Benefits and Risks of the Combination of Clopidogrel and Aspirin in Patients Undergoing Surgical Revascularization for Non–ST-Elevation Acute Coronary Syndrome

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial

Keith A.A. Fox, MBChB, FRCP, FESC; Shamir R. Mehta, MD, MSc, FRCPC; Ron Peters, MD; Feng Zhao, MSc, MPH; Nasser Lakkis, MD; Bernard J. Gersh, MBChB, DPhil, FRCP; Salim Yusuf, DPhil, FRCPC

Background—Antiplatelet therapy and antithrombin therapy have been demonstrated to reduce the risk of cardiac events in patients presenting with acute coronary syndrome, yet all effective therapies also increase the risk of bleeding.

Methods and Results—In the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial, 12,562 patients were randomized to clopidogrel or placebo in addition to aspirin, and the primary outcome was cardiovascular (CV) death, myocardial infarction (MI), or stroke. The benefits were consistent among those undergoing percutaneous coronary intervention (PCI) [9.6% for clopidogrel, 13.2% for placebo; relative risk (RR), 0.72; 95% CI, 0.57 to 0.90], coronary artery bypass grafting (CABG) surgery (14.5% for clopidogrel 16.2% for placebo; RR, 0.89; 95% CI, 0.71 to 1.11), and medical therapy only (8.1% for clopidogrel, 10.0% for placebo; RR, 0.80; 95% CI, 0.69 to 0.92; test for interaction among strata, 0.53). For CABG during the initial hospitalization (530 for placebo, 485 for clopidogrel), the frequency of CV death, MI or stroke before CABG was 4.7% for placebo and 2.9% for clopidogrel (RR, 0.56; 95% CI, 0.29 to 1.08). For the entire study, there was a 1% excess of major bleeding but no significant excess of life-threatening bleeding. Among patients undergoing CABG, the rates of life-threatening bleeding were 5.6% for clopidogrel and 4.2% for placebo (RR, 1.30; 95% CI, 0.91 to 1.95; both nonsignificant).

Conclusions—The benefits versus risks of early and long-term clopidogrel therapy (freedom from CV death, MI, stroke, or life-threatening bleeding) are similar in those undergoing revascularization (CABG or PCI) and in the study population as a whole. Overall, the benefits of starting clopidogrel on admission appear to outweigh the risks, even among those who proceed to CABG during the initial hospitalization. (Circulation. 2004;110:1202-1208.)

Key Words: clopidogrel ■ coronary artery bypass ■ revascularization ■ coronary disease

Platelet aggregation and thrombus formation play a critical role in the initiation and development of key complications of acute coronary syndromes (ACSs). Antiplatelet therapy and antithrombotic therapy have been demonstrated to favorably modify clinical outcome, and recent trials of revascularization in ACSs have demonstrated a reduction in the frequency of major cardiac events.1–13 Antiplatelet and antithrombin therapy can have synergistic actions that reduce the risk of spontaneous or revascularization, especially percutaneous coronary intervention (PCI)–related events. Yet, all effective antithrombotic agents also increase the risk of bleeding, especially bleeding that results from vascular access or associated with surgery, including coronary artery bypass grafting (CABG).

The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial demonstrated that the combination of clopidogrel and aspirin was superior to aspirin alone for patients hospitalized with non–ST-elevation ACSs.4 The therapy was in addition to the current standard of care, including heparin or low-molecular-weight heparin, antiangiinal therapy, and revascularization.45 For some patients who require revascularization, the distribution or position of coronary lesions is such that surgical rather than percutaneous revascularization is the preferred therapeutic option. Among

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From the Royal Infirmary of Edinburgh, Edinburgh, UK (K.A.A.F.); Division of Cardiology (S.R.M.) and Canadian Cardiovascular Collaboration Project Office (F.Z., S.Y.), Population Health Research Institute, McMaster University, Hamilton, Canada; Academic Medical Center, Amsterdam, Netherlands (R.P.); Baylor Hospital, Houston, Tex (N.L.); and Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minn (B.J.G.).

