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CURRENT OPINION

Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery

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Introduction

Coronary artery bypass grafting (CABG)-related bleeding complications and perioperative coronary events are strongly influenced by the management of antithrombotic therapy before and after CABG. Bleeding but also blood products transfusion increase the risk of death and compromise the long-term benefits of CABG.[1] The use of new $P2Y_{12}$ inhibitors, increasing pre-CABG percutaneous coronary interventions (PCI) with drug eluting stents (DES) requiring specific antiplatelet regimens, and advances in surgical technique has prompted the ESC Working Group on Cardiovascular Surgery and the ESC Working Group on Thrombosis to review the evidence of peri-CABG recommendations on antithrombotic management. Due to the paucity of randomized trials, most of the evidence is still derived from observational studies and expert consensus, further reinforcing the importance of a multidisciplinary consultation for optimal decision making.

Risks and benefits of preoperative exposure to antiplatelet therapy

Benefits of preoperative aspirin

Aspirin (acetylsalicylic acid, ASA) is recommended as secondary prevention therapy for all patients with proven coronary artery disease (CAD) and without contraindications. Its indication is even stronger for post-CABG patients (recommendation IA).[2] The general consensus is that ASA treatment withdrawal has ominous prognostic implications in patients with CAD, especially in those with intracoronary stents, and should be advocated only when the bleeding risk clearly outweighs that of atherothrombotic events.[3]

The benefits of continuing ASA until the day of CABG ('preoperative ASA') are less clear and may explain the wide variability in the management of ASA therapy in the perioperative period and differences between guidelines endorsed by different professional and scientific societies (Supplementary material online, *Table S1*). This was based on the demonstration that ASA started the day before surgery was no more effective than ASA started 6 h after surgery at improving early (7- to 10-day) graft patency, but was associated with increased bleeding complications.[4] More recent evidence suggests, however, that ASA use within 5–7 days prior to CABG halves mortality without significant increase in haemorrhage, blood product requirements, or related morbidities[5] and reduces late infarction and repeat revascularization.[6] Retrospective data show consistent benefit of preoperative aspirin within 5 days of surgery, including a reduction in cerebrovascular events and 30-day mortality.[7]

Risks of preoperative aspirin

Evidence that preoperative ASA increases the risk of transfusion, re-exploration rate, and chest tube drainage was derived from

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Table 1 Management of antiplatelet therapy before coronary artery bypass grafting surgery

Assessment of the risk of bleeding and ischaemia is recommended when making the decision of CABG surgery (whether with aspirin or DAPT).	I	C	
Low-dose ASA (75–160 mg daily) should be maintained in patients undergoing CABG surgery.	I	C	3,5,10
In patients with increased bleeding risk and in those who refuse blood transfusion, cessation of ASA 3–5 days before surgery is recommended based on individualized assessment of ischaemic and bleeding risks.	I	C	10,11
In patients on $P2Y_{12}$ inhibitors who need CABG, it is recommended to postpone surgery for 5 days after interruption of ticagrelor or clopidogrel, and 7 days for prasugrel, unless the patient is at high risk of ischaemic events	I	B	12,13

randomized controlled trials (RCTs) conducted in the late 80s when blood conservation and cardiopulmonary bypass (CPB) techniques were very different, such as little off-pump CABG surgery and higher aspirin ASA dosage.[8] More recent analysis still suggests an increase in blood loss and more frequent use of blood products in patients exposed to ASA within 7 days of surgery.[9] However, the underpowered nature of subanalyses precludes any strong recommendation on the time delay from ASA discontinuation to CABG in those at high risk of bleeding.[10] Aspirin interruption 3 days prior to CABG may be considered in patients at very high risk for bleeding after individualized assessment or in patients who refuse blood transfusions[11] (*Table 1*).

