

Peri-operative management of antiplatelet therapy in patients with coronary artery disease

Joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (ÖGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC)

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Summary

An increasing number of patients suffering from cardiovascular disease, especially coronary artery disease (CAD), are treated with aspirin and/or clopidogrel for the prevention of major adverse events. Unfortunately, there are no specific, widely accepted recommendations for the perioperative management of patients receiving antiplatelet therapy. Therefore, members of the Perioperative Haemostasis Group of the Society on Thrombosis and Haemostasis Research (GTH), the Perioperative Coagulation Group of the Austrian Society for Anesthesiology, Reanimation and Intensive Care (ÖGARI) and the Working Group Thrombosis of the European Society of Cardiology (ESC) have created this consensus position paper to provide clear recommendations on the perioperative use of anti-platelet agents (specifically with semi-urgent and urgent surgery), strongly supporting a multidisciplinary approach to optimize the treatment of individual patients with coronary artery disease who need major cardiac and non-cardiac surgery. With planned

surgery, drug eluting stents (DES) should not be used unless surgery can be delayed for ≥ 12 months after DES implantation. If surgery cannot be delayed, surgical revascularisation, bare-metal stents or pure balloon angioplasty should be considered. During ongoing antiplatelet therapy, elective surgery should be delayed for the recommended duration of treatment. In patients with semi-urgent surgery, the decision to prematurely stop one or both antiplatelet agents (at least 5 days pre-operatively) has to be taken after multidisciplinary consultation, evaluating the individual thrombotic and bleeding risk. Urgently needed surgery has to take place under full antiplatelet therapy despite the increased bleeding risk. A multidisciplinary approach for optimal antithrombotic and haemostatic patient management is thus mandatory.

Keywords

Antiplatelet agents, surgery, atherothrombosis, coronary syndrome, atherosclerosis

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Introduction

An increasing number of patients who are suffering from or are at risk for cardiovascular disease, especially coronary artery disease (CAD), is treated with aspirin or clopidogrel for the prevention of major adverse events. In congruence, the number of patients that receive percutaneous coronary intervention (PCI) with stent implantation continues to increase and therefore, the need for treatment with dual antiplatelet therapy (usually aspirin plus clopido-

grel) is also augmented. In addition, an increased use of new and possibly more effective antiplatelet agents, e.g. prasugrel or ticagrelor, can be expected in the near future (1, 2). At present, 6–8% of patients with dual antiplatelet therapy also need oral anticoagulation with vitamin K antagonists (VKA) due to atrial fibrillation, mechanical heart valves or a history of venous thromboembolism. Given these facts, physicians nowadays face situations in which the peri-operative bleeding risk has to be balanced against the individual risk of thrombotic complications. Although the pathophysiol-

ogy underlying peri-operative cardiovascular events remains to be completely elucidated, it is well known that inflammatory, hypercoagulable and hypoxic states are associated with plaque instability and peri-operative arterial thrombosis. Increased coronary shear stress after stress hormone release can lead to consecutive platelet activation, thus further adding to the risk for acute coronary thrombosis (3). On the other hand, platelet inhibition reduces inflammatory marker expression (4).

These considerations highlight that peri-operative platelet inhibition may prevent cardiovascular events, especially CAD-related events. Unfortunately, there are no specific, widely accepted recommendations for the peri-operative management of patients receiving antiplatelet therapy.

Accordingly, the authors, all experts in cardiology, anesthesiology and haematology as well as members of three different working groups from three different societies, have written this position paper, based on the available evidence.

Antiplatelet therapy in patients at risk for or with known cardiovascular disease

Bleeding risk of antiplatelet therapy in the peri-interventional setting

Most studies and meta-analyses describe an increased risk of peri-operative blood loss and transfusions of blood products with the peri-operative use of aspirin (5–9), but one recent small trial suggests possible benefits (10). A large study in hip surgery found aspirin to reduce thromboembolic events but at a cost of a modest increase in bleeding complications (11). Bleeding complications in some types of surgery, e.g. dermatologic or ophthalmologic surgery (12), are usually not increased. In a meta-analysis, aspirin did not increase the severity of bleeding complications (with the exception of intracranial surgery and transurethral prostatectomy) but bleeding episodes were more frequent (13). It is unclear whether different aspirin doses might alter the frequency or the intensity of bleeding complications (14, 15).