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Correspondence to Professor K.A.A. Fox, Cardiovascular Research, Division of Medical and Radiological Sciences, University of Edinburgh, Chancellor’s Building, 49 Little France Crescent, Edinburgh EH16 4SB UK. E-mail k.a.a.fox@ed.ac.uk

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the 12,562 patients in the CURE trial, 2072 (16.5%) underwent CABG and 2658 (21.2%) underwent PCI. This report examines the benefits versus risks of clopidogrel treatment among 2072 patients undergoing CABG during initial hospitalization or follow-up and examines the consistency of these results with those observed in 2658 patients undergoing PCI and the 7985 patients treated medically and without revascularization. Analysis of trial data subdivided by a postrandomization variables has methodological limitations but is of value in examinations of the consistency of results by different treatment strategies in a trial such as CURE in which there is a clear overall treatment effect. Such analyses can be used to explore the consistency of benefits and risks across various strata defined by management strategies.

Methods

Study Design

CURE is a large-scale, randomized, double-blind, placebo-controlled trial comparing clopidogrel with placebo in patients presenting with an ACS without ST-segment elevation. Both treatment groups received aspirin 75 to 325 mg for the duration of the trial. The design and rationale of the study have been reported previously. A brief description follows.

Patients

Patients were eligible for inclusion in CURE if they had symptoms indicative of an ACS within the preceding 24 hours in the absence of ST-segment elevation of >1 mm on the ECG. Other supporting evidence of ischemia was required in the form of ECG criteria or elevated concentrations of cardiac enzymes or troponin at least twice the upper limit of normal. Patients were excluded if they had NYHA class IV heart failure, PCI or CABG within the preceding 3 months, contraindications to antithrombotic or antiplatelet therapy, disabling or hemorrhagic stroke or intracranial hemorrhage, or clinically severe thrombocytopenia. Patients were excluded if they required antiaggregants or nonstudy antiplatelet agents or if they had severe allergic reaction to aspirin or hemorrhagic stroke or intracranial hemorrhage, or medically severe thrombocytopenia. Patients were excluded if they required oral anticoagulants or nonstudy antiplatelet agents or if they had received a glycoprotein IIb/IIIa inhibitor within the preceding 5 days.

Study Procedures

Patients were randomly assigned to clopidogrel (loading dose of 300 mg orally and then 75 mg daily) or matching placebo on a double-blind basis and continued for 3 to 12 months. Aspirin (recommended dose, 75 to 325 mg) was started or continued with the study drug. Cardiac catheterization was performed at the discretion of the local investigator, and the blinded study drug was continued during the procedure. For patients proceeding to CABG, the timing of discontinuation of the study drug before surgery (and aspirin) was at the discretion of the surgeon (and local surgical policy) rather than dictated by the protocol.

All trial outcomes, including the safety outcomes involving bleeding, were adjudicated independently and blindly. Major bleeding was defined as not life threatening and life threatening. Non-life-threatening bleeding was defined as bleeding that required ≥2 units blood or was significantly disabling or intraocular. Life-threatening bleeding was defined as bleeding that was fatal, that led to a decrease in hemoglobin concentration of >5 g/dL, that caused significant hypotension requiring intravenous inotropes or surgical intervention, or that resulted in symptomatic intracranial hemorrhage or necessitated transfusion of ≥4 units of blood. For comparison, bleeding events were also classified with the TIMI and GUSTO criteria for major bleeding.

Statistical Analysis

An intention-to-treat analysis was performed as the primary analysis. Comparisons between clopidogrel and placebo were made with the log-rank test. Time-to-event curves for the primary and other major outcomes were generated through Kaplan-Meier cumulative hazard estimates. Risk ratios (RRs) and 95% CIs were derived by use of the Cox proportional-hazards model. Interpreting the subdivision of data based on postrandomization variables (eg, revascularization) requires caution because treatment could affect the rates of these procedures. In CURE, there were no significant differences in overall rates of revascularization for those randomized to clopidogrel or placebo, although fewer patients received revascularization during the initial hospitalization in the clopidogrel group. These subgroup analyses were used to explore the consistency of the risks and benefits across different management practices.

Results

Overall Results

Overall, 582 of 6259 patients (9.3%) in the clopidogrel group experienced a primary outcome compared with 719 of 6303 (11.4%) in the placebo group (RR, 0.80; 95% CI, 0.72 to 0.90). Additionally, there were reductions in in-hospital refractory ischemia (8.7% versus 9.3%), recurrent angina (20.9% versus 22.9%), and heart failure (3.7% versus 4.4%).

