CANADIAN CARDIOVASCULAR SOCIETY POSITION STATEMENT

Dual antiplatelet therapy in patients requiring urgent coronary artery bypass grafting surgery: A position statement of the Canadian Cardiovascular Society

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Acute coronary syndrome (ACS) guidelines recommend that most patients receive dual antiplatelet therapy with clopidogrel and acetylsalicylic acid (ASA) at the time of presentation to prevent recurrent ischemic events. Approximately 10% of ACS patients require coronary artery bypass grafting surgery (CABG) during the index admission. Most studies show that patients who receive ASA and clopidogrel within five days of CABG have an increase in operative bleeding. Current consensus guidelines recommend discontinuation of clopidogrel therapy at least five days before planned CABG to reduce bleeding-related events. However, high-risk individuals may require urgent surgery without delay, to reduce the risk of potentially fatal ischemic events. The present multidisciplinary position statement provides evidence-based recommendations for the optimal use of dual antiplatelet therapy to balance ischemic and bleeding risks in patients with recent ACS who may require urgent CABG.

Recommendations:

1. All ACS patients should be considered for dual antiplatelet therapy with ASA and clopidogrel at the earliest opportunity, despite the possibility of a need for urgent CABG.
2. For patients who have received clopidogrel and ASA, and require CABG:
   - Those at high risk of an early fatal event (eg, with refractory ischemia despite optimal medical treatment, and with high-risk coronary anatomy (eg, severe left main stenosis with severe right coronary artery disease), should be considered for early surgery without discontinuation of clopidogrel.
   - In patients with a high bleeding risk (eg, previous surgery, complex surgery) who are also at high risk for an ischemic event, consideration should be given to discontinuing clopidogrel for three to five days before surgery.
   - Patients at a lower risk for ischemic events (most patients) should have clopidogrel discontinued five days before surgery.
3. For patients who have CABG within five days of receiving clopidogrel and ASA, the risk of major bleeding and transfusion can be minimized by applying multiple strategies before and during surgery.
4. Patients who receive clopidogrel pre-CABG for a recent ACS indication should have clopidogrel restarted after surgery to decrease the risk of recurrent ACS.
5. For patients with a recent coronary stent, the decision to continue clopidogrel until the time of surgery or to discontinue will depend on the risk and potential impact of stent thrombosis. Restarting clopidogrel after CABG will depend on whether the stented vessel was revascularized, the type of stent and the time from stent implantation. Clopidogrel should be restarted when hemostasis is assured to prevent recurrent acute ischemic events.

Key Words: *Acute coronary syndromes; Clopidogrel; Coronary artery bypass surgery; Dual antiplatelet therapy*

Une bithérapie antiplaquettaire chez des patients ayant besoin d'un pontage aortocoronarien d'urgence : Un document de principes de la Société canadienne de cardiologie

Selon les lignes directrices sur le syndrome coronarien aigu (SCA), la plupart des patients doivent recevoir une bithérapie antiplaquettaire de clopidogrel et d'acétylsalicylique (ASA) à leur admission pour prévenir des événements ischémiques récurrents. Environ 10 % des patients atteints de SCA ont eu besoin de subir un pontage aortocoronarien (PAC) pendant la période d'admission de référence. La plupart des études révèlent que les patients qui reçoivent de l'ASA et du clopidogrel dans les cinq jours précédant le PAC ont plus de saignements opératoires. Les lignes consensuelles actuelles recommandent d'interrompre le traitement au clopidogrel au moins cinq jours avant un PAC planifié pour réduire les événements liés aux saignements. Cependant, les personnes à haut risque peuvent avoir besoin de se faire opérer sans délai afin de réduire le risque d'événements ischémiques au potentiel fatal. Le présent document de principes multidisciplinaire fournit des recommandations probantes sur l'utilisation optimale d'une bithérapie antiplaquettaire afin d'équilibrer les risques d'ischémie et de saignement chez les patients ayant récemment subi un SCA et qui sont susceptibles de recevoir un PAC d'urgence.

