

Theme Issue Article

Individualized antithrombotic therapy in high risk patients after coronary stenting. A double-edged sword between thrombosis and bleeding

Andreas E. May, Tobias Geisler, Meinrad Gawaz

Medizinische Klinik III (Kardiologie und Kreislauferkrankungen), Eberhard Karls Universität, Tübingen, Germany

Summary

Dual antiplatelet therapy with aspirin and clopidogrel is currently the standard therapy after coronary stent implantation to prevent a life-threatening stent thrombosis. However, a variety of procedural and individual factors contribute to the individual patient risk and have to be taken into account to allow for an individual recommendation for both the duration and intensity of the antiplatelet therapy. Obviously, the benefit of the prevention of stent thrombosis by antithrombotic therapy has to outweigh the risk of severe bleeding complications. Depending on the individual clinical situation and procedural characteristics (stent type, length, angiographic result etc.), the recommended duration of the combined antiplatelet therapy currently varies

from four weeks to at least one year. These recommendations are mainly based on large, prospective, randomized trials and evidence-based guidelines. However, in a subgroup of high-risk patients there is insufficient evidence for the benefit of conventional dual antiplatelet regimen. These include i) patients with an indication for anticoagulation, ii) patients with urgent need for an operation requiring a perioperative withholding of antiplatelet therapy, as well as iii) clopidogrel low responders. This review aims to provide a stratification to define patient collectives who may benefit from more individualized antithrombotic regimens on behalf of currently available literature and guidelines.

Keywords

Antiplatelet agents, antiplatelet drugs, clinical trials, atherothrombosis, atherosclerosis, acute myocardial infarction

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Introduction

In patients with coronary stent implantation, antiplatelet therapy using aspirin and a thienopyridine (usually clopidogrel) is the current standard strategy to prevent stent thrombosis (1). The duration of this so-called dual antiplatelet therapy varies from 3–4 weeks in patients with elective bare-metal stent (BMS) implantation to one year in patients receiving drug-eluting stents (DES) or patients with acute coronary syndrome (ACS) (1, 2). After an intensive worldwide debate concerning the safety of DES and, consequently concerning the minimal duration of dual antiplatelet therapy there is a consensus at present: Taken together, the international guidelines recommend a duration of 6–12 months after DES implantation and 9–12 months after ACS (independent of the type of therapy) (1–4). Based on these guidelines, Figure 1 shows a practical algorithm for the duration of the dual anti-

platelet therapy. In DES-patients this algorithm takes additional procedural and patient characteristics into consideration that – if present – enhance the risk for stent thrombosis and should stimulate prolonged dual antiplatelet therapy over at least 12 months (Table 1).

However, a growing number of patients appear to require a more individualized antithrombotic regimen. These patients include those with an additional indication for anticoagulation (e.g. atrial fibrillation, mechanical valve prosthesis, venous thrombosis etc.), patients that need unplanned non-cardiac surgery within the time interval at high risk for stent thrombosis or low responders to the treatment with clopidogrel. In these high-risk patients, the individual decision making regarding both the intensity and duration of antithrombotic therapy has to take the individual risk of severe bleeding complications into account.

Correspondence to:
PD Dr. Andreas E. May
Medizinische Klinik III, Eberhard Karls Universität Tübingen
Otfried-Müller-Straße 10, D-72076 Tübingen, Germany
Tel.: +49 7071 29 83688, Fax: +49 7071 29 4473
E-mail: andreas.may@med.uni-tuebingen.de