Outcomes Among Those Undergoing CABG

Of the 12,562 patients, 2072 underwent CABG. Of these, 1061 were randomly assigned to placebo and 1011 to clopidogrel. The median time from randomization to CABG was 25.5 days (interquartile range, 12 to 70.5 days). The time to CABG for those undergoing the procedure during the initial hospitalization (n=1013) was 12 days (interquartile range, 8 to 19 days) for the placebo group and 13 days (interquartile range, 8 to 21 days) for the clopidogrel group. For those undergoing later CABG (n=1057), the respective figures are 73 days (interquartile range, 36 to 129) for placebo and 67.5 days (interquartile range, 38 to 141 days) for clopidogrel. The baseline characteristics for CABG patients are shown in Data Supplement Table 1, available at http://www.circulationaha.org.

The primary outcome occurred in 16.2% of placebo-treated patients and 14.5% of clopidogrel-treated patients (RR, 0.89; 95% CI, 0.71 to 1.11) undergoing CABG (Data Supplement Table 2). For those undergoing surgical revascularization during the initial hospitalization (530 placebo and 485 clopidogrel patients), 16.4% of the placebo-treated and 13.4% of the clopidogrel-treated patients experienced cardiovascular death, myocardial infarction (MI), or stroke (RR, 0.81; 95% CI, 0.59 to 1.12). These findings are consistent with the treatment effect observed in the entire CURE trial (RR, 0.80; 95% CI, 0.72 to 0.90) (Data Supplement Table 2 and Figure 1).

Among patients undergoing CABG surgery, benefits were observed mainly before the procedure; 71 patients (6.7%) experienced a primary end point in the placebo group compared with 57 (5.6%) in the clopidogrel group (RR, 0.82; 95% CI, 0.58 to 1.16). After CABG surgery, similar numbers of events occurred in the placebo and clopidogrel groups (112 versus 103; RR, 0.97; 95% CI, 0.74 to 1.26). However, the study medication was stopped for a median of 10 days after surgery and was restarted in
75.3% (1451 of 1928) of those who stopped the drug before surgery.

Outcomes Among Patients Undergoing PCI

The number of patients who underwent PCI (1345 placebo patients and 1313 clopidogrel patients) were similar to the number who underwent CABG. This amounts to 21.2% of the entire study population. Compared with 126 clopidogrel-treated patients (9.6%), 177 (13.2%) placebo-treated patients experienced the primary outcome (RR, 0.72; 95% CI, 0.57 to 0.90; *P*<0.004). Detailed analysis of this subset has been published previously.5

Thus, the relative risk reduction in the primary end point is consistent in those undergoing CABG revascularization, those undergoing PCI, and those who did not undergo revascularization procedures (Figure 2).

Bleeding Risks Among Patients Undergoing or Not Undergoing Revascularization

Overall Findings

For the entire study, major bleeding occurred in 169 placebo patients (2.7%) and 231 clopidogrel patients (3.7%; RR 1.38, 95% CI, 1.13 to 1.67; *P*=0.001). However, the impact on life-threatening bleeding was not statistically significant: 112 placebo patients (1.8%) and 135 clopidogrel patients (2.2%; RR, 1.21; 95% CI, 0.95 to 1.56; *P*=0.13).

There was no excess when bleeding was classified according to TIMI major bleeding criteria: 73 placebo patients and 68 clopidogrel patients experienced excess bleeding (RR, 0.94; 95% CI, 0.68 to 1.30). There was a nonsignificant trend for an excess when GUSTO criteria for severe and life-threatening bleeding were applied (70 placebo and 78 clopidogrel patients; RR, 1.12; 95% CI, 0.81 to 1.55).

CABG and Bleeding

Of patients who underwent CABG after randomization, 80 placebo patients (7.5%) and 97 clopidogrel patients (9.6%) experienced major bleeding (RR, 1.27; 95% CI, 0.96 to 1.69; *P*=0.095; Figure 3). Of these, 60 placebo patients (5.7%) and 71 clopidogrel patients (7.0%) fulfilled the CURE criteria for life-threatening bleeding (RR, 1.24; 95% CI, 0.89 to 1.73; *P*=0.20).

