The impact and management of acquired platelet dysfunction

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Summary
Platelet function can be abnormally increased, as in association with acute vascular events, or defective, as in a variety of clinical settings. Acquired platelet dysfunction may occur at any age and range in severity from mild to life-threatening hemorrhages. Diagnostic work-up of platelet disorders requires meticulous evaluation of medical history, specifically of any drugs interfering with platelet function, careful clinical examination and a staged laboratory protocol to assess the underlying platelet defect(s). To identify hyperactive platelets ex vivo, costly procedures may be required using flow cytometry and district epitope-specific monoclonal antibodies. Currently, this approach can be recommended for research purposes only. Drugs represent the most common cause of platelet dysfunction in our overmedicated society. While aspirin, clopido- grel (more recently also prasugrel) and integrin αIIbβ3 receptor antagonists (abciximab, epifibatidine and tirofiban) are well-known prototypes of antiplatelet drugs, other widely used agents (e.g. nonsteroidal anti-inflammatory drugs, antibiotics, serotonin reuptake inhibitors and volume expanders) can also impair platelet function and thus cause or aggravate hemorrhages. Identification of individual patients with pre-existing hemostatic defects remains crucial (i) to prevent bleeding complications, (ii) to manage symptoms adequately, (iii) to minimize the risk from invasive procedures, and (iv) to avoid unnecessary exposure to blood products. Screening for platelet dysfunction can be performed by point-of-care testing followed by platelet aggregometry in response to various agonists. While mild bleeding episodes due to antiplatelet therapy can be managed by withdrawal of the drug(s), severe hemorrhages may require immediate platelet transfusions. Apart from that, the prohemostatic armamentarium is limited to desmopressin, antifibrinolytic agents, and recombinant factor VIIa.

Schlüsselwörter
Plättchenhyperaggregabilität, prothrombotische Zustände, antithrombozytäre Substanzen, erworbene Plättchenfunktionsdefekte, Blutungen, Hämotherapie

Zusammenfassung

Keywords
Platelet hyperaggregability, prothrombotic states, antiplatelet agents, acquired platelet dysfunction, bleeding, haemotherapy

Bedeutung und Behandlung erworbener Plättchenfunktionsstörungen
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Blood platelets play a pivotal role in haemostasis and arterial thrombogenesis (1–3). Recent studies have highlighted a different but equally relevant contribution of platelets to other physiological and pathophysiological processes, including immune-mediated responses to microbial and viral pathogens, inflammation, and cancer metastasis (4–7).

Upon release from their bone marrow precursor cells (megakaryocytes) into the circulation, platelets contribute essentially to survey the integrity of the vascular system. Specifically, they respond immediately to vascular lesions by becoming adherent within milliseconds and by forming aggregates at sites of injured endothelial cells or exposed subendothelial matrix structures. Following activation, platelets provide a highly effective catalytic membrane surface for the generation of thrombin which, in turn, accelerates recruitment of circulating resting platelets and, particularly, formation of fibrin necessary to stabilize thrombi and to prevent their detachment by flowing blood (8). Once stimulated, platelets respond uniformly and do not distinguish between traumatic injury and atherothrombotic or inflammatory damage of the vessel wall (2, 3). While their physiological function is to support arrest of bleeding, to contribute to host defense and wound healing, and to restore vessel wall integrity, platelets can form occlusive thrombi as a consequence of vascular diseases, such as atherosclerosis. Thus, under pathological conditions, platelet responses can result in acute ischaemic syndromes of the heart, brain, and other organ systems.

Antiplatelets are therefore widely used to prevent and treat thrombotic and thromboembolic events (9–12). A plethora of randomized trials has evaluated the effectiveness and safety of different antiplatelet regimens comparing antiplatelet monotherapy with dual antiplatelet or combined antiplatelet and anticoagulant treatment. Overall, it has been shown that dual antiplatelet therapy or a combination of anticoagulant and antiplatelet therapy is more effective than antiplatelet monotherapy or anticoagulation alone (13, 14). However, it has been also documented that the risk of severe bleeding increases, the more intense antiplatelet regimens are administered (13–15). This is especially true in co-morbid patients with preexisting haemostatic defects of any kind. Such disorders may remain compensated, unless platelet function is not inhibited pharmacologically (12).