Recommandations

1. Il faudrait envisager une bithérapie antiplaquettaire de clopidogrel et d'ASA chez tous les patients ayant subi un SCA le plus rapidement possible, malgré la possibilité d'un PAC d'urgence.
2. Pour les patients qui ont reçu du clopidogrel et de l'ASA et qui doivent subir un PAC :
   - Il faut envisager d'opérer les personnes vulnérables à un événement fatal (p. ex., ayant une ischémie réfractaire malgré un traitement médical optimal) et ayant une anatomie coronarienne à haut risque (p. ex., sténose de l'artère coronaire gauche principale accompagnée d'une grave coronaropathie droite) sans interrompre le clopidogrel.
   - Chez les patients ayant un risque marqué de saignement (p. ex., opération antérieure, chirurgie complexe) également très vulnérables à un événement ischémique, il faut envisager d'interrompre le clopidogrel de trois à cinq jours avant l'opération.
   - Les patients moins vulnérables à un événement ischémique (c'est-à-dire la plupart des patients) devraient arrêter de prendre du clopidogrel cinq jours avant l'opération.
3. Chez les patients qui ont subi un PAC moins de cinq jours après avoir reçu du clopidogrel et de l'ASA, on peut réduire le risque d'hémorragie majeure et de transfusion grâce à de multiples stratégies avant et pendant l'opération.
4. Les patients qui prennent du clopidogrel avant le PAC et qui ont récemment souffert d'un SCA devraient recommencer à prendre du clopidogrel après l'opération pour réduire le risque de SCA récurrente.

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5. Chez les patients à qui on a récemment implanté une endoprothèse coronaire, la décision de poursuivre ou d'interrompre le traitement au clopidogrel jusqu'à l'opération dépend du risque et des effets possibles de thrombose de l'endoprothèse. Pour décider de reprendre le clopidogrel après le PAC, il faut établir si le vaisseau ayant reçu l'endoprothèse est revascularisé, le type d'endoprothèse et le délai depuis l'implantation de l'endoprothèse. Il faut recommencer à donner du clopidogrel s'il est assuré que l'hémostasie préviendra une récurrence d'événements ischémiques aigus.

Antiplatelet therapy with the combination of acetylsalicylic acid (ASA) and clopidogrel reduces thrombotic events more than ASA alone in patients with acute coronary syndromes (ACS), and in patients following percutaneous coronary intervention (PCI), who received coronary stents. The benefits of clopidogrel and ASA in patients with recent ACS are observed irrespective of whether the patient undergoes medical treatment (1), or receives thrombolysis (2,3) or revascularization by either PCI (4) or coronary artery bypass grafting surgery (CABG) (1). Preoperative treatment with clopidogrel reduced recurrent ischemic events before surgery by 44% in the 1015 patients in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial who had CABG during the index hospitalization (5). However, an increased risk of perioperative bleeding was observed when patients received clopidogrel and ASA within five days of surgery. Yet, withdrawal of dual antiplatelet therapy to reduce surgical bleeding may increase the risk of recurrent ischemic events. In addition, because of the bleeding risk, timely CABG surgery may be delayed in high-risk patients. Consequently, the challenge is to optimize the timing of surgery to minimize the risk of potentially fatal ischemic events before CABG and at the same time, reduce the incidence and consequences of serious surgical bleeding. The risk of bleeding associated with the currently available dual antiplatelet drugs, ASA and clopidogrel, is likely to increase when more powerful antiplatelet agents such as prasugrel and ticagrelor become available. This further underscores the importance of developing strategies to optimize the management of ACS patients who are potential candidates for CABG surgery and have received antiplatelet therapy.

The adverse impact of perioperative CABG-related bleeding on outcome is not appreciated by all physicians involved in the management of patients with ACS. The problem is compounded by the wide variation in the approach of cardiac surgeons toward patients in need of urgent CABG who have recently received dual antiplatelet therapy. Only with shared understanding between cardiologists, anesthesiologists and the cardiac surgical community can we develop strategies to optimally manage patients at increased risk for both recurrent ischemic events and CABG-related bleeding.

