after the first ACS event and may decline in the weeks or months that precede elective CABG.

Whether a reduced risk of bleeding is worth an increased risk of additional ischemic events remains an issue for continued debate. Adding to this debate are important considerations regarding the direct and indirect economic and social costs of hospitalization on patients and their families resulting from potentially unnecessary delays in CABG. In one study comparing resource use in a CABG patient cohort, the costs for those who underwent nonelective CABG were 33% higher than the costs for those who underwent elective CABG, a difference due almost entirely to costs incurred during a longer preoperative length of stay.²³ Prolonged lengths of stay also expose patients, particularly those who are elderly, to the development of comorbid conditions related to long hospital stays, including decubitus ulcers (bed sores) and nosocomial infections. One way to limit the overall impact of a clopidogrel washout period may be to discharge patients to home, as results of a retrospective analysis of 125 patients who received CABG within 3 to 5 days of clopidogrel cessation showed that those discharged to home had similar intraoperative and postoperative outcomes as those who remained hospitalized.²⁴ Overall, additional information on the risks of clopidogrel washout before CABG is needed.

FUTURE DIRECTIONS

The absence of reliable, easy, and quick platelet function testing for patients receiving a wide variety of antiplatelet drugs is a serious problem. There are several commercially available platelet function tests, but the overall utility of platelet function testing is limited by poor reproducibility and comparability among tests. Variability in response to antiplatelet agents, perhaps especially marked for the prodrugs, makes estimation of dosing and timing of antiplatelet administration very difficult. Furthermore, if physicians were able to more precisely determine which patients were at the greatest risk of bleeding, as well as the time at which antiplatelet-exposed patients could be safely operated on, appropriate upstream initiation of therapy might increase. For such a scenario to come to fruition, a single reproducible and inexpensive test to measure platelet inhibition is necessary.

CONCLUSION

Antiplatelet therapy is a mainstay of care for patients with ACS, and the majority of these patients benefit from its early use, as evidenced by a reduced risk of cardiovascular events while awaiting interventional revascularization. The vast majority of patients with ACS receive PCI as opposed to

CABG; therefore, waiting to confirm coronary anatomy before initiating antiplatelet therapy would be to the detriment of 90% to 95% of patients if one considers that only 5% to 12% of patients with ACS undergo CABG.^{14,15}

Although antiplatelet therapy is associated with clinical benefit in patients undergoing CABG, it also increases the risk of bleeding in some, but not all, patients. Although prolonged cessation of clopidogrel in patients undergoing CABG before the procedure is associated with a reduction in perioperative blood loss and blood product usage and a reduced risk of re-exploration, these benefits come at the expense of a 1% increase in the risk of MI while awaiting surgery.²² Inasmuch as previous bleeding concerns associated with aspirin use before CABG have been overcome with increased clinical experience, the risk of bleeding with dual antiplatelet therapy may be reduced with increased operator experience and adjunctive therapeutic agents such as the lysine analogs to reduce surgical bleeding. Overall, strategies aimed at reducing the risk of bleeding should not compromise the clinical benefit of antiplatelet therapy. In the future, platelet function testing may increase the use of appropriate upstream antiplatelet therapy by helping surgeons determine when the risk of bleeding is lessened in antiplatelet-exposed patients.

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TABLE E1. Benefit of aspirin after CABG