The increased blood loss associated with peri-operative aspirin use in coronary artery bypass grafting with or without valve surgery can be counteracted by the use of antifibrinolytics (16); and first evidence exists from a very large, randomised and placebo-controlled trial that antifibrinolytic therapy is also beneficial in non-cardiac surgery patients with interventions such as trauma patients (17). Alternatively, it is likely that the use of platelet concentrates might lead to a similar effect, but there are no prospective trial data available and there is thus need for further research.

Dual antiplatelet therapy and peri-operative bleeding risk

Concerns on peri-operative bleeding still lead to premature discontinuation of antiplatelet therapy pre-operatively in daily prac-

tice. However, despite the increased risk for oozing and diffuse haemorrhage, the transfusion rate in patients with or without dual antiplatelet therapy was not found to be significantly different in three different studies in general surgery (18–20). In contrast, significant increases in major bleeding (odds ratio [OR] 1.8; 95% confidence interval [CI] 1.1 – 3.0) and re-operation (OR 4.6; 95% CI 1.4 – 14.5) were seen in patients with acute coronary syndromes (ACS) requiring coronary artery bypass graft (CABG) with cardiopulmonary bypass (21). Excess major bleeding (with or without CABG [22, 23]) and blood product use (in patients undergoing CABG [6, 23]) were also demonstrated if clopidogrel was not stopped at least five days before the intervention. On the other hand, no significant increase of bleeding complications was described despite continuation of dual antiplatelet therapy in patients with ACS and off-pump bypass surgery (24); this might therefore be a preferred method of surgical therapy in this very specific patient population on dual antiplatelet therapy. However, if additional thromboprophylaxis is given in patients undergoing various cardiosurgical procedures while on continuous mono- or dual antiplatelet therapy, an increased periprocedural bleeding risk is to be observed (25, 26).

As mentioned above, the peri-operative bleeding risk is related to the type of surgery: minor surgical interventions like dental procedures, cataract surgery, dermatologic operations, as well as angiographic diagnostic procedures or diagnostic endoscopies can apparently be performed under full anti-platelet therapy if no additional bleeding risks exist. A clear increase in haemorrhagic risk with dual antiplatelet therapy, however, has to be acknowledged in vascular, visceral and transbronchial surgery (27–29).

In patients on dual antiplatelet therapy undergoing any type of semi-urgent or urgent surgery, stopping antiplatelet therapy will not reduce platelet inhibition in a timely manner and multidisciplinary preparations for potential haemorrhagic complications should be undertaken. The pharmacokinetics of the respective platelet inhibitor used should be taken into consideration if platelet transfusion is planned.

Primary prophylaxis

Observations suggesting a preventive effect of aspirin on the occurrence of cardiovascular disease date back to the 1970s (30). The Physician's Health Study reported a highly significant 44% reduction in the risk of myocardial infarction (MI) for aspirin users along with a two-fold increased risk of haemorrhagic stroke, but no reduction in overall cardiovascular mortality or first time occurrence of angina (31). Risk reduction for MI occurred primarily in patients 50 years and older, but a risk increase for gastric ulcers and the need for blood transfusions was also seen (32). A cohort study in nurses confirmed the risk reduction for MI with primary prophylaxis in women (33).

The Thrombosis Prevention Trial was performed in a general practitioner's setting and evaluated aspirin and/or VKA (placebo controlled) for primary prevention of ischaemic heart disease (coronary death plus MI). Warfarin (all arms) reduced ischaemic heart disease by 21%, mainly by reducing fatal events. Aspirin (all arms)

reduced ischaemic heart disease by 20%, almost entirely by reducing non-fatal events. The combination of warfarin and aspirin reduced ischaemic heart disease by 34% compared to placebo alone, but also increased haemorrhagic and fatal strokes (34). A recent review of the literature suggests that primary prevention with aspirin reduces the risk for MI in men and stroke in women, while increasing the risk for (predominantly gastrointestinal) serious bleeding events; aspirin in primary prevention does not seem to affect cardiovascular mortality or all-cause mortality in either men or women (35).