The goal of the present position paper is to discuss the impact of dual antiplatelet therapy in patients who require early CABG surgery, and provide evidence-based recommendations, whenever available, for the management of these high-risk patients.

THE ROLE OF ANTIPLATELET THERAPY FOR PREVENTION OF ISCHEMIC EVENTS AFTER ACS

Recurrent ischemic events within the first 30 days after ACS occur in up to 15% to 20% of patients. Platelet activation and aggregation plays a pivotal role in the pathogenesis of acute coronary occlusion and recurrent ischemic events (6). ASA improves both short- and long-term outcomes in patients with unstable angina and myocardial infarction (MI) (7-9), yet recurrent ischemic events continue to occur, especially in patients with a reduced response to ASA (10,11). Consequently, strategies have been developed to achieve more effective and reliable platelet inhibition than is achieved with ASA alone.

Clopidogrel is an irreversible antagonist of the platelet ADP P2Y12 receptor. It acts synergistically with ASA (12) to inhibit platelet activation and block fibrinogen binding, thus reducing platelet aggregation and clot stabilization. Both ASA and clopidogrel affect platelets for their lifespan (approximately eight to nine days) (13). However, following discontinuation of antiplatelet agents, effective platelet function may return faster than predicted by the lifespan of the irreversibly inhibited platelets, because new platelets not affected by the antiplatelet agents are produced continuously. When ASA was stopped after 14 days of treatment in healthy young men, platelet aggregation returned to normal in 50% of individuals within three days and in 80% within four days (14).

CLOPIDOGREL USE BEFORE CABG

Need for urgent CABG

Risk stratification in patients with non-ST segment elevation ACS (NSTE-ACS) by clinical, electrocardiographic (ECG) and biomarker findings selects high-risk patients who benefit from early (within 48 h) revascularization by either PCI or CABG (15,16). Patients with ACS and refractory myocardial ischemia (especially when associated with ECG changes and/or hemodynamic disturbances despite medical treatment) require consideration for emergency revascularization (17,18). Recent global data show 7% to 12% of patients with NSTE-ACS and 4% with ST elevation MI (STEMI) (19) will have CABG during the same admission. Data from the Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial suggest a higher (16.5%) CABG rate in Canada for patients with NSTE-ACS (Dr Shamir Mehta, personal communication).

Preoperative clopidogrel use

Recent registries show that up to 70% of ACS patients receive clopidogrel at the time of presentation (20,21), as is recommended by current guidelines (17,18). In addition, there are patients who are already receiving chronic clopidogrel with or without ASA for the secondary prevention of coronary or cerebrovascular ischemic events, for the prevention of coronary stent thrombosis, for platelet inhibition in ASA-intolerant patients (22,23) and for the prevention of embolic stroke in patients with atrial fibrillation who are unable to take coumadin (24).

The dilemma

For the patient in need of urgent CABG, the recent administration of dual antiplatelet therapy poses a dilemma for both the referring cardiologist and the cardiac surgeon. Should the patient undergo immediate CABG with a higher risk of both perioperative bleeding and blood product use, or should the patient discontinue the dual antiplatelet therapy and wait five days for surgery, with a risk of recurrent ischemic events during the waiting period? Furthermore, the sudden withdrawal of clopidogrel in unstable patients could provoke ischemic events (25), because discontinuation of clopidogrel may result in a rebound increase in platelet activity (26) and has been associated with an increase of ischemic events (27).