Study	Patients	Outcome in ASA recipients	Outcome in ASA nonrecipients	Risk reduction
Goldman et al ^{E1}	406 men who underwent elective CABG followed by coronary angiography at 1 year (299 received ASA, 107 did not)	15.8% of grafts were occluded on angiography	22.6% of grafts were occluded on angiography ($P = .029$ vs those who received ASA)	Not reported
Dacey et al ^{E2}	1056 CABG recipients (368 received ASA, 688 did not)	31% experienced in-hospital death	37% experienced in-hospital death	ASA reduced the risk of in-hospital death by 45% on multivariate analysis (OR, 0.55; 95% CI, 0.31–0.98; $P = .04$)
Brown et al ^{E3}	127 CABG patients who underwent CABG followed by coronary angiography at 1 year (38 received ASA alone, 45 received ASA + DP, 44 received placebo)	12% of grafts in ASA-only recipients were occluded 14% of grafts in ASA + DP recipients were occluded	21% of grafts were occluded	ASA alone reduced the odds of occlusion at 1 year by 53% (OR, 0.47; $P = .04$) ASA + DP reduced the odds of occlusion at 1 year by 50% (OR, 0.50; $P = .04$)
Gavaghan et al ^{E4}	231 patients who underwent CABG followed by coronary angiography at 1 week (126 received ASA, 105 did not)	4.0% of grafts were occluded	14.3% of grafts were occluded ($P = .003$ vs those who received ASA)	Not reported
Gavaghan et al ^{E4}	219 patients who underwent CABG followed by coronary angiography at 1 year (119 received ASA, 100 did not)	11.9% of grafts were occluded	29.5% of grafts were occluded ($P < .002$ vs those who received ASA)	Not reported
Mangano ^{E5}	5022 CABG recipients (2999 received ASA, 2023 did not)	1.3% experienced in-hospital all-cause death; 1.1% experienced in-hospital cardiac death; 2.8% experienced in-hospital MI; 1.3% experienced in-hospital stroke	4.0% experienced in-hospital all-cause death; 3.1% experienced in-hospital cardiac death; 5.4% experienced in-hospital MI; 2.6% experienced in-hospital stroke	ASA significantly reduced the odds of in-hospital all-cause mortality, cardiac mortality, MI, and stroke ($P \leq .01$ for each)

ASA, Aspirin; CABG, Coronary artery bypass grafting; CI, confidence interval; DP, dipyridamole; MI, myocardial infarction; OR, odds ratio.

TABLE E2. Blood loss, blood product usage, and rates of reoperation for bleeding in the different eras of antiplatelet therapy