Benefits of aspirin use for primary prevention are not equally distributed but depend on various patient characteristics, e.g. the degree of the vasculopathic process (36) and the presence of hypertension (37) or diabetes (38, 39). A certain prothrombotic effect through cyclooxygenase-2 inhibition after aspirin withdrawal has recently been postulated (40). Moreover, primary prevention data for aspirin from one country might not be easily applied to other countries, as shown for the US and Japan (41). And the peri-operative use of aspirin is associated with an increased bleeding risk (see above). Therefore, there are insufficient data supporting the efficacy and safety of antiplatelet drugs for primary prevention (42, 43). A large randomised controlled trial, currently underway, will hopefully help to answer the question on platelet inhibition for the primary prevention of cardiovascular events (44).

Given the above data, primary prevention with aspirin seems to have its place in patients with identifiable risk factors for cardiovascular disease, while at the same time the peri-operative use of aspirin is associated with increased bleeding hazards. Therefore, the US Preventive Services Task Force recommends to use aspirin for primary prophylaxis only in men between 45 and 80 years of age for MI prevention and in women between 55 and 80 years of age for stroke prevention (35, 45).

As the peri-operative use of aspirin is associated with increased blood loss and blood product use and as patients undergoing primary prophylaxis show no manifestation of any cardiovascular disease, this expert group suggests that aspirin given for primary prevention should be stopped 5–7 days before any type of surgery (46, 47). Further trials are required in order to confirm or refute this recommendation in the future.

Secondary prophylaxis

The German-Austrian Study Group has shown many years ago in a placebo-controlled prospective trial that platelet inhibition with high-dose aspirin (1,500 mg/day) as compared to oral anticoagulation is of benefit to prevent recurrent MI, specifically in male patients (48). A double-blind randomised trial with aspirin or placebo in patients with stable angina showed a clear benefit for the prevention of MI and sudden death (49). Moreover, a subgroup analysis from the Physician's Health Study showed a similar benefit of aspirin on the progression of CAD in patients with stable angina (50).

In line with these observations, an extensive meta-analysis on discontinuation or non-adherence to aspirin therapy indicated an increased risk for cardiovascular events (OR 3.1, 95% CI 1.7–5.6), especially in patients undergoing PCI with stent implantation (OR 89.8, 95% CI 29.9–269.6) (51).

Data from a registry suggest that a considerable proportion of patients leaving the hospital after a MI have not received aspirin in the past, which in turn was associated with a high degree of cardiovascular morbidity and mortality within one year of follow-up (52).

Based on these data from trials and meta-analyses, aspirin or clopidogrel monotherapy (53) have favourable effects in preventing major adverse events in secondary prophylaxis of CAD; at the same time, the peri-operative bleeding rate and blood loss are increased in coronary bypass and orthopaedic surgery (5–8, 11). Interpretation of data on clopidogrel monotherapy in non-cardiac surgery is not trivial due to the small cohort sizes, heterogeneity of procedures, and absence of clear control groups (54).

In summary, there is likely a favourable peri-operative benefit-to-risk profile for antiplatelet monotherapy (aspirin or clopidogrel) in secondary prevention with the exception of specific types of surgery and situations where the additional bleeding implies an important risk to the patient.

This expert group therefore recommends the continuation of aspirin (or clopidogrel) monotherapy for secondary prevention during most types of surgery. Only in patients undergoing surgical procedures in areas of closed space (e.g. intracranial neurosurgery, posterior chamber of the eye, medullary canal etc.) or when major bleeding complications are to be expected, stopping monotherapy with aspirin or clopidogrel 5–7 days pre-operatively should be evaluated on a case by case basis. Further clinical trials are warranted.

Dual antiplatelet therapy following stent implantation in stable coronary artery disease and in acute coronary syndromes

The guidelines of international cardiologic societies (ACC/AHA and ESC) (55–58) recommend dual antiplatelet therapy for a period of four (to six) weeks in patients undergoing elective PCI with bare-metal stents (BMS); 12 months are recommended when drug-eluting stents (DES) are used. Twelve months of dual antiplatelet therapy are also recommended after ACS, i.e. non ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), no matter which type of therapy was applied (conservative treatment, reperfusion therapy with PCI ± stenting, or pharmacologic reperfusion with thrombolytic agents); the optimal duration of antiplatelet therapy is still under discussion and investigation (59, 60).