Drugs represent the most common cause of acquired platelet dysfunction in our medicated society.

Apart from well-known prototypes of antiplatelet agents such as acetylsalicylic acid, thienopyridines and GPIIb-IIIa receptor antagonists, other widely used drugs such as nonsteroidal anti-inflammatory drugs, antibiotics, serotonin reuptake inhibitors and volume expanders can also impair platelet function and, consequently, cause or aggravate haemorrhages (15).

This review will consider both sides – increased and defective platelet function disorders with regard to selected clinical settings – corresponding diagnostic techniques, and appropriate therapeutic intervention. Special emphasis is placed on the evaluation of antiplatelet treatment in patients with high risk for re-thrombosis or bleeding.

Increased platelet function
Platelet hyperaggregability and prethrombotic state(s)

Numerous experimental and clinical studies have documented that acute vascular events cause platelet activation and formation of platelet thrombi which, in turn, can lead to acute coronary syndromes, manifest myocardial infarction, or stroke (1, 16, 17). For example, platelet activation occurs at the site of a fissured coro-nary atherosclerotic plaque with exposure of highly thrombogenic substances.

We have examined the effect of angio-plasty-injured coronary arteries on platelet activation (18). Using flow cytometry techniques in combination with specific conformation-dependent monoclonal antibodies, activated platelets could be demonstrated in patients undergoing percutaneous transluminal coronary angioplasty (Fig. 1). By contrast to these conditions in which platelet activation and thrombus formation emerge in response to the exposure of subendothelial extracellular matrix proteins, less well documented, and perhaps less frequent, are several clinical settings in which an acute vascular event appears to result from intrinsic platelet activation.

Moreover, we studied 47 young patients (< 45 years) with ischaemic stroke of unknown cause (12 men, 35 women) and 36 patients (6 men, 30 women, mean age 38 years) suffering from migraine accompanied (17). Elevated plasma concentrations of platelet-specific proteins, including β-thromboglobulin (βTG) and platelet factor 4 (PF4) were found in 33 of the 47 patients with stroke (70%) and in 25 of the 36 patients with migraine accompanied (69%). Interestingly, the plasma levels of βTG and PF4 correlated inversely (r = −0.72, p < 0.001) with the interval between time of the migraine attack and blood collection (Fig. 2), suggesting a direct association of increased platelet secretion with clinical symptoms (17). This observation is in accord with findings from others who reported on an augmented rate of circulating platelet aggregates in patients with migraine accompanied, in particular at the time of a migraine attack (19).

Along with such findings, it has been postulated clinically that hyperactive or hyperreactive platelets exist in affected individuals (20, 21). From a laboratory point of view, this condition has been termed platelet hyperaggregability, defined as a feature in which the threshold concentration for aggregating agents, including adenosine diphosphate (ADP), epinephrine, and collagen, is lowered in patients (20, 22) and, as very recently demonstrated, also in healthy individuals (21). This phenomenon has to be carefully distinguished from the so-called ‘sticky platelet syndrome’. This autosomal dominant platelet disorder is characterized by hyperaggregability of platelets in response to ADP and epinephrine (type I), epinephrine alone (type II), or ADP alone (type III) and associated with arterial and/or venous thromboembolic events (23). In a more general way, the term ‘prethrombotic state’ has been introduced. This state is postulated to represent a condition which precedes clinically overt thrombosis, during which the haemostatic function is altered in a way that promotes formation or
deposition of platelet thrombi and generation of fibrin (20). This definition has raised several questions, in particular
● what are markers of such a prethrombotic state?
● What is its molecular nature?
In this context, distinct polymorphisms of platelet membrane glycoprotein receptors have come into the focus of interest.