Guideline recommendations

The American College of Cardiology/American Heart Association (ACC/AHA) 2004 guideline update for CABG surgery (28) states that "If clinical circumstances permit, clopidogrel should be withheld for 5 days before performance of CABG surgery" (class I recommendation, level of evidence B). This is in agreement with guidelines from the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists and the European Association of Cardiothoracic Surgeons (29,30). However, approximately 20% of patients with NSTE-ACS have refractory myocardial ischemia with a high risk for life-threatening ischemic events despite optimal medical treatment (31). These patients are likely also the group at highest risk for recurrent ischemic events if antiplatelet therapy is withdrawn, and the patients who will benefit most from urgent surgical revascularization. In the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor

Suppression Using Integrilin Therapy (PURSUIT) trial (32), 14% of patients with NSTE-ACS required CABG surgery during the index admission, and 25% of these patients needed urgent surgery within 72 h of admission.

RISKS AND BENEFITS OF PREOPERATIVE DUAL ANTIPLATELET THERAPY IN PATIENTS WHO REQUIRE CABG SURGERY – THE EVIDENCE

The impact of clopidogrel-induced CABG-related bleeding has been assessed in randomized controlled clinical trials, observational studies and registries.

Randomized controlled clinical trials

For patients who underwent CABG in the CURE trial (n=2072) and received preoperative clopidogrel, there was a trend toward a reduction in MI, stroke and cardiovascular mortality (14.5% for clopidogrel, 16.2% for placebo; RR 0.89 [95% CI 0.71 to 1.11]), and a nonsignificant increase in life-threatening bleeding (5.6% for clopidogrel and 4.2% for placebo; RR 1.30 [95% CI 0.91 to 1.95]) (5). However, more than one-half of the patients undergoing CABG had clopidogrel discontinued at least five days before surgery. In the subset of patients who underwent surgery within five days of discontinuation of clopidogrel or placebo (n=912), there was a 50% increase in life-threatening or non-life-threatening major bleeds (9.6% for clopidogrel, 6.3% for placebo; RR 1.53 [95% CI 0.97 to 2.40]).

The Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction (CLARITY-TIMI 28) study (33) evaluated the benefit of clopidogrel added to ASA in 3491 patients with STEMI who had received thrombolysis. Among the patients referred for surgery (12%, n=419), there was no difference in major or minor bleeding complications in patients who received clopidogrel within five days of surgery (9%) compared with those who did not receive clopidogrel (8%). The Clopidogrel for the Reduction of Events During Observation (CREDO) trial (34) evaluated short-term (one month) and longer-term (one year) administration of clopidogrel in patients undergoing coronary artery stenting. Of the 83 patients (4%) who underwent PCI and were subsequently referred for CABG, there was no significant increase in bleeding in the patients receiving clopidogrel.

Observational studies

Observational studies of the effect of preoperative clopidogrel administration on bleeding in patients undergoing CABG have reached conflicting conclusions, most likely explained by systematic differences between the treated and untreated patients that impact on outcomes. These differences include the indication for surgery, patient comorbidity, physician bias, surgical expertise, elective versus urgent surgery, preoperative anticoagulation and thrombolysis, and preoperative use of autologous blood products (35,36). Several studies have shown that treatment with clopidogrel before CABG is associated with increased postoperative bleeding, transfusion, re-exploration rates, overall length of hospital stay and increased mortality (37,38). A recent large retrospective cohort study (39), with propensity scoring adjustment, compared the impact of recent (less than five days) versus no recent use of clopidogrel in 596 ACS patients undergoing CABG in 14 hospitals. Significant increases in major bleeding, reoperation and length of hospital stay were observed among the 298 patients in the early use group. A regression analysis showed clopidogrel use less than five days before CABG had the highest risk for both reoperation (OR 4.6) and major bleeding (OR 1.8). In contrast, a Canadian series of patients (40) undergoing urgent CABG (n=451) compared 189 patients who received clopidogrel within five days of CABG with a cohort of 262 patients who underwent urgent CABG and had never received clopidogrel, or had the drug stopped more than five days previously, and showed no significant difference in major bleeding or mortality. Another recent series (41) that included 332 patients who had received clopidogrel within five days before CABG also suggested that clopidogrel use was not associated with reoperation or a hematocrit drop of more than 15%. Clopidogrel use was modestly associated with the need for red cell transfusion, but other factors, including the experience of the surgeon, were more important. In an observational study (42), patients undergoing off-pump CABG who received clopidogrel had no increased bleeding compared with individuals who did not receive clopidogrel. However, those undergoing CABG with conventional cardiopulmonary bypass had significantly increased bleeding ($P<0.02$), transfusion requirement ($P<0.01$), intensive care ($P<0.03$) and hospital stays ($P<0.03$).