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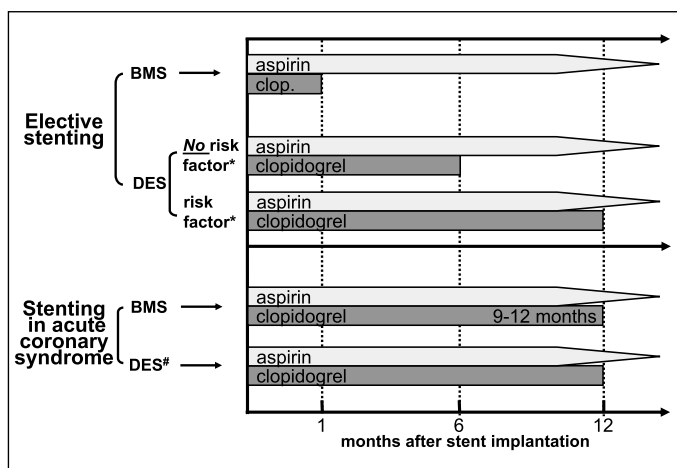


Figure 1: Antiplatelet therapy after coronary stent implantation in "standard" patients. Algorithm for intensity and duration of dual antiplatelet therapy. Aspirin 75–150 mg/day; clopidogrel 75 mg/day; *risk factors for stent thrombosis: see Table 1; #DES should be avoided in patients with acute coronary syndrome.

Coronary stenting in patients with an indication for anticoagulation

Approximately 10% of all patients requiring a percutaneous coronary intervention (PCI) have an indication for anticoagulation. The main dilemma is that antiplatelet agents significantly reduce the risk of stent thrombosis, however, fail to prevent from thromboembolic complications in patients with e.g. atrial fibrillation, mechanical valve prosthesis, or venous thrombosis (5–7). Even a combined antiplatelet therapy does not sufficiently protect from thromboembolic complications in these high risk patient collectives (ACTIVE-W) (6). For example, the ACTIVE-W study had to be stopped recently due to clear superiority of anticoagulation therapy over dual antiplatelet therapy in stroke prevention in patients with atrial fibrillation (ACTIVE-W) (6).

Risk stratification and prevention of stent thrombosis

Studies in the nineties have clearly shown that dual antiplatelet therapy reduces the risk of subacute stent thrombosis to < 1 % as

compared to $\geq 5\%$ with the treatment with aspirin plus heparin/vitamin K antagonist (8–10). To date, it is unclear whether the combination of a thienopyridine (e.g. clopidogrel) with anti-coagulation sufficiently protects from stent thrombosis. Although Karjalainen et al. did not detect any stent thrombosis in 45 patients treated with this combination (11), the limited current database does not allow drawing of a definitive conclusion (or even recommendation) on this combination. Together, the currently available data suggest that only the dual combination of aspirin with a thienopyridine can reduce the rate of stent thrombosis to below 5%. Although the overall incidence of stent thrombosis is rare, it still presents a serious and considerable clinical problem due to high mortality especially in cases of late stent thrombosis with DES (12). Since the risk of stent thrombosis is highest during the first month after stent implantation, we are convinced that (almost) all patients should receive dual antiplatelet therapy for at least four weeks.

Risk stratification and prevention of thromboembolic events

Patients with a general recommendation for anticoagulation carry a variable and individual absolute risk profile. Optimal antithrombotic therapy has to carefully weigh up the risk of bleeding and the risk of thromboembolic events under the respective antithrombotic therapy in every individual patient (5, 7).

Table 2 is an attempt to identify patients at *high risk* (>5 events/100 patient years) for thromboembolic complications when permanent anticoagulation is discontinued. This group comprises patients with mechanical prosthetic heart valves, patients with a history of venous thrombosis plus persistent risk factors (e.g. neoplasms, thrombophilic disorders, antiphospholipid syndrome, immobilisation etc.) and patients with a history of venous thrombosis within the last six months and reversible risk factors. In addition, selected patients with atrial fibrillation plus certain clinical or echocardiographic characteristics should be considered as high-risk patients (13, 14). Clinical characteristics are defined by the CHADS₂-score ≥ 2 (see Table 2), since these patients carry a risk of >4.5 events/100 patient years even with aspirin treatment (14). Echocardiographic parameters additionally allow the identification of patients with atrial fibrillation at high risk. These include poor left ventricular function (LVEF < 30%), atrial dilatation >50 mm or a mitral valve stenosis or regurgitation with a severity > grade II (13, 14).