"Triple" antithrombotic therapy following stent implantation

The working group on thrombosis of the European Society of Cardiology (ESC) together with the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) has recently commented on the management of antithrombotic therapy in atrial fibrillation patients after stent implantation, who need both, dual antiplatelet therapy and anticoagulation (61). The authors advocate a restrict-

ive use of DES in patients who require anticoagulation with VKA i.e. patients with atrial fibrillation and a CHADS₂ (Cardiac Failure, Hypertension, Age, Diabetes, Stroke_[doubled]) score (62) of >1. "Triple" therapy is recommended for different time intervals based on the type of stent used and the individual risk of the patient for thrombotic and bleeding complications; this „triple“ therapy is then followed by combined antithrombotic treatment (VKA plus aspirin or clopidogrel) for up to 12 months. Most importantly, if VKA is combined with clopidogrel and/or aspirin, the target international normalized ratio (INR) should be 2.0–2.5, with careful monitoring in short time intervals (41).

Risk of premature discontinuation of antiplatelet therapy and overall thrombotic risk after coronary stenting

Although reasons for the development of stent thrombosis are multifactorial, premature discontinuation of antiplatelet therapy has been found to be the most important risk factor after implantation of BMS (54) as well as DES (63). Surgical interventions were the reason for premature discontinuation of therapy in about 30–40% of patients (63). In patients with coronary stents and a variety of elective non-cardiac surgery within one year of stenting, the major adverse event rate was very high (45%) and mainly due to cardiac events. This was despite the fact that patients were continued on or only very briefly interrupted (< 3 days before surgery) antiplatelet therapy plus regular peri-operative venous thromboprophylaxis with heparins; the risk for adverse events doubled if surgery was performed less than 35 days after stenting (64). Besides early discontinuation of dual antiplatelet therapy, different clinical and angiographic factors contribute to an increased risk for the development of stent thrombosis: advanced age, co-morbidities like diabetes, renal dysfunction, low ejection fraction, and ACS; coronary stenting in specific situations like multiple lesions, long lesions, bifurcations and ostial lesions; suboptimal stent deployment and overlapping stents (58). In addition, a reduced response to clopidogrel therapy is an important predictor of adverse outcome including stent thrombosis (65–67), suggesting that individualised therapy using specific devices might be advantageous (68–71).

Recommendations regarding premature discontinuation of antiplatelet therapy

Based on the subsequent risk of stent thrombosis and its potential consequences (MI, cardiovascular death) after premature discontinuation of antiplatelet therapy, especially in patients with DES, the ACC/AHA Science Advisory Panel recommends a) to avoid DES in patients likely not to comply with 12 months of thienopyridine therapy; b) that patients in need for elective surgery within 12 months of PCI be considered for BMS or balloon angioplasty; c) that patients be adequately informed and educated on the importance of thienopyridine therapy; d) that healthcare providers only discontinue antiplatelet therapy after discussion with the patients'

cardiologist; e) that patients need to undergo a minimum of one month of thienopyridine treatment after BMS or 12 months after DES implantation; d) that aspirin be continued in patients with DES undergoing procedures that require discontinuation of thienopyridines; and that thienopyridines be restarted as soon as possible; and e) that drug costs should not lead to early discontinuation of thienopyridine therapy (72). Similar recommendations exist from other multidisciplinary boards (73).

Our group suggests that elective surgery be deferred until dual antiplatelet therapy is no longer necessary. In patients under dual antiplatelet therapy requiring closed space surgery (e.g. intracranial neurosurgery, posterior chamber of the eye, medullary canal) or other interventions associated with an increased haemorrhagic risk, stopping clopidogrel 5–7 days pre-operatively while continuing aspirin therapy should be considered. The group also suggests that short-term peri-operative venous thromboprophylaxis (unfractionated heparin or low-molecular-weight heparin [LMWH]) should only be started after the surgical procedure. If semi-urgent or urgent surgery is necessary, potential haemorrhagic complications and therefore the potential need for the respective management and therapy (such as multidisciplinary consulting, platelet transfusion and/or other pro-coagulant interventions, monitoring in a critical care environment, possibility for onsite cardiovascular intervention or transfer etc.) must be anticipated.

Peri-operative "bridging" of antiplatelet therapy

Neither unfractionated heparin nor LMWH can provide the antiplatelet effects associated with the use of clopidogrel and/or aspirin. If full antiplatelet therapy is required until the time of surgery but aspirin and/or clopidogrel cannot be used, the short-acting platelet antagonists eptifibatid (74) or tirofiban (75) might be considered up to a few hours before surgery as a „bridging“ therapy. These protocols have been successfully used in small patient series (75), but there is currently no controlled evidence to support their use. Therefore, future research should address the question how to best manage high-risk patients under antiplatelet therapy in the immediate peri-operative period.