Study	Blood lost (mL)	Reoperation for bleeding (n; %)	Blood transfused (U/patient; %)	FFP transfused (U/patient; %)	Platelets transfused (U/patient; %)
A. Studies comparing aspirin vs no aspirin					
Michelson et al ^{E6}	ASA: 919±491 ^{a,b} No ASA: 437±244 ^a	NR	ASA: 1.1±1.3 ^a ; 55.6 No ASA: 1.3±1.5 ^a ; 68.8	NR	NR
Ferraris et al ^{E7}	ASA: 1513±977 ^{a,b,c} No ASA: 916±482 ^{a,c}	ASA: 2; 12.5 No ASA: 0	ASA: 4.4±3.5 ^{a,b} No ASA: 1.8±1.3 ^a	ASA: 3.6±4.9 ^{a,b} No ASA: 0.7±1.6 ^a	ASA: 1.3±1.3 ^{a,b} No ASA: 0.16±0.38 ^a
Taggart et al ^{E8}	75 ASA: 1150 (820, 1380) ^{b,d} 150 ASA: 1360 (1020, 1730) ^{b,d} 300 ASA: 1100 (810, 1340) ^{b,d} No ASA: 870 (790, 960) ^d	ASA: 7; 6.9 No ASA: 6; 5.9	75 ASA: 4.0 (2.5, 4.5) ^{b,e} 150 ASA: 4.0 (2.5, 5.0) ^{b,e} 300 ASA: 3.0 (1.5, 4.5) ^{b,e} No ASA: 2.0 (1.5, 2.5) ^e	NR	NR
Goldman et al ^{E9}	325 ASA: 965 ^{b,e} 325 ASA tid: 1175 ^{b,e} ASA/DP: 1000 ^{b,e} Sulf: 775 ^e Placebo: 805 ^e	325 ASA: NR; 9.3 ^f 325 ASA tid: NR; 6.3 ^f ASA/DP: NR; 3.9 ^f Sulf: NR; 2.1 Placebo: NR; 1.3	NR	NR	NR
Dacey et al (a) ^{E2}	ASA: 1318±2078 ^a No ASA: 1255±1498 ^a	ASA: NR; 32.9 No ASA: NR; 33.0	ASA: 3.0±4.1 ^a No ASA: 3.3±4.3 ^a	ASA: 3.4±5.7 ^a No ASA: 3.5±5.5 ^a	ASA: 3.6±8.3 ^a No ASA: 5.4±10.6 ^a
Dacey et al (b) ^{E2}	ASA: 822±590 ^a No ASA: 799±774 ^a	ASA: NR; 7.1 No ASA: 8.1	ASA: 1.4±1.7 ^a No ASA: 1.4±2.0 ^a	ASA: 0.9±1.9 ^a No ASA: 1.1±2.9 ^a	ASA: 1.1±3.3 ^a No ASA: 1.2±4.0 ^a
Kallis et al ^{E10}	ASA: 1185 ^{b,g} Placebo: 791 ^g	ASA: 4 ^b ; 8 No ASA: 0	ASA: 3.1 ^{b,g} No ASA: 2.1 ^g	ASA: 0.4 ^{b,g} No ASA: 0 ^g	ASA: 0.5 ^{b,g} No ASA: 0 ^g
Tuman et al ^{E11}	ASA: 627±388 ^a No ASA: 658±465 ^a	ASA: 4; 1.3 No ASA: 0	ASA: 1.4±1.9 ^a No ASA: 1.3±2.0 ^a	ASA: 0.5±1.3 ^a No ASA: 0.4±1.1 ^a	ASA: 0.5±1.2 ^a No ASA: 0.5±1.1 ^a
Vuylsteke et al ^{E12}	ASA: 685±327 ^a No ASA: 654±289 ^a	ASA: 1; 1.2 No ASA: 1; 1.7	ASA: 1.1±1.8 ^a No ASA: 1.5±3.2 ^a	ASA: 0.1±0.6 ^a No ASA: 0.2±0.2 ^a	ASA: 0.2±0.5 ^a No ASA: 0±0.8 ^a
B. Studies comparing clopidogrel vs no clopidogrel					
