Continuing Antiplatelet Therapy Before Cardiac Surgery With Cardiopulmonary Bypass: A Meta-Analysis on the Need for Reexploration and Major Outcomes

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Objective: **To determine major adverse outcomes, including the risk of mediastinal reexploration, death, stroke and myocardial infarction, associated with continuing antiplatelet therapy in patients undergoing surgery with cardiopulmonary bypass.**

Design: **A meta-analysis of parallel randomized, controlled trials published in English.**

Setting: **A university-based electronic search.**

Participants: **Patients undergoing surgery with cardiopulmonary bypass (CPB).**

Intervention: **Continuing antiplatelet therapy versus stopping antiplatelet therapy before the surgery.**

Measurements and Main Results: **A search was conducted in PubMed, EMBASE, MEDLINE(R), and the Cochrane Central Register of Controlled Trials. Twelve studies were retained for analysis. Continuing antiplatelet drugs for CPB increases the rate of reexploration by a standardized mean difference (SMD) 0.22, 95% confidence interval (CI) 0.06, 0.39; I-square 0%; p value 0.01; classical fail-safe number 5. The number needed to harm (NNTH) is 87 (95% CI 390, 44). There was no statistical difference for death at 30 days and 1 year, myocardial infarction at 30 days, and stroke at 30 days. Continuing antiplatelet drugs increases blood loss, SMD 0.27 (95% CI 0.09, 0.45), I-square 73.1%; p = 0.003.**

Conclusions: **Continuing antiplatelet therapy for patients undergoing surgery with CPB is associated with a low risk for reexploration.**

KEY WORDS: antiplatelets, reexploration, blood loss, red blood cells, fresh frozen plasma, platelets, death, myocardial infarction, stroke, cardiopulmonary bypass, cardiac surgery

DUAL ANTIPLATELET THERAPY is recommended for 4 to 6 weeks after the insertion of a bare metal coronary artery stent and for 6 to 12 months after a drug-eluting one. Premature cessation of this antiplatelet therapy increases the risk of stent thrombosis, a highly lethal condition.[1] Bridging therapy has been proposed as a solution to decrease both the time when the patient is at increased risk for thrombosis when oral antiplatelet drugs are stopped prior to surgery and to minimize surgical blood loss by allowing timed perioperative cessation of antiplatelet activity. Oral drugs are stopped 5 to 7 days prior to surgery, and the bridge therapy with a short-acting drug is introduced 2 to 3 days prior to surgery and stopped shortly (usually a few hours) before the surgery. Results with bridging therapy have, however, been disappointing. Heparin usually is not considered an optimal bridging agent as it does not offer protection against stent thrombosis equivalent to antiplatelet drugs.[2] Potent short-acting antiplatelet drugs such as the small molecule glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) or a reversible P_2Y12 platelet inhibitor (cangrelor) have been identified as the most promising solutions for bridging therapy. The inhibition of tirofiban and eptifibatide wears off in 4 to 6 hours, and the inhibition of cangrelor wears off within 1 hour.

Unfortunately, a recent randomized controlled trial (RCT) evaluating cangrelor as a bridging agent to prevent preoperative thrombotic events did not demonstrate the expected benefit of short-acting antiplatelet drugs.[3] In this trial, 210 patients with either an acute coronary syndrome or treated with a coronary stent and receiving a thienopyridine (ticlopidine, clopidogrel or prasugrel) were randomized to either cangrelor, 0.75 μg/kg/min (a dose determined as being capable of maintaining the level of platelet reactivity identical to the one expected if the thienopyridine drugs had not been discontinued), or a placebo while awaiting coronary artery bypass graft (CABG) surgery. Aspirin therapy was maintained as per routine local practice. In this trial, the pre-procedural achievement of composite endpoints (death/myocardial infarction/need for urgent revascularization) was similar for both groups: 3/106 and 4/101 for cangrelor and placebo, respectively. Therefore, the extra cost associated with bridging therapy that requires hospitalization for IV administration of the short-acting antiplatelet drugs may not be justified in view of the lack of benefit.