Overview of the net clinical benefit of dual antiplatelet therapy

Dual antiplatelet therapy (DAPT), the combination of ASA with a $P2Y_{12}$ inhibitor, namely clopidogrel, prasugrel, or ticagrelor (*Table 1*), has become the cornerstone of antiplatelet treatment before, during and after PCI, with significant reductions of stent thrombosis and ischaemic events compared with either aspirin alone or aspirin and anticoagulant drugs.[14–16] This combination increases the risk of major bleeding to an extent that appears to be associated with the degree of $P2Y_{12}$ inhibition achieved and all Phase 3 studies of $P2Y_{12}$ inhibitors vs. placebo or vs. clopidogrel, have excluded patients at high risk of bleeding. In the absence of contraindications, DAPT is currently recommended for 9–12 months following ACS based on evidence of enduring benefit over this time course in studies of clopidogrel, prasugrel, and ticagrelor.[14–17] There is no clear evidence for defining the optimal duration of DAPT after elective stenting. Indeed, none of the randomized trials were powered for ischaemic endpoints; all were open label and the time from stenting to randomization varied.[18–21] Therefore, weighing the quality of available evidence is difficult and these inferences need to be confirmed by ongoing mega trials. Usually, it is recommended to continue DAPT for 1 month after BMS implantation in stable angina,[22] 6–12 months after DES implantation in all patients,[22] and up to one 1 year in all patients after ACS, irrespective of revascularisation strategy.[23]

Coronary artery bypass grafting-related risk on Clopidogrel

Clopidogrel is a second-generation thienopyridine characterized by a large interindividual variability in pharmacodynamic response that has a significanct impact on clinical outcomes[24] (Supplementary material online, *Table S2*). This is because clopidogrel is a prodrug that requires biotransformation into its active metabolite.[25] Polymorphisms in genes encoding the cytochrome P450 (CYP) system, especially CYP2C19, are key players and clopidogrel-treated PCI patients who carry genetic variants associated with CYP2C19 loss-of-function have a three- to six-fold higher risk of stent thrombosis.[26] However, polymorphic variation in CYP2C19 explains <20% of the response variability with clopidogrel, leaving variation in bioactivation of clopidogrel largely unexplained. So far, there is no convincing evidence that genetic testing or functional platelet assays that measure platelet reactivity may improve clinical outcomes in clopidogrel-treated patients undergoing PCI.[27,28]

Observational studies

Observational studies have demonstated that the increase in postoperative chest tube drainage, transfusion, reoperation rates, hospitalization stay, and mortality observed when DAPT (aspirin and clopidogrel) is maintained during CABG[29–37] is blunted when DAPT is stopped 5 days or more prior to CABG.[38,39] Shorter windows of clopidogrel interruption have been suggested but time delay alone does not solely account for the difference in the observed magnitude of clopidogrel effect on bleeding. Differences in patient response to $P2Y_{12}$ inhibitors, outcome definitions, transfusion triggers, use of antifibrinolytics, and surgeon-related factors may have been sources of bias. Few studies have reported on ischaemic event rates in ACS patients waiting for CABG. In the CURE trial, patients exposed to clopidogrel had a non-significantly lower MACE rate than the placebo group (2.9 vs. 4.7, 1.8% ARR, RR: 0.56, 95% CI: 0.29–1.08).[40] Overall, current evidence suggests that clopidogrel should be stopped 5 or more days prior to CABG to avoid bleeding complications that may increase perioperative mortality except if there is uncontrolled ischaemia (*Table 1*).

Meta-analysis data

Higher blood loss, transfusion, and reoperation rates associated with pre-CABG clopidogrel exposure <5 days have been confirmed by five meta-analyses[41,42] (Supplementary material online, *Table S3*). Mortality is increased in observational studies except in patients with ACS,[12,13] although patient status (stable vs. ACS), type of surgery (urgent vs. elective), and the absence of appropriate study matching may confound the effect of recent clopidogrel exposure (*Table 2*). Importantly, discontinuation of clopidogrel for 5–7 days before operation does not seem to confer increased cardiac risk.