The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial investigators (43) examined the impact of upstream clopidogrel in patients with NSTE-ACS requiring CABG. Clopidogrel dosing and timing were left to the discretion of the investigator. Of the 1539 patients undergoing CABG (11.1% of total enrolled), 50.9% had received clopidogrel before surgery. Clopidogrel-exposed patients had fewer ischemic events (death, MI or unplanned revascularization: no clopidogrel 17.3%, clopidogrel 12.7%; $P<0.01$), yet no increase in major bleeding or transfusion requirements. Compared with the patients undergoing CABG within five days of receiving clopidogrel (67.8%), composite ischemic events were actually more frequent than in patients who had received clopidogrel more than five days before surgery (14.5% versus 8.8%, $P=0.03$). Blood transfusion was also more frequent in the patients undergoing CABG within five days of receiving clopidogrel (41.8% versus 31.3%). Because this study was a retrospective analysis of an unblinded nonrandomized subgroup, the conclusions are subject to the limitations of nonrandomized studies. However, the reduction of ischemic events in the group receiving clopidogrel before surgery does support the ACC/AHA guideline recommendation for upfront clopidogrel in patients with NSTE-ACS before cardiac catheterization.

The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry (44), with 264 hospitals enrolling 2858 patients, evaluated the patterns of clopidogrel use before CABG in community practice and the risks for postoperative transfusion among non-STEMI patients. In this registry, 30% of non-STEMI patients received clopidogrel within 24 h of hospital admission and almost 90% of these patients had CABG surgery within five days of receiving clopidogrel. Clopidogrel administration within five days of surgery was associated with a significant increase in blood transfusion and the need for four or more units of packed red blood cells. In contrast, increased bleeding was not observed if clopidogrel was discontinued more than five days before surgery. However, mortality rates were not significantly different in the patients who underwent either early CABG or delayed CABG after waiting for clopidogrel washout.

Systematic reviews and meta-analyses

A structured review (45) that included randomized controlled trials, prospective observational trials and retrospective trials concluded that clopidogrel exposure within seven days before CABG is associated with an increase in major bleeding, hemorrhage-related complications and transfusion requirements, and potentially leads to greater consumption of health care resources. Similar conclusions were reached from a meta-analysis of observational studies (46).

Summary

Randomized clinical trials suggest that patients undergoing CABG after receiving clopidogrel benefit from the anti-ischemic effects of the antiplatelet agent without an increase in life-threatening bleeding. However, both clinical trials and observational studies indicate that clopidogrel administered less than five days before surgery results in an increased incidence of major bleeding. The true impact of CABG-related bleeding associated with clopidogrel administration in the real world, especially in critically ill patients, is difficult to estimate.

IDENTIFICATION OF PATIENTS NEEDING CABG

If it were possible to predict which patients with ACS, at the time of presentation and before coronary angiography, will likely require urgent CABG, it might be possible to withhold clopidogrel in these patients. An ordinal risk score, developed from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis In Myocardial Infarction (TACTICS-TIMI 18) trial population and subsequently validated in the TIMI IIIb trial and TIMI III registry population (47), identified six multivariate parameters that were associated with a need for early revascularization by CABG in patients with high-risk non-STEMI ACS. Unfortunately, although the CABG risk score had a high (98.4%) negative predictive value, it suffered from poor (55%) sensitivity and would lead to denying treatment to a large group of patients for the possible benefit of a small minority who may require early CABG. Hence, this score cannot be considered clinically useful.