**Polymorphisms of platelet membrane glycoproteins**

Polymorphisms are stable DNA sequence variations that occur in more than 1% of chromosomes in the general population. Platelet membrane glycoproteins (GP) are highly polymorphic and can be recognized as self-antigens or alloantigens. Incompatibility of distinct epitopes, also known as human platelet antigens, on various platelet membrane receptors is responsible for alloimmune thrombocytopenias and some cases of platelet transfusion refractoriness (24). Moreover, ‘mismatches’ play an important role in the pathogenesis of fetal or neonatal alloimmune thrombocytopenia and posttransfusion purpura.

**Fig. 1**

Flow cytometric detection of circulating activated platelets in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Blood was sampled continuously via a heparin-coated catheter placed in the coronary sinus before vascular intervention and remained in situ 30 min after termination of the dilatation procedure to allow further collection of blood samples. Binding of fluoresceinated monoclonal antibodies specific for activation-dependent platelet epitopes, including activated αIIbβ3 (PAC1), fibrinogen bound to αIIbβ3 (9F9), ligand-induced binding sites (LIBS) on β3 (anti-LIBS1), and P-selectin, an a-granule membrane protein expressed on the platelet surface after secretion (S12), was evaluated by one-color flow cytometry.

a) Quantification of activated subplatelet subpopulations: For each monoclonal antibody, a gate within the fluorescence profile at baseline level (dotted line) was set to define a 2% (left panels) and 10% (right panels) platelet subpopulation as indicated. Increase in platelet number with high fluorescence was detected in blood during PTCA (solid line). Representative histograms are shown for immunofluorescence of fluorescein isothiocyanate (FITC)-PAC1, FITC-9F9, FITC-anti-LIBS1, and FITC-S12.

b) Effect of PTCA on relative proportion of activated platelet subpopulations: As depicted in A, a 2% platelet subpopulation with the brightest membrane fluorescence intensity at baseline level was analyzed separately and quantified for relative increase in platelet number after PTCA. Bars represent mean ± SD. P-values for increased binding of PAC1, anti-LIBS1, and 9F9 were <0.01, <0.01, and 0.03, respectively. Adapted from Scharf et al. (18) and reprinted with permission of the publisher.
Platelet integrin αIIbβ3, also known as GPIIb-IIIa, can interact with fibrinogen, von Willebrand factor, fibronectin, vitronectin, or thrombospondin and is the principal receptor for platelet aggregation. αIIbβ3 carries the human platelet antigen (HPA) 1 and other well-defined diallelic alloantigen systems (24). The HPA-1 polymorphism arises from a single $T \rightarrow C$ nucleotide substitution at position 1565 in exon 2 of the β3 gene, which, in turn, leads to an amino acid change at position 33 in the β3 subunit (GPIIa) with leucine in HPA-1α (Leu33) and proline in HPA-1β (Pro33) (25). Importantly, the HPA-1β allele is not rare; approximately 25% of Europeans have at least one allele (24).

### Polymorphisms of α2β1

Platelets contain several receptors for collagen, including GPVI and integrin α2β1, also known as GPIa-IIa, both of which are important for platelet adhesion. α2β1 exhibits at least three alleles of the α2 gene which are defined by eight nucleotide polymorphisms (807C/T; 837T/C; 873G/A; 1648G/A) (15, 16). This integrin is expressed at low density on the platelet surface (1000 to 3000 receptor copies per platelet). Interestingly, there is a wide, approximately 10-fold, variation among normal individuals that can modulate platelet responses to collagen (26, 27). Allele 1 (807T/837T/873A/1648G), also referred to as α2β1, is associated with increased surface expression of α2β1 (high-density variant), while alleles 2 (807C/837T/873G/1648G) and 3 (807C/837C/873G/1648A), also designated α2 807C, are associated with low surface expression of the receptor (27). Indeed, in whole blood, the rate of platelet adhesion onto type I collagen under high-shear conditions (1500 s$^{-1}$) is proportional to the density of α2β1 receptor copies on the platelet surface (27). The frequency of allele 1 and 2 is 39% and 53%, respectively, that of allele 3 is 7% (26).