Coronary artery bypass grafting-related risk on prasugrel

Prasugrel is the third generation oral thienopyridine with faster onset and a more consistent irreversible platelet $P2Y_{12}$ blockade than the second-generation oral thienopyridine clopidogrel. This pharmacodynamic advantage over clopidogrel translated into a 19% relative risk reduction in ischaemic events in ACS patients undergoing PCI

Table 2 Bridging therapies and platelet function monitoring

The risks of bleeding and thrombosis and decision-making regarding DAPT and timing of surgery should be assessed by the heart team prior to CABG surgery	I	C	
Bridging with cangrelor, if available, is recommended in high-risk patients	I	B	43
Bridging with short-acting intravenous GPIIb/IIIa inhibitors may be considered in patients at high risk for ischaemic events	IIb	C	44
It is reasonable to base timing of surgery on **platelet function monitoring** rather than arbitrary use of a specified period of delay in patients on DAPT.	IIa	B	45

at the expense of increased major and fatal bleeding[15,46] (Supplementary material online, *Table S2*). Prasugrel (60-mg loading dose, 10-mg daily dose) in addition to aspirin is recommended over clopidogrel in $P2Y_{12}$ inhibitor-naïve ACS patients undergoing PCI with no history of prior stroke/TIA and in whom coronary anatomy is known.[23,47] A lower maintenance dose of 5 mg is recommended in patients <60 kg or >75 years.[48] In the TRITON-TIMI 38 study, a total of 368 (2.7%) ACS patients received at least one dose of study medication and subsequently underwent CABG surgery out of a total of 13 608 patients.[49] Despite an increase in observed TIMI major bleeding (OR: 4.73, CI: 1.9–11.8), platelet transfusion and surgical re-exploration for bleeding, prasugrel was associated with a lower rate of death after CABG compared with clopidogrel (2.3 vs. 8.7%; OR_{ad} 0.26; $P = 0.025$). More than 60% of patients received the last dose of study medication 5 or more days prior to CABG surgery, with the imbalance in the number of deaths attributable to patients who received last dose of study medication 4 or more days prior to surgery. It is recommended to discontinue prasugrel 7 days prior to CABG surgery, but it is also recognized that the level of platelet inhibition during prasugrel maintenance therapy tends to be less and more variable than in the days following a loading dose,[50,51] raising the question as to whether platelet function testing may be useful under some circumstances to guide timing of cessation prior to surgery.

Coronary artery bypass grafting-related risk on ticagrelor

Ticagrelor is a direct-acting and reversible inhibitor of the $P2Y_{12}$ receptor and is additionally an inhibitor of adenosine reuptake (Supplementary material online, *Table S2*). Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with clopidogrel leading to a better outcome in ACS patients, irrespective of revascularization strategies, including a mortality benefit.[16] Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy and including those pretreated with clopidogrel.[23,47] In addition, it has a more rapid and consistent offset of action related to its reversible receptor binding and plasma half-life of 6–12 h.[52] In patients with stable CAD, recovery of platelet aggregation is almost complete at 5 days after cessation of ticagrelor, with substantially more recovery than seen with good responders to clopidogrel.[53] For patients in the PLATO study who underwent CABG surgery within 7 days of the last dose of study medication, there was evidence of early mortality reduction in the ticagrelor group and this was accounted for by fewer deaths associated with bleeding and infection as well as ischaemic events (4.6 vs. 9.2%; $P = 0.0018$).[54,55]

The strategies to reduce bleeding during CABG surgery have been added as Supplementary material online, *Table S5*.

Risk stratification, bridging therapies, and platelet function monitoring

The need for urgent CABG on DAPT arises in ACS patients or after recent stent PCI. In the absence of robust evidence from RCTs, the key issues are[(i)] individual risk stratification of bleeding vs. ischaemia according to patient clinical characteristics and[(ii)] time interval from treatment interruption to CABG with or without bridging therapy.