Antithrombotic therapy and bleeding complications

A number of studies exist comparing the benefit and bleeding complications of dual antiplatelet therapy versus aspirin plus heparin / vitamin K antagonist. These studies revealed that the combination of aspirin with anticoagulation is not only associated with a higher risk for stent thrombosis and myocardial infarction, but also with increased severe bleeding complications (15). To our knowledge, there are only a few studies concerning the risk of bleeding under triple antithrombotic therapy using aspirin, clopidogrel and a vitamin K antagonist. The patient collectives in these studies were relatively small and the study design retrospective (11, 16–19). These studies showed enhanced bleeding complications under antithrombotic triple therapy, as expected. However, Buresly et al. found in 144 elderly patients

Table 1: Risk factors for stent thrombosis.

Patient /clinical	Interventional
Early cessation of antiplatelet therapy	Suboptimal result (e.g. dissection, stent malapposition)
Stenting in ACS	Bifurcation / ostial stenting
Renal impairment	Long (>18mm) / multiple stents
Diabetes	Overlapping stents
Low ejection fraction	Small stents (\varnothing <3.0mm)
Advanced age	

ACS, acute coronary syndrome.

(>65 years) receiving triple therapy after myocardial infarction only one bleeding complication that required rehospitalisation (18). Notably, two studies on short-term triple therapy only described a moderate rate of severe bleeding complications (<2%) (16, 20). For example, Porter et al. found severe bleeding complications in only 1.1% (2 of 180) patients receiving short-term triple therapy (30 days) (16). We have performed a follow up in 55 consecutive patients with mechanic valve prosthesis or high-risk atrial fibrillation who received triple therapy for at least one month after coronary stent deployment. In these patients only one patient (1.8%) suffered from major bleeding complications within the period of triple treatment (30 days) (see Table 3) supporting the concept that short-term triple therapy can be applied to selected patient collectives. Obviously, large randomized trials are warranted to underline the safety of this therapeutic regimen.

Practical approach

Currently, there are no evidence-based guidelines on the management of patients with an indication for anticoagulation after coronary stent implantation. Various antithrombotic combinations have been used in the past and are currently used in daily clinical practice depending on the respective interventionalist. Based on the above described risk stratification including thromboembolic and bleeding complications we present a practical approach (see Fig. 2):

Patients at high risk for thromboembolic complications

It is generally accepted, that a certain patient collective at *high risk* for thromboembolic complications (see Table 2) requires *permanent* anticoagulation. After coronary stent implantation, these patients appear to have benefit from short-term triple antithrombotic therapy including aspirin, thienopyridine (e.g. clopidogrel), plus anticoagulation using heparin/vitamin K antagonist. In order to limit the risk of bleeding, the time interval of triple therapy should be as short as possible and only cover the time frame for the highest risk for stent thrombosis. This time period comprises four weeks in patients with BMS. Notably, the use of DES should be avoided in patients requiring anticoagulation (1). This intensive antithrombotic treatment implies an interdisciplinary risk stratification to evaluate individual bleeding tendencies (e.g. gastrointestinal). During this period for high risk of bleeding we additionally treat selected patients with a proton pump inhibitor. Thereafter, dual antithrombotic therapy using one antiplatelet agent (aspirin *or* clopidogrel) plus vitamin K antagonist is used, until – at six months after stent implantation – we stop antiplatelet therapy and continue with long-term monotherapy using the vitamin K antagonist. However, it should be noted that it is currently unclear, whether patients with an indication for anticoagulation and a severe coronary risk profile gain benefit from long-term therapy using aspirin (or clopidogrel) plus vitamin K antagonist. In a large prospective and randomized trial, Hurlen et al. found that the combination of low-dose aspirin (75 mg) plus low-intensity warfarin (International Normalized Ratio [INR] 2–2.5) did not increase the risk of bleeding compared with warfarin treated patients (INR 2.8–4.2) (22). However, these patients did not have a classical indication for anticoagulation. Therefore, these data do not allow one to directly

Table 2: Patients at high risk for thromboembolic events requiring permanent anticoagulation.