### Prothrombotic platelet receptor variants

#### Clinical association studies

In 1996, Weiss et al. first reported on an association between the HPA-1b genotype and the risk of myocardial infarction or unstable angina (28). The prevalence of HPA-1b in patients admitted to a cardiac care unit was significantly higher than in hospitalized patients without coronary artery disease (39.4% vs. 19.1%, odds ratio 2.8, $p = 0.01$). In patients whose cardiovascular event occurred prior to the age of 60 years, there was an even greater difference between cases and controls (50% vs. 13.9%, odds ratio 6.2, $p = 0.002$) (29). These two studies may be representative for discrepant results published in subsequent papers (for review: 30, 31).

Since then, the reasons for the conflicting findings have been a matter of ongoing debate. The same is true for the C807T polymorphism of integrin α2β1. In 1999, Moshfegh et al. found a significant higher prevalence of the α2 807TT genotype in patients with myocardial infarction as compared to healthy controls (16.4% vs. 2.6%, $p = 0.022$) (32). However, this association appeared highly doubtful since the control group was rather small and the prevalence of 5.6% in the controls differed from the expected prevalence in Caucasians which is about 15% for the α2 807TT genotype (31).

In a large study with 2,237 male patients, no significant association of the α2β1 receptor variant and myocardial infarction was observed (33). However, in subgroups of younger patients (<62 years or <49 years), an increased risk for carriers of the T-allele was shown (odds ratio 1.57, $p = 0.004$, and 2.61, $p = 0.009$, respectively). Again, the re-
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Fig. 3 Hypothetical model of how a thrombogenic risk factor coupled to the presence of atherosclerotic lesions becomes effective. The left panel shows progression of coronary artery disease. This progression is accelerated in carriers patients with prothrombotic platelet receptor variants such as HPA-1b of αIIbβ3 or α₂B37T of α2β1. By contrast, these prothrombotic risk factors remain without any effect in the absence of an atherosclerotic burden. This model also includes the contention that different types of risk factors exist, i.e. various "traditional" risk factors causing atherosclerosis and risk factors leading to increased platelet thrombogenicity. CAD: coronary artery disease; MI: myocardial infarction.

results of these association studies have been discussed controversially (31).

To address this issue, we performed a retrospective study of 298 men, including 124 individuals with myocardial infarction, 83 individuals with coronary artery disease but no history of myocardial infarction, and 91 control patients who all had undergone coronary angiography (34). The overall prevalence of HPA-1b among case patients with myocardial infarction (23%) and control patients (25%) did not differ (p = 0.75). This finding confirmed the Physician’s Health Study (29). However, a further analysis of our data revealed that the prevalence of HPA-1b was related to the patients’ age and dependent on the time after myocardial infarction with highest values in younger patients (<60 years) with myocardial infarction and patients with recent onset (<1 year) myocardial infarction (45% vs. 23% in controls, odds ratio 2.0, p = 0.007). Thus, we could document a significant association between the HPA-1b genotype and acute or recent onset myocardial infarction and thereby confirm the observation of Weiss et al. (28). Moreover, we found that patients with coronary artery disease who are carriers of the HPA-1b allele experience a myocardial infarction earlier in life than patients who are HPA-1b negative (34). The findings of our study have led to the following preliminary conclusion: The HPA-1b genotype of integrin αIIbβ3 is not a risk factor for atherosclerosis but a risk factor for arterial thrombosis.