Risk stratification

In urgent CABG indications, exposure to the full effect of DAPT may lead to increased major bleeding, a complication that is associated with poor outcome due to haemodynamic instability, need for reoperation, or red blood cell transfusion-related inflammation and ischaemia.[56] Red blood cell transfusion during CABG is associated with a two-fold increase in 5-year mortality rates and with significantly more frequent sternal wound infection, severe sepsis, and renal dysfunction.[1,57,58]

Risk factors for increased perioperative bleeding and transfusion during CABG have been identified:[(i)] upstream antithrombotic therapy,[(ii)] patient nongenetic factors (age, female gender, small body size, preoperative anaemia, and comorbidities including COPD, liver disease, cardiac failure, and renal insufficiency),[(iii)] patient genetic factors (variability in clopidogrel response, hereditary deficiencies in coagulation factors/platelet function), and[(iv)] surgical factors (complex/redo procedures, urgent/emergent procedures).[45,59,60] However, there is no easy-to-use scoring system available and the surgeon performance is not taken into account, although it has been shown to be of importance.[61] In addition, although severity of CAD, clinical presentation, and patient co-morbidities may assist in risk stratification for ischaemic events, no available scoring systems for ACS presenters undergoing PCI or medical management have ever been tested in CABG-eligible patients. It appears reasonable to recommend the use of scores which encapsulate the common comorbidities of the CABG-eligible population to better risk stratify (*Table 1*). The combination of the GRACE and the CRUSADE risk scores appears relevant in such context.

Premature interruption of DAPT is the most important risk factor for early stent thrombosis.[62–64] In addition to comorbidities (diabetes, renal failure), the initial clinical presentation, stent length, stent undersizing, complex and/or bifurcation lesions, coronary dissection, genetic factors influencing clopidogrel metabolism,

and high platelet reactivity have all been associated with stent thrombosis.[65,66]

Bridging therapy and timing of cessation

Time delay from oral antiplatelet treatment cessation to coronary artery bypass grafting surgery

The rate of ischaemic events occuring from $P2Y_{12}$ inhibitor interruption prior to CABG has never been estimated precisely and the safety of delaying surgery to allow for the washout of $P2Y_{12}$ inhibitors is uncertain. As a consequence, the time delay from $P2Y_{12}$ inhibitor interruption to CABG is best determined by multidisciplinary clinical judgment based on risk assessment and pharmacodynamic studies.[22,23,47,50,52,53]

Bridging therapies

Bridging may provide an optimal platelet inhibition up to the day of CABG surgery using short-acting drugs started after oral $P2Y_{12}$ inhibitor interruption several days before (*Table 2*). This may prevent not only ischaemic events between discontinuation of $P2Y_{12}$ inhibitors and surgery but also bleeding events or the use of transfusion. The intravenous (i.v.) GPIIb/IIIa antagonists eptifibatide and tirofiban were studied in ACS patients eligible for CABG surgery and in whom coronary stents were recently implanted.[44] These feasability studies demonstrated that a 'bridging strategy', using i.v. tirofiban in patients with a recently implanted DES and high-risk characteristics for stent thrombosis needing urgent surgery, allowed temporary withdrawal of oral clopidogrel without increasing the risk of perioperative bleeding.

Cangrelor, a non-thienopyridine adenosine triphosphate analogue, is an i.v. antagonist of the $P2Y_{12}$ receptor characterized by rapid, potent, predictable, and reversible platelet inhibition with rapid offset of effect[67] (Supplementary material online, *Table S1*). It has been demonstrated to reduce the rate of ischaemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding as compared with oral clopidogrel in patients not pretreated prior to randomization at the time of PCI.[68] In the BRIDGE trial, the use of cangrelor compared with placebo maintained platelet inhibition in patients who discontinued thienopyridine therapy prior to cardiac surgery.[43] Excessive CABG surgery-related bleeding occurred in 11.8 (12 of 102) vs. 10.4% (10 of 96) in the cangrelor and placebo groups, respectively (RR: 1.1 [95% CI: 0.5–2.5]; $P = .763$). There were no significant differences in major bleeding prior to CABG surgery. Cangrelor is not yet approved for bridging in CABG patients, nor for any other indication, but it has been submitted to FDA and EMA.