New antiplatelet drugs and new anticoagulants

The European Medicines Agency (EMA, EMA) approved prasugrel, a third generation thienopyridine, in late February 2009. The possible advantages of the irreversible adenosine diphosphate (ADP) receptor blocker prasugrel over clopidogrel include a faster onset of action, a more potent platelet inhibition (76), as well as less inter-individual variability of action of the agent. In patients with ACS and scheduled PCI, the use of prasugrel as compared to clopidogrel is associated with a lower event rate but a higher rate of clinically relevant bleeding (1). Ticagrelor is an oral, reversible and also more potent P2Y₁₂ antagonist than clopidogrel and has shown better efficacy with a comparable overall major bleeding risk and a minor but significant increase in non-procedure-related

major surgery and	how to proceed	exception	how to proceed with exception
aspirin for primary prevention ♦	stop aspirin 5 days before surgery ♦		
aspirin in high-risk patients ♦ (diabetes, history of CV events, documented CV disease, increased global risk)	continue aspirin ♦	surgery in closed space, expected major bleeding complications	<ul style="list-style-type: none"> • stop aspirin 5 days before surgery ♦ • consider restarting within 24h ♦
aspirin plus clopidogrel in high risk patients	<ol style="list-style-type: none"> 1. elective surgery: delay until no dual inhibition necessary 2. semi-urgent surgery: continue aspirin ± clopidogrel on a case by case basis 3. urgent surgery (within 24 h): continue aspirin and clopidogrel 	surgery in closed space, expected major bleeding complications	<p><i>If delaying surgery not possible / semi-urgent surgery necessary:</i></p> <ul style="list-style-type: none"> • stop clopidogrel 5 days before surgery, consider bridging (short acting GPIIb/IIIa antagonist) • consider stopping also aspirin in particular patients • consider resuming dual antiplatelet therapy asap

♦ extends also to patients on clopidogrel monotherapy

Minor Surgery: do not stop antiplatelet therapy.
Implement **multidisciplinary consult** in patients with (potential) bleeding complications.
Low molecular weight heparin: NOT a substitute for platelet inhibiting drugs.
Avoid plasmatic anticoagulation (LMWH, OAC) during surgery.

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Figure 1: Summary of the expert group's recommendation.

bleeding, including more fatal intracranial bleeding episodes and fewer fatal bleeding episodes of other types (77). The agent might enter the market soon as it is currently under evaluation for approval by the FDA and the EMA. The appearance of further new antiplatelet (78) and other antithrombotic agents, i.e. direct inhibitors of factor Xa or thrombin and the respective indications for these new drugs will necessitate continued consideration and repeated updating of recommendations such as the ones presented here.

Our group emphasises a careful decision-making process of all involved relevant specialties in the pre-operative assessment phase for patients with coronary stents under dual antiplatelet therapy as indicated by international guidelines. However, the adherence to such guidelines is low (79) and our working group therefore re-emphasises the necessity of a multidisciplinary approach for the individual patient, mirrored by the different disciplines represented within our group.

Conclusion

Many treatment decisions have to be made in patients with CAD who need cardiac (such as on- and off-pump CABG or valve surgery) and non-cardiac surgery. The group believes that multidisciplinary discussions between cardiologists, anesthesiologists, haematologists and surgeons are needed to optimise the treatment of the individual patient.

Primary prophylaxis with antiplatelet drugs should be stopped five days ahead of surgery.

When the need for surgery becomes apparent during the time of recommended dual antiplatelet therapy (or triple therapy), surgery should be delayed for the whole time of recommended dual antiplatelet therapy in patients in whom it can be performed electively.

In patients in whom surgery is imminent or urgent, the operation has to take place under full antiplatelet therapy despite the increased bleeding risk. It should be kept in mind that an increased bleeding risk under dual antiplatelet therapy could turn into an acute thrombotic risk if measures to improve haemostasis are necessary to reduce the bleeding risk.

In patients with a semi-urgent operation, the decision to prematurely stop one or both antiplatelet agents (at least five days before surgery) has to be made in close cooperation of the different involved specialties, whereby the individual risk of thrombosis versus bleeding has to be carefully evaluated.

These recommendations are summarised in ► Figure 1.

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