Hongo et al ^{E13}	CLO: 1124±1119 ^{a,b} No CLO: 775±727 ^a	CLO: 4; 6.8 ^b No CLO: 1; 0.6	CLO: 2.51±2.41 ^{a,b} ; 79.7 ^b No CLO: 1.74±2.16 ^a ; 50.8	CLO: 0.68±1.69 ^{a,b} No CLO: 0.24±0.85 ^a	CLO: 0.86±1.20 ^{a,b} ; 50.8 ^b No CLO: 0.24±0.60 ^a ; 18.2
Englberger et al ^{E14}	CLO: 1485±310 ^{a,b} No CLO: 780±105 ^a	CLO: 8; 5.9 ^b No CLO: 5; 1.2	CLO: 4.6±2.3 ^{a,b} ; 92 ^b No CLO: 1.5±2.2 ^a ; 47	CLO: 0.9±1.4 ^a ; 42 ^b No CLO: 0.3±0.9 ^a ; 13	CLO: 2.6±1.1 ^{a,b} ; 71 ^b No CLO: 0.2±0.6 ^a ; 9
Karabulut et al ^{E15}	CLO: 719±265 ^a No CLO: 612±350 ^a	CLO: 0 No CLO: 16; 1	CLO: 0.5±0.9 ^a No CLO: 0.4±0.9 ^a	CLO: 1.1±1.2 ^a No CLO: 0.9±1.1 ^a	NR CLO: 0.7 (0.6–1.2) ^b ; 5.1 ^b
Kapetanakis et al ^{E16}	CLO: 400 (100–6000) ^b No CLO: 400 (100–2000) ^b	CLO: 24; 5.8 ^b No CLO: 25; 1.3	CLO: 2.0 (1.0–8.0) ^{b,h} ; 30.4 ^b No CLO: 2.0 (1.0–7.0) ^b ; 22.1	CLO: 1.5 (0.8–3.1) ^b ; 3.9 ^b No CLO: 1.9 (0.1–3.8) ^b ; 1.6	CLO: 0.7 (0.2–1.3) ^b ; 1.8
Mehta et al (a) ^{E17}	NR	NR	CLO: 2 (0, 4) ^{b,i} No CLO: 1 (0, 3) ⁱ	NR	CLO: NR; 33.7 ^b No CLO: NR; 20.3
Mehta et al (b) ^{E17}	NR	NR	CLO: 2 (0, 4) ⁱ No CLO: 2 (0, 4) ⁱ	NR	CLO: NR; 17.7 No CLO: NR; 15.0
Berger et al ^{E18}	NR	CLO: 14; 4.7 ^b No CLO: 4; 1.3	NR	NR	NR
Kim et al ^{E19}	NR	CLO: 11; 3.3 No CLO: 116; 2.6	CLO: NR; 70.2 No CLO: NR; 68.2	NR	NR
C. Studies comparing other antiplatelet regimens (combination vs monotherapy, antiplatelet vs no antiplatelet, different time frames of antiplatelet exposure)					
Yende and Wunderink ^{E20}	NR	ASA + CLO: 5; 10.4 ^j ASA: 3; 2.3 ^j Neither: 0 ^j	ASA + CLO: 2.9 ^{g,k} ; 70.8 ^k ASA: 1.8 ^g ; 53.9 Neither: 1.1 ^g ; 46.9	ASA + CLO: 1.2 ^g ; 31.3 ASA: 0.7 ^g ; 23.9 Neither: 0.5 ^g ; 17.2	ASA + CLO: 4.6 ^{g,k} ASA: 2.1 ^g Neither: 0.7 ^g
Ray et al ^{E21}	NR	NR	ASA + CLO: 2.4±2.3 ^{a,j} ASA: 1.9±2.4 ^{a,j} CLO: 2.9±3.4 ^{a,j} Neither: 1.4±2.0 ^a	ASA + CLO: 3.1±5.4 ^{a,j} ASA: 2.3±4.4 ^{a,j} CLO: 2.5±5.4 ^{a,j} Neither: 1.6±2.9 ^a	ASA + CLO: 3.7±5.2 ^{a,j} ASA: 1.3±3.1 ^{a,j} CLO: 3.6±6.0 ^{a,j} Neither: 1.0±3.7 ^{a,j}