To avoid the possibility that the impact of the study drug on bleeding may be obscured by consideration of only the overall bleeding frequency, data were also analyzed for bleeding within 7 days after CABG surgery or from CABG to the end of follow-up (Data Supplement Table 3).

To explore the relationship between the timing of study drug cessation before surgery and bleeding risk, the hazards were examined according to whether the study drug was stopped for ≤5 days before surgery (a period determined by the biological half-life of the drug) compared with >5 days...
before surgery (Data Supplement Table 3b). Whereas no excess in any bleeding was observed for those stopping the drug for \( \frac{5}{10022} \) days before surgery, a nonsignificant excess in major bleeding was seen for those who continued the drug within 5 days of surgery. The relationship between the duration of study drug discontinuation and bleeding frequency within 7 days after CABG surgery is shown in Data Supplement Table 4. Although the excess bleeding risk for those on clopidogrel within 5 days of CABG was not statistically significant, the consistency of this effect with the duration of effect of clopidogrel on platelets in the circulation suggests that there may be a modest excess risk, which is likely to be real.

Before CABG, 1928 (93.1%) of the patients who proceeded to CABG stopped the study drug before CABG, and 66 (3.2%) continued the drug (data on timing was not available for 78 patients). Of the 1928 patients who stopped the study drug before CABG, 1451 (75.3%) restarted after CABG. The median time off the study drug before CABG was 17 days (interquartile range, 9 to 33) and the median time after CABG was 10 days (interquartile range, 6 to 25).

Overall, there was no excess in the need for reoperations for bleeding within 7 days after CABG in the clopidogrel group compared with the placebo group (23 placebo versus 25 clopidogrel patients). The rates of reoperation were not increased for those who stopped clopidogrel \( \frac{5}{10022} \) days before surgery (12 of 454 placebo patients, 7 of 456 clopidogrel patients; RR, 0.58; 95% CI, 0.23 to 1.46). For those who continued the drug within 5 days before surgery, there was a trend for an excess in reoperation (11 of 476 placebo patients, 18 of 436 clopidogrel patients), but the numerical excess was small (n=7), the differences are not statistically significant, and the 95% CI for the RR (1.79) is wide (95% CI, 0.85 to 3.74).

For patients proceeding to CABG during the initial hospitalization (530 placebo, 485 clopidogrel patients) the frequency of cardiovascular death, MI, or stroke before CABG was 4.7% for placebo and 2.9% for clopidogrel patients (RR, 0.56; 95% CI, 0.29 to 1.08; Figures 4 and 5). Conversely, for those proceeding to later CABG (531 placebo, 526 clopidogrel patients), 8.7% placebo patients and 8.2% clopidogrel patients (RR, 0.95; 95% CI, 0.63 to 1.44) sustained the same end points before CABG. These findings suggest no excess hazard among the clopidogrel group for those undergoing later CABG.

For patients undergoing CABG, an absolute excess of 2.8% (n=10) more patients experienced life-threatening bleeding within 7 days after CABG surgery among those who continued the study drug \( \frac{5}{10022} \) days before CABG (clopidogrel versus placebo, Data Supplement Table 4). However there was no excess (2 fewer) life-threatening bleeds for those stopping the study drug \( \frac{5}{10022} \) days prior to CABG. Considering life-threatening or non–life-threatening major bleeds, 24 of 454 placebo-treated patients (5.3%) and 20 of 456 clopidogrel-treated patients (4.4%) experienced such events (RR, 0.83; 95% CI, 0.46 to 1.48).

When the TIMI criteria for major bleeding after CABG surgery (within 7 days) were applied, 25 placebo patients (2.4%) and 22 clopidogrel patients (2.2%) fulfilled the criteria (RR, 0.90; 95% CI, 0.52 to 1.63), a trend for a risk reduction. When the GUSTO criteria for severe or life-threatening bleeding in the same time interval were applied, 30 placebo patients (2.8%) and 40 clopidogrel patients (4.0%) experienced these adverse events (RR, 1.40; 95% CI, 0.88 to 2.23), a nonsignificant trend for excess bleeding.