Atrial fibrillation <i>plus</i>
- CHADS ₂ -score* ≥ 2 <i>or</i>
- LV-EF < 30% <i>or</i>
- atrial diameter > 50 mm <i>or</i>
- mitral valve stenosis/regurgitation ≥ grade II
Mechanical valve prosthesis
Venous thrombosis < 3 weeks <i>plus</i> persistent risk factors#
LV-thrombus

*CHADS₂-score: congestive heart failure, hypertension, age ≥75 years, diabetes (1 point each) and history of stroke/TIA (2 points); #risk factors: immobilisation, neoplasia, thrombophilia etc.; LV, left ventricle; EF-ejection fraction.

Table 3: Adverse events in 55 patients with short-term (30 days) triple therapy after coronary stent implantation.

Myocardial infarction / stent thrombosis	0/55
Ischemic stroke	0/55
Cardiovascular death	0/55
*Bleeding	
Major bleeding	1/55
Minor bleeding	0/55
Minimal bleeding	5/55

*Bleeding classification according to the TIMI-score (21): Major bl.: Hb↓ >5g/dl or Hk↓ >15%; Minor bl.: Hb↓ 4.0 – 4.9g/dl or Hk↓ 12 –15%; or Hb↓ 3.0–3.9 g/dl with identifiable bleeding source; Minimal bl.: Any clinically overt sign of haemorrhage associated with a Hb↓ <3g/dl or a Hk↓ <9%.

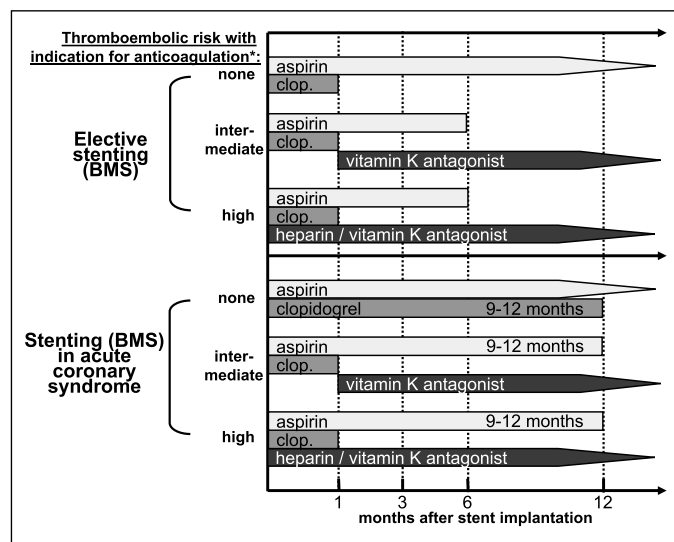


Figure 2: Antiplatelet therapy after coronary stent implantation in patients with indication to anticoagulation. Proposed algorithm for a standardized choice of intensity and duration of combined antithrombotic therapy using aspirin (75–150 mg/day), and/or clopidogrel (75 mg/day) and/or anticoagulation using heparin intravenously and overlapping vitamin K antagonist (e.g. coumadin or cumarin) for limited time intervals. The algorithm discriminates between patients without indication for anticoagulation (no risk), patients who should tolerate a short-term cessation of anticoagulation (intermediate risk, e.g. atrial fibrillation with a CHADS₂-score 1) and patients requiring permanent anticoagulation (high risk, see Table 2).