TABLE E2. Continued

Study	Blood lost (mL)	Reoperation for bleeding (n; %)	Blood transfused (U/patient; %)	FFP transfused (U/patient; %)	Platelets transfused (U/patient; %)
Leong et al (a) ^{E22}	ASA + CLO: 503 (225–1230) ^h ASA: 570 (100–3675) ^h CLO: 573 (140–1365) ^h Neither: 503 (225–1230) ^h	ASA + CLO: 0 ASA: 0 CLO: 0 Neither: 0	ASA + CLO: 0 (0–0) ^h ASA: 0 (0–4) ^h CLO: 0 (0–2) ^h Neither: 0 (0–10) ^h	ASA + CLO: 0 (0–0) ^h ASA: 0 (0–2) ^h CLO: 0 (0–0) ^h Neither: 0 (0–0) ^h	ASA + CLO: 0 (0–0) ^h ASA: 0 (0–6) ^h CLO: 0 (0–0) ^h Neither: 0 (0–0) ^h
Leong et al (b) ^{E22}	ASA + CLO: 803 (300–3780) ^{h,k} ASA: 620 (58–4500) ^h CLO: 585 (200–1755) ^h Neither: 603 (50–2908) ^h	ASA + CLO: 27; 3.4 ASA: 1; 1.5 CLO: 0 Neither: 1; 0.5	ASA + CLO: 1 (1–30) ^h ASA: 1 (0–12) ^h CLO: 1 (0–10) ^h Neither: 1 (0–21) ^h	ASA + CLO: 0 (0–4) ^h ASA: 0 (0–11) ^h CLO: 0 (0–2) ^h Neither: 0 (0–3) ^h	ASA + CLO: 0 (0–5) ^h ASA: 0 (0–6) ^h CLO: 0 (0–1) ^h Neither: 0 (0–7) ^h
Nurozler et al ^{E23}	ASA + CLO: 1180 ± 280 ^{a,j} ASA: 660 ± 110 ^{a,j} CLO: 1210 ± 260 ^{a,j} Neither: 625 ± 90 ^a	ASA + CLO: 3; 6.1 ^j ASA: 1; 1.4 ^j CLO: 2; 7.1 ^j Neither: 0	ASA + CLO: 3.9 ± 0.8 ^{a,j} ASA: 1.4 ± 0.3 ^{a,j} CLO: 3.7 ± 1.0 ^{a,j} Neither: 1.2 ± 0.4 ^a	ASA + CLO: 1.4 ± 0.6 ^{a,j} ASA: 0.7 ± 0.4 ^{a,j} CLO: 1.3 ± 0.7 ^{a,j} Neither: 0.4 ± 0.3 ^a	ASA + CLO: 2.0 ± 1.2 ^a ASA: 0.2 ± 0.5 ^a CLO: 2.2 ± 1.1 ^a Neither: 0.3 ± 0.4 ^a
Hekmat et al ^{E24}	APT: 1123 ± 573 ^{a,b} No APT: 874 ± 351 ^a	APT: 4; 2.8 No APT: 5; 3.4	APT: 2.6 ± 2.5 ^{a,b} No APT: 1.6 ± 1.8 ^a	APT: 2.0 ± 2.2 ^{a,b} No APT: 1.3 ± 2.0 ^a	APT: 1.2 ± 1.8 ^{a,b} No APT: 0.2 ± 0.8 ^a
Shim et al ^{E25}	APT ≥ 6 d: 265 ± 146 ^{a,l} APT 3–5 d: 330 ± 191 ^{a,l} APT ≤ 2 d: 323 ± 187 ^{a,l} APT ≥ 6 d: 756 ± 408 ^{a,m} APT 3–5 d: 729 ± 485 ^{a,m} APT ≤ 2 d: 627 ± 257 ^{a,m}	NR	APT ≥ 6 d: 1.1 ± 1.8 ^a ; 39 APT 3–5 d: 1.9 ± 0.8 ^a ; 48 APT ≤ 2 d: 1.6 ± 1.9 ^a ; 26	APT ≥ 6 d: NR; 11 APT 3–5 d: NR; 8 APT ≤ 2 d: NR; 5	APT ≥ 6 d: NR; 0 APT 3–5 d: NR; 2 APT ≤ 2 d: NR; 5

If no percentage is reported, it was not available in the original manuscript. For details of the individual studies (study design, number of subjects, and antiplatelet regimens studied), see Table E4. APT, Antiplatelet; ASA, aspirin; CABG, coronary artery bypass grafting; CLO, clopidogrel; d, day; DP, dipyridamole; FFP, fresh frozen plasma; NR, not reported; *sulf*, sulfapyrazole; *tid*, three times daily. ^aMean ± standard deviation; ^b $P \leq .05$ vs control; ^c12 hours postoperative; ^dmean (95% confidence interval); ^emedian (95% confidence interval); ^f $P < .01$ for all ASA vs no ASA; ^gmean; ^hmedian (range); ⁱmedian (interquartile range); ^j $P \leq .05$ for trend; ^k $P \leq .05$ vs no ASA; ^lin the operating room; ^m24 hours postoperative.