**Bleeding Risk in the Context of the Timing and Frequency of Surgical Revascularization Seen in FRISC 2 and TACTICS-TIMI-18**

In FRISC 2, 1222 patients underwent an invasive strategy; 430 patients proceeded to CABG and 522 to PCI. Of the 430 proceeding to CABG, 10% had CABG within 5 days. Pro rata, this is equivalent to 35 CABGs within 5 days per 1000 patients randomized to intervention.\(^9\) CURE had an excess of 28 life-threatening bleeds per 1000 patients undergoing CABG. Thus, if a strategy of routine cardiac catheterization similar to that of the intervention arm of FRISC 2 were used (antithrombin therapy and angiography at a median of 4 days), \( \frac{1}{1000} \) additional life-threatening bleed in CABG patients...
would occur per 1000 ACS patients treated with clopidogrel (assuming all clopidogrel-treated patients continued the drug until surgery).

In TACTICS-TIMI-18, 220 of the 1114 patients in the invasive strategy group underwent CABG during the initial hospitalization, and of those, 139 (≈50%) of the CABGs were undertaken in the first 5 days. The proportionate excess in expected bleedings when the CURE results are applied amounts to ≈3 patients with life-threatening bleeds per 1000 ACS patients treated with clopidogrel (139 patients underwent CABG within 5 days of admission, and as above, the calculation assumes that all these patients continued clopidogrel until surgery). However, it is more realistic that most patients will discontinue clopidogrel for 5 days. If one quarter of all the CABG surgeries were undertaken within 2 days, then the excess in CABG-related bleeds amounts to <1 (0.87) per 1000 ACS patients treated with clopidogrel. The anticipated benefit of clopidogrel in patients undergoing CABG surgery are ≈17 fewer cardiovascular deaths, MI, and strokes per 1000 patients treated (Data Supplement Table 2).

**Risks and Benefits**

Risks and benefits overall may be considered by combining the primary end point and life-threatening or major bleeding (Data Supplement Table 5). Overall, for the primary end point or life-threatening bleeding, the RR is 0.84 (95% CI, 0.76 to 0.93), very similar to those treated by medical therapy only (RR, 0.82; 95% CI, 0.72 to 0.95). Including major bleeding and refractory angina with the primary end point gives an RR of 0.87 (95% CI, 0.79 to 0.96; P=0.005). In those treated by any revascularization, the RR is 0.87 (95% CI, 0.75 to 1.01). For those undergoing CABG, the corresponding RR is 0.98 (95% CI, 0.80 to 1.19).

**Discussion**

**Rates of Revascularization in CURE in the Context of Other Recent Trials and Registries**

Among the 12,562 patients randomized in the CURE trial, 16.5% of patients underwent CABG and 21.2% underwent PCI (total revascularization rate, 36.4%). The frequency of these interventions is similar to that observed in recent clinical trials and large-scale international registry studies. In trials of ACS in which intervention was at the discretion of the clinician rather than dictated by protocol, rates of surgical revascularization were similar to that in CURE (PURSUIT, 14% CABG; PRISM, 17% CABG; GUSTO IV, 11% CABG). Similarly, in the GRACE registry (11,543 patients from 94 centers in Europe, North and South America, Australia, and New Zealand), for patients with non-ST-segment elevation MI, 9.4% (273 of 2893) underwent CABG during the initial hospitalization, and for unstable angina, without enzyme/marker release, 5.1% (225 of 4393). Thus, the frequency of surgical revascularization in CURE is similar to that observed in recent ACS trials and in large-scale contemporaneous registry studies.

In some countries, including the United States, invasive procedures are performed early during the hospital stay. To examine the impact of using clopidogrel in such patients, we measured outcomes among those undergoing surgical revascularization during the index hospitalization. The results indicate ≈1.8% absolute risk reduction before CABG (4.7% of placebo patients, 2.9% of clopidogrel patients for the primary end point; RR, 0.56; 95% CI, 0.29 to 1.08), indicating that the CURE results are likely to apply to settings in which physicians opt for a relatively early invasive strategy.