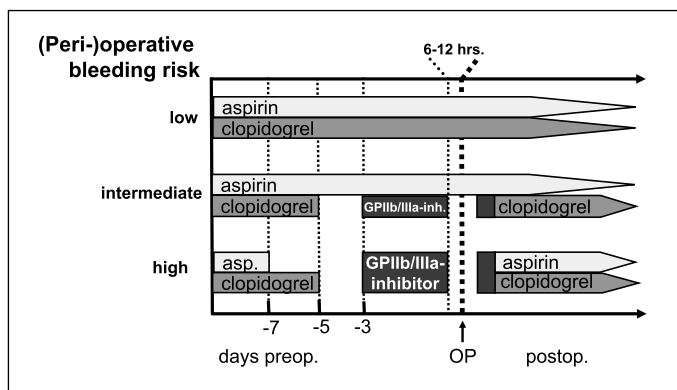


Figure 3: Perioperative antiplatelet management in patients with recently implanted coronary stents. Proposed algorithm for a standardized bridging of patients with coronary stents which have been implanted within the last four weeks (elective stenting using BMS), or within the last 12 months (stenting in acute coronary syndrome, DES). Depending on the estimated perioperative bleeding risk, the current antiplatelet therapy may be continued, or it may be helpful to bridge the interruption of oral antiplatelet therapy with a short-acting intravenous GPIIb/IIIa-inhibitor as indicated.

draw conclusions regarding treatment of our patient collective. Similarly, a recent metaanalysis of a total of 25,307 patients showed that patients with ACS treated with aspirin and warfarin had two-fold increased risk of bleeding complications but significantly reduced major adverse events in comparison to aspirin alone (23). In the patients discussed here, the decision to prescribe long-term aspirin in addition to a vitamin K antagonist is a risk-benefit discussion, which still awaits clarification.

Patients at intermediate risk for thromboembolic complications
In patients with a given indication for anticoagulation at an *intermediate risk* for thromboembolic complications the risk of fatal bleeding under triple therapy appears to exceed the risk of thromboembolic complications under short-term dual antiplatelet therapy. Therefore, this patient collective may derive most benefit from short-term (4 weeks) dual antiplatelet therapy without additional anticoagulation followed by dual antithrombotic therapy using one antiplatelet agent (aspirin *or* clopidogrel) plus vitamin K antagonist. At six months after stent implantation we stop antiplatelet therapy and continue with long-term monotherapy using a vitamin K antagonist.

The optimal therapeutic strategy for patients requiring anticoagulation is complex and requires an individualized approach. Although we have tried to define an algorithm suitable for most patients, the individual risk profile has to be taken into account in every single patient. Individual age, comorbidity and patient compliance should be carefully considered prior to the decision to perform a coronary intervention in these high risk patients. One important aspect, for example, is the fact that advanced age is a risk factor for stent thrombosis (24), thromboembolic complications in e.g. atrial fibrillation (13, 14) and fatal bleeding complications (25).

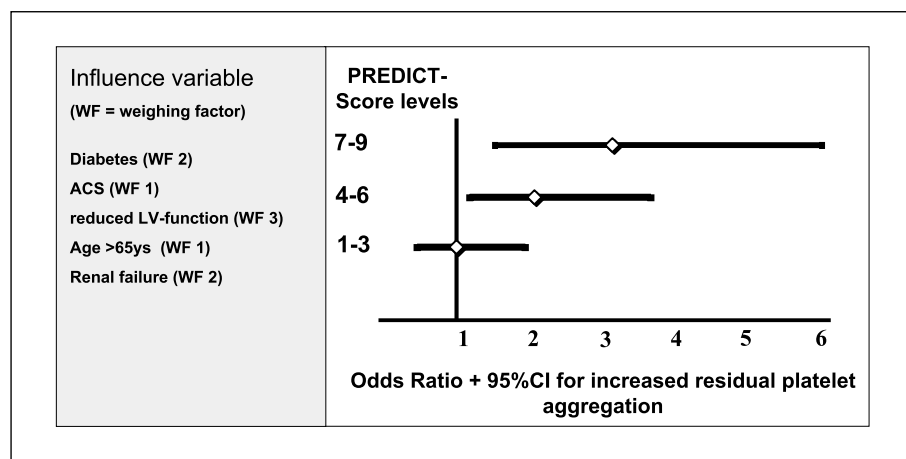
Perioperative management during non-cardiac surgery