TABLE E3. Details of studies reporting correlations between aspirin and clopidogrel therapy and blood loss, blood product usage and reoperation for bleeding

Study reference	Description	Total (N)	Antiplatelet regimen (n)
Berger et al. <i>J Am Coll Cardiol.</i> 2008;52:1693-701 ^{E18}	Retrospective, multicenter study of patients who underwent CABG within 7 d of ACS	596	CLO $\leq$ 5 d before CABG (298) ^a No CLO (298)
Dacey et al. (a) <i>Ann Thorac Surg.</i> 2000;70:1986-90 ^{E2}	Retrospective, multicenter, case-control study of patients who died after CABG	368	ASA (114) No ASA (254)
Dacey et al. (b) <i>Ann Thorac Surg.</i> 2000;70:1986-90 ^{E2}	Retrospective, multicenter, case-control study of patients who survived CABG	688	ASA (254) No ASA (434)
Englberger et al. <i>Eur J Cardiothorac Surg.</i> 2004;26:96-101 ^{E14}	Prospective, single-site study of patients undergoing consecutive CABG procedures	505	CLO $\leq$ 72 h before CABG (136) ^b No CLO (369)
Ferraris et al. <i>Ann Thorac Surg.</i> 1988;45:71-4 ^{E7}	Nonblinded, single-site randomized study of patients undergoing CABG procedures	34	ASA the day before surgery (16) No ASA (18)
Goldman et al. <i>Circulation.</i> 1988;77:1324-32 ^{E9}	Randomized, multicenter study of patients undergoing CABG procedures	772	325 mg/d ASA <48 h of surgery (154) 325 mg tid ASA (155) 325 mg ASA + 75 mg DP tid (162) 267 mg tid sulf (148) Placebo (153)
Hekmat et al. <i>Curr Med Res Opin.</i> 2004;20:1429-35 ^{E24}	Retrospective, single-site study of patients undergoing CABG procedures	290	APT $\leq$ 5 d before CABG (145) No APT (145)
Hongo et al. <i>J Am Coll Cardiol.</i> 2002;40:231-7 ¹³	Prospective, single-site study of patients undergoing CABG procedures	224	CLO $\leq$ 7 d before CABG (59) ^c No CLO (165)
Kallis et al. <i>Eur J Cardiothorac Surg.</i> 1994;8:404-9 ^{E10}	Randomized, single-site study of patients undergoing elective CABG procedures	100	300 mg/d ASA until time of surgery (50) Placebo (50)
Kapetanakis et al. <i>Eur Heart J.</i> 2005;26:576-83 ^{E16}	Retrospective, single-site study of patients undergoing CABG procedures	2359	CLO $\leq$ 7 d before CABG (415) ^a No CLO (1944)
Karabulut et al. <i>Eur J Cardiothorac Surg.</i> 2004;25:419-23 ^{E15}	Retrospective, single-site study of CABG procedures	1628	CLO $\leq$ 2 d before CABG (48) ^d No CLO (1580)
Kim et al. <i>Am Heart J.</i> 2008;156:886-92 ^{E19}	Retrospective, single-site study of CABG procedures	4794	CLO $\leq$ 5 d before CABG (332) ^e No CLO (4462)
Leong et al. (a) <i>Ann Thorac Surg.</i> 2005;80:928-33 ^{E22}	Retrospective, single-site study of patients undergoing OPCABG procedures	109	ASA + CLO $\leq$ 7 d before CABG (2) ASA alone (75) CLO alone (6) Neither drug (26)
Leong et al. (b) <i>Ann Thorac Surg.</i> 2005;80:928-33 ^{E22}	Retrospective, single-site study of patients undergoing CABG CPB procedures	810	ASA + CLO $\leq$ 7 d before CABG (59) ASA alone (523) CLO alone (18) Neither drug (210)
Mehta et al. (a) <i>J Am Coll Cardiol.</i> 2006;48:281-6 ^{E17}	Retrospective, multisite study of patients undergoing CABG procedures performed $\leq$ 5 d of symptom onset	2565	CLO (739) ^f No CLO (1826)
Mehta et al. (b) <i>J Am Coll Cardiol.</i> 2006;48:281-6 ^{E17}	Retrospective, multisite study of patients undergoing CABG procedures performed > 5 d after symptom	293	CLO > 5 d before CABG (113) ^g No CLO (180)