Platelet function monitoring

The interindividual variability in pharmacodynamic response to clopidogrel leads to variability in the time taken to recover normal platelet reactivity following cessation of clopidogrel.[50] This is important because several studies have shown that the level of platelet reactivity at the time of surgery can predict the risk of CABG-related bleeding.[69–71] Although bedside platelet function testing has not, so far, been successful in guiding antiplatelet therapy during PCI to prevent ischaemic events,[27,28] treatment monitoring using bedside testing has been suggested as an option to guide treatment interruption rather than arbitrary use of a specified period of delay.[72] Platelet inhibitory response to clopidogrel determines CABG-related bleeding and a strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients led to ≈50% shorter waiting time than recommended in the current guidelines.[72] For these reasons, the 2012 Update of the Society of Thoracic Surgeons Guideline suggested that a delay of even a day or 2 is reasonable to decrease bleeding and thrombotic risk in ACS patients.[73] Point-of-care monitoring of platelet aggregation or whole-blood clot properties is associated with reduced perioperative bleeding and ischaemic complications especially during off-pump CABG surgery.[69,70] Bedside platelet function testing has been evaluated during clopidogrel exposure but might also be useful in prasugrel- or ticagrelor-treated patients, as recently shown for prasugrel.[71] A proposed strategy for preoperative management of $P2Y_{12}$ inhibitors and bridging is shown in *Table 3*. When the bleeding risk is low, short timing of cessation of $P2Y_{12}$ inhibitors prior to CABG surgery is encouraged in addition to bridging therapies that should be used when the thrombotic risk appears high. Platelet function testing may be used when the bleeding risk is low and the thrombotic risk is low. Evidence for PFT is derived from a single randomized study that was performed without point-of-care assay[72] and the interpretation of high platelet reactivity in patients at risk for bleeding remains unclear.

Table 3 Proposed strategies for discontinuation of $P2Y_{12}$ inhibitors prior to coronary artery bypass grafting surgery

		Bleeding risk	
		High[a]	**Low**
Thrombotic risk	High[b] ACS or recent stent PCI	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 5 days before and bridge for 4 days. Prasugrel: stop 7 days and bridge for 5 days	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 3 days before and bridge for 2 days. Prasugrel: stop 5 days before and bridge for 3 days
	Low	Early Heart Team Consultation Clopidogrel/ticagrelor: stop 5 days before. Prasugrel: stop 7 days prior to CABG	Clopidogrel/ticagrelor: stop 5 days before or less if indicated by platelet function test. Prasugrel: stop 7 days before or less if indicated by platelet function test.

[a]Examples of high-bleeding risk: renal or hepatic insufficiency, advanced age, anaemia, small body surface area, cardiac failure, and redoes operation.
[b]Examples of high-thrombotic risk: haemodynamic instability, ongoing ischaemia, complex coronary anatomy, stenting <1 month for BMS, and <6 months for DES.
CABG, coronary atery bypass grafting.

Table 4 Resuming antiplatelet therapy after coronary artery bypass grafting surgery

ASA 75–160 mg/day should be restarted within the first 24 h and preferably within 6 h after CABG surgery and maintained lifelong.	I	B	74–76
In case of aspirin intolerance or contraindication, a loading dose of clopidogrel 300 mg as soon as bleeding is controlled followed by 75 mg/day is recommended lifelong.	I	C	
DAPT with clopidogrel may be considered to be (re-) started after CABG surgery for stable CAD patients as soon as considered safe.	IIb	C	77,78
For patients who undergo CABG within 1 year of ACS, resumption of $P2Y_{12}$ inhibitor should be considered as soon as bleeding is controlled.	IIa	B	54,55
A 300 mg clopidogrel loading dose as soon as bleeding is controlled followed by a 75 mg clopidogrel maintenance dose in addition to aspirin is recommended in stable CAD patients with coronary stent in non-grafted territories for the duration intended following stent implantation.	I	C	77