The simple option of continuing the dual antiplatelet therapy through surgery usually is not adopted in patients scheduled for CABG with cardiopulmonary bypass (CPB) in view of the increased risk of surgical bleeding associated with it. Continuation may be an acceptable solution in patients at high risk for stent thrombosis if it does not increase the risk of death or permanent injury because, on the other hand, a stent thrombosis may do so. The present meta-analysis was undertaken to quantify the risk of the need for reexploration for bleeding associated with continuing antiplatelet therapy in patients undergoing CABG with CPB.

METHODS

The intervention was defined as continuing antiplatelet therapy until the surgery (versus stopping). A search was conducted in PubMed (up to November 13, 2012), EMBASE (1974-2012 Week 45), MEDLINE (R) (1946-November Week 1 2012) and the Cochrane Central Register of Controlled Trials (November 2012) for all RCTs that compared the intervention to no intervention for adult cardiac surgery with CPB. The reference lists of all studies retained and the ones of the recent (≥2009) previous meta-analyses on the topic also were checked. The exact search strategy is provided in Figure 1. When data were published in more than 1 report, available reports were consulted, but the study (not the report) was considered the unit; therefore, no study was considered more than once. As recommended by the Cochrane Collaboration, the

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RCTs were judged on the information contained in the reports without any assumption of the following: (1) adequate sequence generation (quasi-randomized studies were rejected), (2) allocation concealment (inability of the person who was recruiting the patient to know in advance to which group the patient would be assigned), (3) blinding of patients, the personnel, and the assessor for the outcomes of interest, (4) incomplete outcome data addressed (clear description of the fate of all patients included in the study), (5) free of selective reporting (outcomes of interest specified in the methods of the study clearly available for all patients included in the study or acceptable number of patients lost to follow-up, similar for all groups and with acceptable reasons mentioned in the report), and (6) free of other bias (any other possible factor that could have influenced the results). Outcomes were defined as reexploration for bleeding, blood loss and blood product administration, death (all causes) at 30 days and at 1 year (cumulative), myocardial infarction at 30 days, stroke at 30 days, and renal insufficiency at 30 days. At least 1 of these outcomes had to be among the primary objectives of the original study. *Post hoc* analyses from RCTs designed for another purpose were not retained. *A priori* defined factors for heterogeneity exploration were permanent versus transient inhibition of platelet function, age, ASA physical status, type of surgery (redo versus primary surgery, CPB type and duration, duration of surgery, acuity of surgery), anticoagulants, antifibrinolytics (single versus dual therapy, bridging, gender), and race. Data were extracted in duplicate from texts, tables, figures, or from previously published meta-analysis as required. For continuous data, the authors kept only the studies in which results were available as mean and standard deviations or sample size and exact p values. Only real data (no estimated figure) were considered. Data were analyzed with RevMan 5 (for the risk of bias assessment) (Version 5.0; The Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta Analysis version 2.2.044 (http://www.Meta-Analysis.com). Random effects models were used for all the analyses. Heterogeneity was assessed by the I^2 value, and 25% was chosen as the cut-off limit for heterogeneity exploration. Heterogeneity exploration was performed by visual inspection of the forest plots followed by the Egger's intercept, meta-regressions, subgroupings, and/or sensitivity analysis as required. Numbers needed to treat (NNT) or harm (NNTH) were calculated on the odds ratios (OR) (http://www.nntonline.net/visualrx/).