TABLE E3. Continued

Study reference	Description	Total (N)	Antiplatelet regimen (n)
Michelson et al. <i>J Thorac Cardiovasc Surg.</i> 1978;76:694-7 ^{E6}	Retrospective, single-site study of patients undergoing CABG procedures	25	ASA in the week before surgery (9) No ASA (16)
Nurozler et al. <i>Interact Cardiovasc Thorac Surg.</i> 2005;4:546-9 ^{E23}	Retrospective, single-site study of patients undergoing CABG procedures	182	ASA + CLO ≤ 3 d before CABG (49) ASA alone (68) CLO alone (28) Neither drug (37)
Ray et al. <i>BMC Cardiovasc Disord.</i> 2003;3:3 ^{E21}	Retrospective, multisite study of patients undergoing CABG procedures	659	ASA + CLO ≤ 7 d before CABG (46) ASA alone (105) CLO alone (11) Neither drug (497)
Shim et al. <i>J Thorac Cardiovasc Surg.</i> 2007;134:59-64 ^{E25}	Prospective, single-site study of patients undergoing OPCABG procedures	106	ASA + CLO ≥ 6 d before CABG (35) ASA + CLO 3–5 d before CABG (51) ASA + CLO ≤ 2 d before CABG (20)
Taggart et al. <i>Ann Thorac Surg.</i> 1990;50:424-8 ^{E8}	Prospective, single-site study of consecutive patients undergoing CABG procedures	202	75 mg/d ASA at time of surgery (44) 150 mg/d ASA (28) 300 mg/d ASA (29) No ASA (101)
Tuman et al. <i>Anesth Analg.</i> 1996;83:1178-84 ^{E11}	Prospective, single-site study of patients undergoing elective CABG procedures	317	ASA ≤ 7 d before surgery (215) No ASA (102)
Vuytsteke et al. <i>J Cardiothorac Vasc Anesth.</i> 1997;11:831-4 ^{E12}	Prospective, single-site study of patients undergoing CABG procedures	144	ASA ≤ 7 d before CABG (86) No ASA (58)
Yende and Wunderink. <i>Crit Care Med.</i> 2001;29:2271-5 ^{E20}	Prospective, single-site study of patients undergoing CABG procedures	245	ASA + CLO ≤ 5 d before CABG (48) ASA alone (130) Neither drug (64)

Studies are listed alphabetically. See Table E2 for study findings. ACS, acute coronary syndrome; APT, Antiplatelet; ASA, aspirin; CABG, coronary artery bypass grafting; CLO, clopidogrel; CPB, cardiopulmonary bypass; d, day(s); DP, dipyridamole; h, hour(s); NR, not reported; OPCABG, off-pump coronary artery bypass grafting; sulf, sulfinpyrazone; tid, three times daily. ^aAll CLO and no CLO recipients received ASA; ^bThe exact percentages of patients taking ASA not reported, although text indicates the use was comparable between CLO and no CLO groups; ^c86.4% of CLO recipients received ASA vs 47.3% of no CLO recipients ($P < .001$); ^d56% of CLO recipients and 65% of no CLO recipients received ASA ($P =$ not significant); ^e76.6% of CLO recipients and 79.2% of no CLO recipients received ASA (P not provided); ^f96.6% of CLO recipients and 94.9% of no CLO recipients received ASA ($P =$ not significant); ^g95.5% of CLO recipients and 90.5% of no CLO recipients received ASA ($P =$ not significant).