Patients who undergo non-cardiac surgery early after coronary stenting with interruption of the combined antiplatelet therapy are at increased risk for stent thrombosis and its potentially fatal consequences (26–28). A recent metaanalysis of eight observational (mainly retrospective) studies showed that the mortality rate in such patients ranged from 2.5–21.4% (29). Therefore, if possible, one should avoid and delay elective non-cardiac surgery in patients who have had recent coronary stenting (1). Consequently, in patients who are scheduled for elective surgery within the next year, DES should not be implanted, since they require prolonged dual antiplatelet therapy. In contrast, patients with DES should not undergo elective surgery within the first year post intervention (1).

However, in many patients unexpected diagnoses mandate urgent surgery. These patients need an individualized pre-, peri- and postoperative management that weighs up the risk of perioperative bleeding versus the risk of stent thrombosis. In order to correctly estimate the risk of stent thrombosis, the date of stent implantation, the type(s) of stent(s), and procedural as well as clinical characteristics (see Table 1) need to be taken into account. Based on these parameters, the time interval of enhanced risk of stent thrombosis can be estimated. In principle, the risk of stent thrombosis should be considered high within the first four weeks after coronary stenting (BMS or DES) and persistent over the first 12 months after drug-eluting stenting. The presence of risk factors (see Table 1) additionally increases the risk within the described time interval and may enhance the risk outside these time periods. Ideally, in the case of urgent surgery, the cardiologist who has implanted the stent should, in conjunction with the surgeon, discuss the optimal individualized perioperative antithrombotic strategy. Based on the surgeons judgement, the perioperative risk of bleeding should be estimated as *low* (aspirin and clopidogrel allowed), *intermediate* (aspirin allowed) or *high* (antiplatelet therapy not allowed).

Based on the surgeons' risk stratification, patients at *low* bleeding risk may continue their current antiplatelet medication throughout the perioperative period. For the treatment of patients at *intermediate or high* bleeding risk no evidence based recommendations currently exist (1). We and others (30, 31) bridge the peri- and postoperative time interval of the interruption of oral antiplatelet therapy by using a short acting intravenous GPIIb-IIIa-inhibitor. Figure 3 presents a treatment algorithm that has proven to be safe and effective in our hands for ≥ 5 years. Depending on the surgeons judgement of the bleeding risk, aspirin and/or clopidogrel treatment are stopped seven or five days, respectively, prior to the scheduled surgery. At three days preoperatively, we start to support the weakening antiplatelet effect of oral agents with intravenous GPIIb-IIIa inhibitor eptifibatide (Integrilin[®], 2 $\mu\text{g}/\text{kg}/\text{min}$; "off-label use") in order to keep the perioperative withholding of antiplatelet therapy as short as possible. In patients with normal renal function, intravenous administration can be discontinued 6–12 hours prior to the scheduled surgery, since platelet aggregation and bleeding time normalize within six hours. In patients with impaired renal function a dose adaptation

Figure 4: PREDICT-score including distinct non-genetic variables influencing increased platelet reactivity despite dual antiplatelet therapy. The score was developed by weighing of the denoted factors. The odds ratios with the 95% confidence interval (bars) for increased residual platelet aggregation are given for each score level (modified according to Geisler et al. [39]).



is needed and the infusion has to be stopped earlier according to the recommendations of the manufacturer. Platelet function tests can verify the normalisation of platelet function before surgery.