Based on this conclusion, we hypothesized that HPA-1b is a prothrombotic risk determinant which requires the presence of an atherosclerotic lesion to become effective. Thus, unlike conventional risk factors, HPA-1b does not represent a risk factor for coronary artery disease itself but appears to be associated with increased platelet thrombogenicity. This contention provides an explanation for some of the conflicting results presented in various clinical associations studies regarding the role of the HPA-1 polymorphism of integrin αIIbβ3 in patients with coronary artery disease. Along with our hypothesis, it can be anticipated that even in prospective studies (e.g., the Physician’s Health Study (29)), the effect of a polymorphism coupled to the presence of coronary artery disease will provide no difference in the prevalence of HPA-1b between a patient group with myocardial infarction and a control group, since the genetically determined receptor variant is not associated with an increased rate of myocardial infarction but a premature onset of myocardial infarction. Our hypothesis is illustrated schematically in Figure 3.

We prospectively determined the HPA-1 genotype in 261 consecutive patients prior to saphenous-vein coronary artery bypass grafting and performed a follow-up for one year (35). Among patients with bypass occlusion, myocardial infarction, or death more than 30 days after surgery, the prevalence of HPA-1b was significantly higher than among patients without postoperative complications (60% vs. 24%, odds ratio 4.7, p < 0.05). Using a stepwise logistic regression analysis with the variables HPA-1b, age, sex, body mass index, smoking, hypertension, diabetes mellitus, cholesterol and triglyceride concentrations, only HPA-1b had a significant association with bypass occlusion, myocardial infarctions, or death after bypass surgery (odds ratio 4.7, p = 0.019) (35). These results are compatible with our hypothesis that HPA-1b is a risk factor for increased platelet thrombogenicity. In the opinion of others (36), this study is remarkable for two reasons:

- It is the only prospective HPA-1b study to examine the outcome after bypass surgery so far.
- The significant association between HPA-1b and poor outcome shows one of highest odds ratios ever reported in any study.

Our hypotheses would be further supported by demonstrating that

- no association between coronary artery disease and the prothrombotic receptor variants exists, and
- patients with coronary artery disease carrying the critical genotypes experience a myocardial infarction earlier in life.

To address these items, we genotyped 3261 extensively characterized and well-documented patients of the prospective Ludwigshafen Risk and Cardiovascular Health (LURIC) project, including 1175 survivors of a myocardial infarction, 1211 individuals with coronary artery disease but no history of myocardial infarction, and 571 control patients without angiographically detectable coronary artery disease and, in addition, 793 blood donors (37). All subgroups and exclusion criteria were specified prior to the initiation of data analysis based on the results of our previous study in another population (34).

In a case-control design, the prevalence of HPA-1b and α₂B37T genotypes did not differ significantly between the patient groups with coronary artery disease or myocardial infarction and patient controls or blood donors. By contrast, using a multivariate case-only design, it was found that
the median age of onset of myocardial infarction was 5.2 yrs. earlier (p=0.006) in carriers of the HPA-1b allele and 6.2 yrs. earlier in carriers of the α_2807TT genotype in 264 survivors of myocardial infarction of recent onset (Fig. 4). A significant interaction with the conventional risk factors such as hypercholesterolaemia, smoking, diabetes mellitus, hypertension, and hyperfibrinogenemia was excluded.

These results document that HPA-1b (Pro33) and α_2807TT are associated with premature manifestation of myocardial infarction but not with coronary artery disease itself. They support the hypothesis that distinct integrin genotypes can lead to increased platelet thrombogenicity. As the effects of these receptor variants are coupled to the presence of coronary artery disease, it is likely that the quality of the atherosclerotic lesion (e.g., plaque instability) becomes a decisive trigger. The remarkable similarity, in which the genetically unlinked markers behave, is in accord with our hypothesis that both receptor variants, HPA-1b of α_{IIb}β_3 and α_2807TT of α_{2β1}, are prothrombotic. In conclusion, both genotypes, HPA-1b and α_2807TT, are risk factors for myocardial infarction in patients with an already existing atheromatous burden, but not risk factors for the development of atheroma.