IMPACT OF CABG-RELATED BLEEDING

CABG-related bleeding and transfusion is more likely to occur in older individuals and those with low preoperative red blood volume (anemia or small body size), as well as those receiving antiplatelet or antithrombotic drugs, with congenital clotting disorders, undergoing reoperation, complex or emergency procedures, and with noncardiac comorbities. The need for blood transfusion (48), even with as little as one to two units, is associated with reduced early and late survival following surgery (49). Bleeding and the need for transfusion of red blood cells (especially older blood [50]) is associated with an increased risk for a wide range of postoperative morbid events including atrial fibrillation (51), renal failure (52), prolonged ventilatory support, serious infection (53), cardiac complications, neurological events (54) and prolongation of intensive care unit stay and hospital admission, and later reduction of quality of life (55). Each unit of red blood cells transfused is associated with an incrementally increased risk for adverse outcome (56). The need for perioperative transfusion is the single most predictive factor for the risk of subsequent postoperative morbid events (56). In addition, resternotomy for bleeding is a marker for increased mortality and morbidity (57,58).

SURGICAL CONSIDERATIONS IN PATIENTS RECEIVING CLOPIDOGREL WITHIN FIVE DAYS OF CABG

The ACC/AHA, the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists and the European Association of Cardiothoracic Surgeons guidelines all recommend, if clinical circumstances permit, that clopidogrel be withheld for five days before CABG surgery (level of evidence B). In patients who do not have very high-risk features, it is likely that the risks of bleeding outweigh the benefits of continuing dual antiplatelet therapy to prevent ischemic events. However, no clinical trial has evaluated the optimal timing of surgery in these patients. There is also considerable variability in both the overall platelet inhibitory response to clopidogrel and in the time taken for platelet activity to return to normal. Consequently, many patients may be able to undergo surgery safely before the usual five-day waiting period. Measurement of in vitro platelet function may, in the future, allow recognition of those at risk and select optimal treatment to prevent bleeding (59). This would ideally require a proven point-of-care platelet activity test, which can identify patients at risk of bleeding, as well as effective strategies to ameliorate risk and improve outcomes.

For patients who are at very high risk from recurrent ischemic events, CABG may have to be performed as an urgent procedure without discontinuing clopidogrel for five days. Patients with very high-risk features include those with:

- Recurrent refractory ischemia and associated ECG ST segment changes despite maximal medical treatment; and
- Very high-risk coronary artery anatomy such as the combination of severe left main coronary artery or proximal left anterior descending stenosis, and critical right coronary disease, especially following a recent ACS.

For patients with very high-risk features, delaying CABG for three to five days is usually not an option. Under these circumstances, surgical technique, anesthetic care and perioperative management need to be optimized to minimize the risks of bleeding and transfusion.

Meticulous surgical technique to ensure hemostasis is imperative. Adjunctive use of antifibrinolytic drugs (epsilon aminocaproic acid or tranexamic acid) improves hemostasis and reduces bleeding in high-risk patients. Preoperative anemia is also a risk factor for transfusion (60,61). While there is no evidence to show that preoperative transfusion for anemic patients improves outcomes, it should be considered in the patient with severe anemia (hemoglobin less than 90 g/L).

In high-risk patients undergoing CABG, platelet dysfunction is not only due to clopidogrel, but may also occur from contact with the extracorporeal cardiopulmonary bypass circuit or intra-aortic balloon pump. Observational data suggest that platelet transfusion, topical hemostatic agents and the use of beating-heart (off-pump) surgery by a surgeon experienced with the technique, to avoid the cardiopulmonary bypass machine, may reduce bleeding in these high-risk patients undergoing urgent surgery within five days of receiving clopidogrel. Transfused platelets should not be affected by previous clopidogrel use, unless surgery is performed within hours of drug administration. The active clopidogrel metabolite is short-lived (62) and it is likely that transfused platelets would be affected only during the first 1 h to 4 h after clopidogrel administration, while the drug is being absorbed and transformed to its active metabolite in the liver.