Postoperatively, antiplatelet therapy should be started as early as possible. Due to the prolonged half-time of aspirin and clopidogrel it may be useful to restart with the short-acting intravenous GPIIb-IIIa inhibitor followed by a delayed administration of oral antiplatelet agents (Fig. 3). We are aware that this perioperative treatment may increase the costs, since patients have to be admitted three days before surgery and are treated with costly drugs. Therefore, future studies are needed to either prove a clinical and/or economical benefit gained by the reduction of acute stent thromboses by this treatment or to identify subcollectives of high risk patients benefiting from this treatment.

The situation is completely different in emergency cases with a vital indication for surgery or in patients with life-threatening trauma. Being on aspirin and clopidogrel, these patients are at high risk for (perioperative) bleeding. In this situation, the only procedure to diminish perioperative bleeding is the administration of platelet concentrates.

On the other hand, patients at high risk for bleeding may require a PCI. This would include patients that are already scheduled for urgent non-cardiac surgery and who develop an ACS or who need revascularization in order to be medically cleared for surgery. Other patients may develop an ACS peri- or postoperatively and require acute PCI. Depending on the respective situation in these selected patients it may be an option to perform balloon angioplasty only in order to minimize the necessity of intensified antiplatelet therapy.

Low responders to clopidogrel

Not only the duration, but also the intensity of platelet inhibition by clopidogrel is a matter of intensive discussion after PCI. Persistent residual platelet activity plays a major role in the cardiovascular outcome after PCI (32–34). Several clinical trials have described a high interindividual variability in response to clopidogrel (35–37). Recently, we and others have shown that patients who were identified as low responders to clopidogrel by a single post-treatment platelet function test are at increased risk for recurrent cardiovascular events (38–40) and subacute stent throm-

bosis (41). Various clinical and demographic variables have been discussed that may influence the response to antiplatelet therapy. Recently, we have presented a simple score system, the PREDICT score, which allows us to identify patients at increased risk for residual platelet reactivity upon clopidogrel administration on the basis of easily available clinical data (42). These clinical variables including age >65 years, ACS, diabetes, renal failure, and reduced left ventricular function, are well known risk factors for stent thrombosis per se (see Table 1). After weighing up these factors we could demonstrate that the score correlates with the risk of developing, high persistent platelet aggregation (see Fig. 4). Thus, we are able to define the risk of suboptimal response based on clinical variables that are easily available from the patients' history. Besides non-genetic factors, variants of CYP450 encoding genes and platelet receptors have been considered to influence antiplatelet drug response. Recently, a number of genetic polymorphisms involving clopidogrel metabolism have been discussed. In this context, we found in a consecutive setting of patients with symptomatic CAD, a loss of function polymorphism of cytochrome 2C19 (CYP2C19*2) is significantly associated with a low response to clopidogrel and that the presence of non-genetic and genetic risk factors both amplify the extent of residual platelet aggregation despite standard antiplatelet therapy (Geisler et al., submitted). Therefore, new strategies to estimate the individual atherothrombotic risk have to be developed, and it might be necessary to individualize not only the duration but also the intensity of antiplatelet therapy according to the individual risk and to adapt dosing of clopidogrel or to switch to alternative compounds in high-risk patients.

For example, there is some initial data suggesting an improved platelet inhibition in poor responders to clopidogrel by means of increased loading dose (45, 46) or higher maintenance dose (47, 48) or alternative thienopyridine treatment (49, 50). Future studies have to evaluate whether all patients undergoing coronary stenting should be tested for their individual response to clopidogrel.

Conclusion

A significant proportion of our patients with coronary stents require an individualized antithrombotic strategy that is cur-

rently not covered by evidence-based data or international guidelines. Here we have presented a practical approach and algorithm on the strategy in high-risk patient collectives after stent implantation. These proposals are mainly based on retrospective obser-

vations or studies with relatively small patient numbers and are based on risk calculations obtained from various studies. Randomized prospective trials are needed to actually prove the benefit or to improve the current strategy.

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