RESULTS

The authors retrieved 12 RCTs.[4–15] Details of the study selection can be found in Figure 1. The quality of the studies retained for analysis is in Figure 2 and the details of those studies can be found in Table 1. Continuing antiplatelet drugs up to the surgery in patients undergoing CPB increases the rate of reexploration: standardized mean difference (SMD) 0.22, 95% confidence interval (CI) 0.06, 0.39; I-square 0%; p value 0.01; classic fail-safe number 5 (Fig 3, Table 2).[4–12,15] The number needed to harm (NNTH) is 87 (95% CI 390, 44), calculated from an expected rate of reexploration of 2.4%.[16] There was no statistical difference for death at 30 days[4,5,15] and 1 year,[15] myocardial infarction at 30 days,[4,6,8,12,15] and stroke at 30 days (Table 2).[6,15] There were no data available for renal insufficiency. Continuing antiplatelet drugs increases blood loss: SMD 0.27 (95% CI 0.09, 0.45), I-square 73.1%; p = 0.003.[4–15] The lack of appropriate clinical information such as use of positive end-expiratory pressure, prophylactic administration of anti-fibrinolytic agents, type of oxygenator, duration of CPB, and surgery in many studies impede clinicians from performing an adequate heterogeneity exploration. There was no statistical difference for administration of red blood cells,[4–6,8,10–15] fresh frozen plasma,[4,6,8,9,12,14] or platelets.[4,6,8,10,12] It is important to note, however, that a high amount of heterogeneity was found for these last three results (Table 2). Only 2 studies mentioned *a priori* trigger point for administration of blood products.[12,14] Data for infection (mediastinitis/wound infection or sepsis) are available for 1 study only that reported 0 wound infections in each group.[6]

DISCUSSION

Although the present meta-analysis confirms that continuing antiplatelet drugs in patients undergoing CABG with CPB increases the need for surgical reexploration and blood

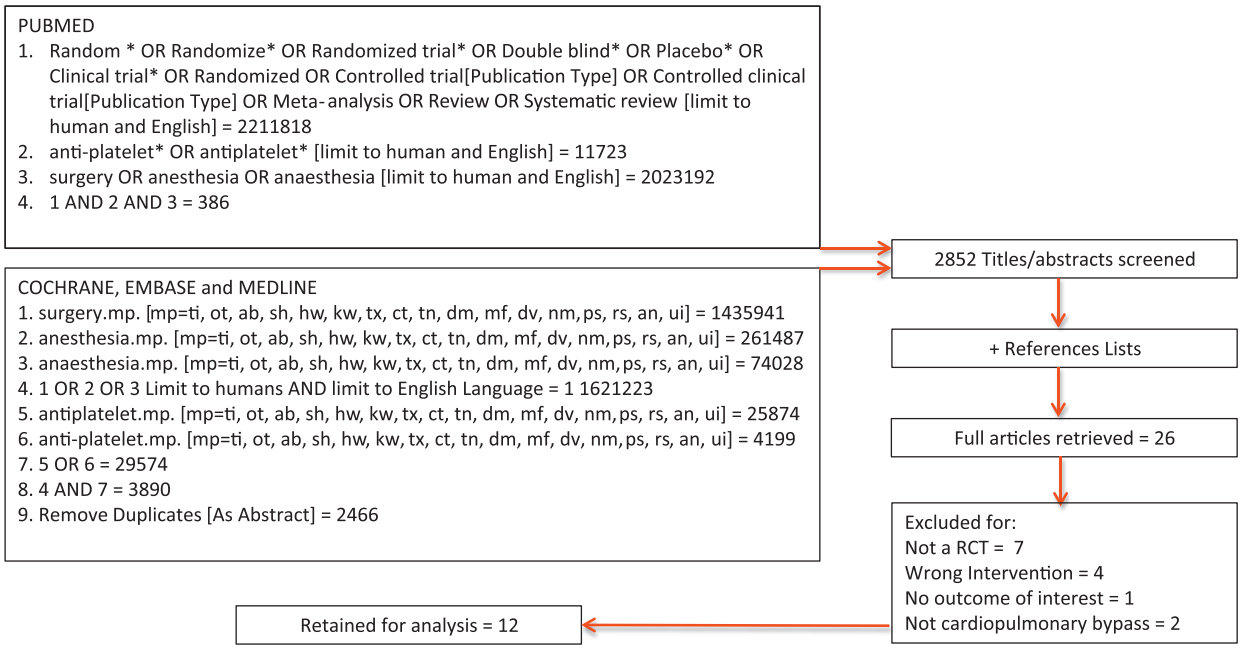

Fig 1. Flow chart of study selection