TABLE E4. Large clinical trials assessing the efficacy and safety of dual antiplatelet therapy in acute coronary syndromes

Study	Patients	Regimen ^a and follow-up period	Primary end point	Absolute risk reduction	Bleeding
CURE ^{E26}	12,562 ACS patients	CLO (300 mg LD, 75 mg/d MD) vs placebo for an average of 9 mo	CV death, nonfatal MI, or stroke	2.1% (9.3% vs 11.4%; $P < .001$)	3.7% vs 2.7% ^b ; $P = .001$
PCI-CURE ^{E27}	2658 ACS patients who underwent PCI	CLO (300 mg LD, 75 mg/d MD) vs placebo	CV death, MI, or urgent revascularization within 30 d of PCI	1.9% (4.5% vs 6.4%; $P = .03$)	1.6% vs 1.4% ^b ; $P = .69$
CABG-CURE ^{E28}	2072 ACS patients who underwent CABG	CLO (300 mg LD, 75 mg/d MD) vs placebo	CV death, MI, or stroke	1.7% (14.5% vs 16.2%) ^c	9.6% vs 7.5% ^b ; $P = .095$
CREDO ^{E29}	2116 patients undergoing elective PCI	CLO (300 mg LD, 75 mg/d MD) vs placebo for 12 mo	All-cause death, MI, or stroke	3.0% (8.5% vs 11.5%; $P = .02$)	8.8% vs 6.7% ^d ; $P = .07$
COMMIT ^{E30}	45,852 STEMI patients	CLO (75 mg/d MD) vs placebo for an average of 15 days	All-cause death, reinfarction, or stroke before hospital discharge (up to 4 wk)	0.9% for combined end point (9.2% vs 10.1%; $P = .002$) 0.6% for death alone (8.1% vs 7.5%; $P = .03$)	0.58% vs 0.55% ^c ; $P = .59$
CLARITY ^{E31}	3491 STEMI patients	CLO (300 mg LD, 75 mg/d MD) vs placebo for 30 d	Composite of an occluded infarct-related artery on angiography or all-cause death or recurrent MI before angiography	6.7% (15.0% vs 21.7%; $P < .001$)	1.3% vs 1.1% ^d ; $P = .64$
PCI-CLARITY ^{E32}	1863 STEMI patients who underwent PCI	CLO (300 mg LD, 75 mg/d MD) vs placebo for 30 d	CV death, nonfatal MI, or stroke from PCI to 30 d	2.6% (3.6% vs 6.2%; $P = .008$)	0.5% vs 1.1% ^d ; $P = .21$
CABG-CLARITY ^{E33}	136 STEMI patients who underwent CABG	CLO (300 mg LD, 75 mg/d MD) vs placebo for 30 d	CV death, MI, or recurrent ischemia requiring urgent revascularization	6.2% (15.2% vs 21.4%; $P = .37$)	7.6% vs 7.1% ^d ; $P = 1.00$

ACS, Acute coronary syndrome; CABG, coronary artery bypass grafting; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; CLO, clopidogrel; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction Trial; CREDO, Clopidogrel for the Reduction of Events During Observation; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; CV, cardiovascular; d, day(s); LD, loading dose; MD, maintenance dose; MI, myocardial infarction; mo, month(s); PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; wk, week(s). ^aAll patients received aspirin in addition to either clopidogrel, prasugrel, or placebo; ^bCURE criteria for major bleeding (substantially disabling bleeding, intraocular bleeding leading to vision loss, bleeding necessitating transfusion of ≥ 2 units of blood); ^c P value not provided; 95% confidence interval (0.71–1.11); ^dTIMI criteria for major bleeding (intracranial bleeding or bleeding associated with a hemoglobin drop ≥ 5 g/dL); ^eCOMMIT criteria for major bleeding (fatal bleeding, cerebral bleeding, any bleeding that required transfusion).

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