**Treatment Effect Overall and in Patients Undergoing CABG or PCI**

Data from the Antiplatelet Trialists’ Collaboration support the use of antiplatelet therapy (mostly data for aspirin) after...
CABG,1 and further data support the initiation of aspirin within 48 hours of CABG.17 The CURE trial provides the opportunity to explore the combined use of aspirin and clopidogrel for those undergoing CABG.

In CURE, on the background of current standard therapy, an overall treatment effect of clopidogrel was observed compared with placebo, with a RR of 0.80 and a narrow confidence interval (9.3% frequency of cardiovascular death, MI, or stroke for clopidogrel treatment versus 11.4% for placebo treatment; 95% CI, 0.72 to 0.90). Similarly, for those undergoing PCI during the study period, the relative risk was 0.69 (95% CI, 0.54 to 0.87 for cardiovascular death or undergoing PCI during the study period, the relative risk was 0.72 to 0.90). Similarly, for those undergoing CABG, the findings (RR, 0.89; 95% CI, 0.71 to 1.11) were consistent with those seen in the CURE trial overall. Consistent benefits were observed among the 1015 patients who underwent CABG during the initial hospitalization (RR, 0.81; 95% CI, 0.59 to 1.2; Figure 4). The trial was not specifically powered to demonstrate an independent treatment effect for the primary end point among those proceeding to CABG, but the results in this subgroup are consistent with the overall benefits. Importantly, lower event rates were observed with clopidogrel treatment before CABG (Figure 5). After CABG, 75.3% (1451 of 1928) of those who stopped the study drug before surgery restarted treatment at a median of 10 days. Thus, there is reduced power to demonstrate a treatment effect after surgery.

Data from the CREDO trial (conducted in the United States) are consistent with the findings in CURE and PCI-CURE and indicate a benefit for clopidogrel treatment in those undergoing PCI (52% with unstable angina as the presentation); by 1 year, 8.5% of clopidogrel-treated patients and 11.5% of placebo-treated patients experienced death, MI, or stroke (RR, 0.73; P=0.02).18 Investigation of the timing of the loading dose of clopidogrel in CREDO suggests an advantage for loading the patient 6 hours before the procedure.18 The rates of major bleeding in CREDO up to 1 year were 8.8% for clopidogrel patients compared with 6.7% for placebo patients. Although this is a nonsignificant trend, it is consistent with the findings in CURE. Similarly, the respective rates of non-procedure-related bleeding were 1.2% versus 0.8% and rates of procedure-related bleeding were 7.7% versus 5.9% (all nonsignificant trends). In absolute numbers, there were 64 CABG-related bleeds with clopidogrel in CREDO compared with 55 with placebo (non-CABG, 17 versus 8, respectively).16 The consistency of the results between CREDO and CURE reinforces our findings of a small excess risk of bleeding (although statistically inconclusive) and clear evidence of benefit. It suggests that the results observed in these trials are applicable across different countries.

The decision to proceed to angiography, PCI, or CABG in CURE was at the discretion of the responsible clinician and was not determined by study protocol. Interestingly, fewer patients proceeded to revascularization during the initial hospitalization in the blinded clopidogrel treatment arm than in the placebo arm (20.7% versus 22.6%; RR, 0.92; P=0.03). This finding is consistent with the observation that refractory ischemia was significantly reduced with clopidogrel. It is likely that patients with the highest clinical or angiographic risk characteristics will proceed to PCI or surgery regardless of study drug. This decision is influenced mainly by the severity of anatomic stenosis, including complex and severe obstructions or left main stem stenosis, and the severity of manifest ischemia. Thus, the lower frequency of revascularization during the index hospitalization in the clopidogrel-treated patients will, if anything, tend to enrich the revascularization population with somewhat higher-risk patients. Consequently, the risk reduction of 24% (RR, 0.76; 95% CI, 0.61 to 0.94) observed among patients undergoing index hospitalization revascularization may be an underestimate of the impact of clopidogrel.

**Risks of Bleeding Overall and in Those Undergoing CABG**

For the entire CURE study, there was a 1% excess of major bleeding (3.7% clopidogrel, 2.7% placebo) but no significant excess of life-threatening bleeding (2.2% clopidogrel versus 1.8% placebo; P=0.13) or hemorrhagic strokes (0.1% versus 0.1%). When the TIMI criteria for major bleeds were used, there was little excess (1.1% clopidogrel versus 1.2% placebo; P=0.70).