Surgeons are often concerned about the impact of loading doses of clopidogrel on platelet function. Studies show the levels of platelet inhibition achieved with a single loading dose of clopidogrel 300 mg are similar to those achieved with a daily treatment dose of 75 mg (63). Thus, there should be no greater concern for the impact of clopidogrel loading doses of 300 mg on bleeding than with the effect of maintenance doses of clopidogrel 75 mg daily. However, a 600 mg loading dose achieves both a faster and greater maximal level of platelet inhibition than a 300 mg dose (64).

Bridge to surgery when clopidogrel is withheld

For the patient with a recent ACS who has been stabilized on medical treatment, discontinuation of clopidogrel five days before CABG is the preferred strategy. During the period before surgery, it is recommended that most patients continue ASA 81 mg daily and heparin. Despite the high risk for serious ischemic events, patients with high operative bleeding risk (with previous CABG or in need of complex procedures, and with noncardiac comorbities) may be considered for 'bridging' antiplatelet therapy with an intravenous short-lived glycoprotein (GP) IIb/IIIa inhibitor (such as eptifibatide or tirofiban) to prevent recurrent ischemic events while waiting for surgery. In unstable patients, an intra-aortic counterpulsation balloon pump for 48 h to 72 h may stabilize the patient, if the perioperative bleeding risk of immediate CABG is considered to be too high.

For the patient who has received a bare-metal stent within the preceding four weeks or drug-eluting stent in the previous three to six months, sudden discontinuation of dual antiplatelet therapy substantially increases the risk for acute stent thrombosis. There is no proven method of protecting these patients should it be considered necessary to stop clopidogrel before CABG surgery. ASA should be continued to attempt to reduce the thrombotic risk (65). The use of low molecular weight heparin has also been suggested, but the rationale for replacing an antiplatelet agent with an anticoagulant in patients with a recent stent is uncertain (65). Furthermore, preoperative use of enoxaparin increases the risk of perioperative bleeding (66). Alternatively, a short-acting small molecule GP IIb/IIIa inhibitor (eptifibatide or tirofiban) can be used as a bridge to protect patients before surgery. The infusion can be discontinued hours before surgery without increased risk for intraoperative bleeding (67).

Restarting dual antiplatelet therapy post-CABG

The decision to reintroduce clopidogrel after CABG depends on the original indication for the agent (ACS, stent or cerebrovascular disease) and whether a stented vessel was surgically revascularized. Patients who have CABG after recent acute coronary events remain at risk for recurrent ischemic events (5). The CURE trial (5) and the analysis of the ACUITY trial (43) showed benefit in patients with recent ACS from dual antiplatelet therapy with clopidogrel and ASA revascularized by bypass surgery, over the long-term follow-up period. Patients can have both ASA and clopidogrel restarted postoperatively, as soon as hemostasis is achieved (68).

For patients who require warfarin after surgery (eg, with atrial fibrillation or mechanical valve), antiplatelet therapy should be individualized according to the evaluated bleeding risk and the potential benefit of triple antithrombotic therapy.

FUTURE DEVELOPMENTS

To improve the response to clopidogrel, loading doses of 600 mg and 900 mg have been advocated based on small studies (64). A 600 mg loading dose of clopidogrel followed by 150 mg daily for one week, compared with the standard dose of 300 mg followed by 75 mg daily, was shown in the CURRENT-OASIS 7 trial (69,70) to reduce the combined end point of cardiovascular death, myocardial infarction and stroke by 15% (hazard ratio 0.85 [95% CI 0.74 to 0.99]; P=0.036). Consequently, it is likely that the higher doses of clopidogrel will be more frequently used in patients with ACS. Newer antiplatelet agents that are rapidly converted to their active metabolite (eg, prasugrel), or that directly and reversibly inhibit the ADP P2Y12 receptor (eg, ticagrelor) are in advanced stages of clinical development.