Postoperative management of antiplatelet therapy

Single antiplatelet therapy

Early thrombosis is the major cause of vein graft attrition during the first month after CABG, with occlusion rates of between 5 and 26% at 1 year, and ASA has been shown to improve 1-year vein graft patency.[74–76] The role of ASA in graft patency becomes substantial when initiated prior to CABG and then restarted ~6 h after surgery.[76] The beneficial effect of ASA on vein graft patency appears attenuated after the first year due to lack of effect on intimal hyperplasia and vein graft atherosclerosis. Although there is no evidence for an effect of ASA on long-term internal mammary artery graft patency, it should be continued indefinitely after CABG given its benefit in preventing subsequent clinical events (*Table 4*).[3] Medium doses of ASA (300–325 mg daily) have not been shown to be more effective than low doses (75–160 mg daily) in preventing graft occlusion and adverse clinical events, although an indirect meta-analysis provided weak evidence that medium doses might be more effective.[79] Inhibition of platelet function by ASA may be impaired after CABG, with or without CPB, in one-third of patients, due to reduced absorption, drug interactions, systemic inflammation, and increased platelet turnover, and these factors may increase the risk of graft occlusion early after CABG.[80,81] This phenomenon is transient and may be addressed by early intravenous or rectal administration followed by oral twice-daily administration early postoperatively.[82] In case of ASA intolerance, clopidogrel is indicated for prevention of ischaemic events.[83]

Dual antiplatet therapy after Coronary artery bypass grafting surgery

Observational studies have demonstrated the safety of early postoperative clopidogrel use following CABG but a meta-analysis of studies reporting on safety/efficacy of clopidogrel use with or without aspirin did not show a clear clinical benefit of clopidogrel when given in addition to aspirin after CABG.[84,85] Several randomized trials have compared the effect of DAPT vs. aspirin on graft patency with diverging results.[86–89] Two meta-analyses of observational studies and RCTs showed that the use of DAPT reduced early vein graft occlusion.[77,78] The meta-analysis by Deo *et al.* also showed, in the ASA-clopidogrel group, a decrease in hospital or 30-day mortality (0.8 vs. 1.9%, $P < 0.0001$) compared with ASA alone and this effect was more pronounced in off-pump patients.[77]

The effects of prasugrel have not yet been studied following CABG surgery but the mortality data from TRITON is supportive of resuming prasugrel following CABG surgery (adj OR: 0.26; 95% CI: 0.08–0.85; $P = 0.025$).[49] In the PLATO study, it was intended that study medication with ticagrelor or clopidogrel should be started as soon as possible after CABG surgery and prior to hospital discharge. Thirty-six percent of CABG patients in the study restarted study medication within 7 days of surgery, 37% did not restart study medication and the rest restarted study medication 7 or more days later. Postoperative mortality was lower in the ticagrelor group compared with the clopidogrel group (HR: 0.49; 95% CI: 0.32–0.77).[54] It is uncertain how much of the benefit of ticagrelor compared with clopidogrel related to preoperative compared with postoperative treatment and further studies will provide more evidence in this area.

Conclusions

Antiplatelet therapy plays a major role in the treatment of CAD and is therefore implicated throughout the CABG pathway. Management of single and DAPT in patients undergoing CABG for ACS, previous PCI, or stable angina impacts on early and late outcomes. Risk stratification for bleeding and recurrent ischaemic events, heart team decision making for temporary interruption of antiplatelet therapy and bridging strategies, the use of platelet function monitoring, and blood sparing management strategies are the key steps to further improve clinical outcome in patients undergoing CABG surgery. Gaps in knowledge remain, especially with respect to identification of the optimal bleeding-thrombotic risk balance before and after surgery. Specific studies for patients undergoing CABG are mandatory.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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