For the patients undergoing CABG, there was a nonsignificant trend of 1 additional patient per 100 experiencing life-threatening bleeding with clopidogrel or an additional 2.0 per 100 for all major bleeds (Data Supplement Table 3, from CABG to end of study). This excess was confined to those patients who continued the study drug within the 5 days before CABG. The contribution of aspirin to this bleeding risk is uncertain because CURE did not record the timing of discontinuation of aspirin, and it is possible that in some patients both drugs were used or discontinued simultaneously. Previous reports of bleeding complications with CABG in small numbers of nonrandomized patients may be difficult to interpret in view of the imbalance of disease severity and the confounding influence of concomitant aspirin treatment. For example, in the report by Hongo et al.,19 there was a total of only 59 patients who received clopidogrel just before CABG. Therefore, the largest and least confounded experience comes from these randomized data from the CURE study, and they suggest an 0.8-fold rate of reoperation for bleeding, as distinct from the 10-fold excess suggested by the smaller nonrandomized study.19 Further data are required from additional trials and registries regarding the bleeding risk of CABG surgery among patients receiving antithrombotic and antiplatelet medications.

**Risk-to-Benefit Ratio**

Overall, 12.5% placebo and 10.6% clopidogrel patients experienced cardiovascular death, MI, stroke, or life-threatening bleeding (RR, 0.84; 95% CI, 0.76 to 0.93; P=0.001), and for the primary end point combined with refractory angina or major bleeding, the corresponding figures are 14.5% versus 12.8% (RR, 0.87; 95% CI, 0.79 to 0.96; P=0.005). For those undergoing any revascularization, the rate of death, MI, stroke, or life-threatening bleeding was 15.9% for placebo patients versus 14.0% for clopidogrel patients (RR, 0.87; 95% CI, 0.75 to 1.01).
Wider Implications of Bleeding Risk and Revascularization Strategies

The hazards of bleeding (1% excess major bleeds) need to be weighed against the overall treatment benefit of treating 1000 patients with clopidogrel (21 fewer cardiovascular deaths, MIs, or strokes in 21 patients or, combined with refractory angina, 27 fewer events in 23 patients). Therefore, even if centers were to use an interventional strategy similar to that in FRISC 2, TACTICS, or RITA 3,[9–11] the likelihood of the benefit substantially outweighs the risks of life-threatening or major bleeding. The benefits of revascularization procedures are generally not realized until several months after the procedure; only very few patients (eg, those with higher-risk anatomy and ongoing ischemia) proceed to very early CABG surgery. Therefore, in most patients who require CABG surgery can be delayed to allow the drugs to be stopped for a few days and the risks of bleeding to be minimized. Therefore, the approach to the timing of CABG (not angiography or PCI) should be individualized to obtain the maximum benefit from pharmacological therapy while mitigating the bleeding risks.

Benefits Versus Risks of Clopidogrel Treatment in ACS

Overall, 10.6% of clopidogrel-treated patients and 12.5% of placebo-treated patients experienced either a primary end point or life-threatening bleeding (RR, 0.84; 95% CI, 0.76 to 0.93). For those undergoing CABG, the primary outcome or life-threatening bleeding occurred in 19.3% of clopidogrel-treated patients and 19.7% of placebo-treated patients (RR, 0.98; 95% CI, 0.80 to 1.19).

Conclusions

Clopidogrel is beneficial in ACS patients whether or not they undergo revascularization. Overall, treating 1000 patients results in 21 fewer cardiovascular deaths, MIs, or strokes. This is against an excess of 7 patients requiring transfusion and a trend for 4 patients to experience a life-threatening bleed. For most patients who require nonurgent CABG after presentation with ACS, benefits may be maximized by initiating clopidogrel and aspirin on admission and then stopping clopidogrel 5 days before surgery to minimize bleeding risk. For centers that perform very early angiography routinely for high-risk patients, the balance of potential risks and benefits of initiating clopidogrel before angiography needs to be considered on an individual basis.

Disclosure

The CURE trial was designed and administered by an independent steering committee and was sponsored by Bristol Myers Squibb and Sanofi.

References

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