Prasugrel is a more powerful and more rapidly active irreversible ADP antagonist than clopidogrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis In Myocardial Infarction (TRITON-TIMI 38) study (71) showed that prasugrel compared with clopidogrel, administered at the time of PCI in patients with a recent ACS, resulted in a 19% reduction of death/MI and stroke, as well as less frequent acute stent thrombosis. However, bleeding was increased by 32%, including a fourfold increase in fatal bleeding events. Patients with a history of stroke had a 37% increase in major bleeding events. For patients undergoing CABG, major bleeding was increased 4.7-fold (71). Ticagrelor, a reversible ADP receptor antagonist, not requiring metabolic conversion, and with greater in vitro platelet inhibition than clopidogrel, was recently shown in the PLATelet inhibition and patient Outcomes (PLATO) study (72) to reduce the composite end point of vascular death, MI and stroke by 16% compared with clopidogrel treatment. CABG was performed in 4.3% of the ticagrelor and 4.7% of the clopidogrel group during the index hospitalization, with no difference in major bleeding rates in the two groups. Platelet aggregation returns to 50% of normal within 24 h of discontinuing ticagrelor, making earlier CABG potentially safer than with clopidogrel.

These new antiplatelet agents, especially the more powerful irreversible agents such as prasugrel, will provide new challenges for the cardiac surgeon and anesthesiologist. Yet, a reversible and shorter-acting agent such as ticagrelor could potentially allow earlier surgery to be performed without any increase of bleeding risk.

RECOMMENDATIONS

1. All patients with ACS, despite the possibility of requiring urgent CABG, should be administered both ASA (initial dose 160 mg to 325 mg, maintenance dose 75 mg to 81 mg) and clopidogrel (initial dose 300 mg, maintenance dose 75 mg) at the earliest opportunity, unless contraindicated due to allergy or high overall bleeding risk.
2. For patients requiring CABG who have received preoperative clopidogrel, the timing of CABG should be determined by weighing the RRs of delaying surgery versus the risks of bleeding if surgery is performed within five days of clopidogrel administration.
   - Patients at high risk for an early, potentially fatal ischemic event (those with refractory ischemia despite optimal medical treatment, and with high-risk coronary anatomy (eg, severe left main stenosis with severe right coronary artery disease) should be considered for early surgery without discontinuation of clopidogrel.
   - Patients with a high bleeding risk (repeat CABG, complex surgery or bleeding diathesis) who are also at high risk for recurrent ischemic events may be best managed by discontinuing clopidogrel for three to five days before surgery. Heparin and a reversible intravenous GP IIb/IIIa inhibitor should be considered as bridge treatment before surgery.
   - Patients with recent ACS who are at a lower risk for recurrent ischemic events should have clopidogrel discontinued for five days before CABG. ASA and heparin should be continued until surgery.
3. For patients who have CABG within five days of receiving clopidogrel, the risk for major bleeding and transfusion, and its impact, can potentially be minimized by strategies that include:
   - Notification of transfusion medicine of the likely need for perioperative support (including availability of platelets);
   - Meticulous hemostasis;
   - Off-pump CABG (by a surgeon experienced with the technique);
   - Use of transfused platelets;
   - Antifibrinolytic agents (epsilon aminocaproic acid or tranexamic acid); and
   - Consider topical hemostatic agents.
4. Patients who have received clopidogrel pre-CABG for a recent ACS indication should have clopidogrel restarted after surgery to decrease the risk of recurrent ACS.
5. For patients with a recent coronary stent, the decision to continue clopidogrel until the time of surgery or discontinue for five days will depend on the risk and potential impact of stent thrombosis. Heparin or a reversible small molecule GP IIb/IIIa inhibitor may be used as a bridge to surgery. The decision to restart clopidogrel after CABG will depend on whether the stented vessel was revascularized, the type of stent and the time from stent implantation. Clopidogrel should be restarted after CABG surgery when hemostasis is assured.

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