Functional properties of platelet integrin variants under arterial flow conditions

To characterize the phenotype of critical integrin variants, HPA-1b (Pro33) of α_{IIb}β_3 and α_2807CC of α_{2β1}, we have used an established in vitro model (38–40). This perfusion system can simulate physiological and pathological flow conditions and, in combination with digital imaging, permits experiments to study shear-induced platelet adhesion and thrombus formation onto thrombogenic surfaces. Using these techniques, we have demonstrated that the HPA-1b variant of α_{IIb}β_3 and the α_2807TT of α_{2β1} have indeed prothrombotic properties. Main characteristics of their phenotype are increased adhesion activity, increased thrombus formation, and increased outside-in signaling (Src pTyr418, ERK2) (31). These findings were confirmed with transfected CHO and HEK293 cells expressing α_{IIb}β_3 of either isoform (HPA-1a or HPA-1b). Upon exposure of adherent cells to increasing shear rates (up to 1600 s^{-1}), HPA-1b cells were significantly more resistant than HPA-1a cells (31).

Along with the clinical results and the experimental findings, we conclude that the increased thrombogenicity of the Pro33 integrin variant is due to an elevated thrombus stability resulting from a polymorphism-dependent modulation in mechanotransduction. Thus, thrombus

**Fig. 4** Distribution of age at onset of myocardial infarction in relation to the HPA-1 (β_3 C1565T) and α_2 (GPIa-IIa) C807T polymorphisms of α_{IIb}β_3 (GPIIb-IIIa) and α_2β_1 (GPIa-IIa), respectively. The plots show the proportion of patients without myocardial infarction (MI) in the subgroup of patients with one- and two-vessel disease and recent onset myocardial infarction recent (< 1 year). The ages at onset of MI are referred to as event times, in relation (a) to HPA-1 and (b) to α_2 (GPIa) C807T. The median age at onset of MI was 54.0 in HPA-1b-positive patients and 59.2 years in the HPA-1b-negative patients (p<0.006 by log-rank test). The median age at onset of MI was 52.5 in carriers of the α_2 807TT genotype and 58.8 years in carriers of the α_2 807CC or α_2 807CT genotype (p<0.006 by log-rank test). Adapted from Zotz et al. (37) and reprinted with permission of the publisher.
formation and thrombus stability would be driven, at least in vitro, by the biophysical transmission of receptor-ligand interactions to the platelet cytoskeleton. In vivo, the prothrombotic character of HPA-1b (Pro33) platelets is linked to the presence of arteriosclerotic vascular lesions (30, 31, 35, 37).

**Management of patients at risk associated with increased platelet function**

Agents that inhibit platelet function are effective in the prevention and treatment of a variety of thrombotic disorders (for review: 9–12). Specifically, antiplatelet drugs are being used in the initial management of acute coronary syndromes (9, 41, 42), for long-term management of coronary, cerebral and peripheral artery disease (9, 41, 43–45) and for prevention of thromboembolism in arterial fibrillation (9, 46). Several clinical settings require more intense antithrombotic regimes, e.g., percutaneous coronary interventions (PCI) including stent placement therapy. Thus, it has been documented that inhibiting cyclo-oxygenase-1 (COX-1) and antagonizing one of the two ADP receptors, P2Y<sub>12</sub>, by combined treatment with acetylsalicylic acid and thiopopyridines (e.g., clopidogrel) is more effective than aspirin alone for the prevention of recurrent thrombotic events in high-risk patients with acute coronary syndromes (47–49). Also blockade of platelet integrin αIIbβ3 (GPIIb-IIIa) by specific receptor antagonists (GPIIb-IIIa inhibitors) such as abciximab (ReoPro®), epitifibatide (Integrilin®), or tirofiban (Aggrastat®) is being used successfully in this setting (50–52). In principle, more intense antithrombotic treatment is provided by combining

- two antiplatelet agents,
- antiplatelet monotherapy with anti-coagulation, or
- anticoagulation with dual antiplatelet therapy (13, 14).

However, it has been also documented that the risk of severe bleeding increases, the more intense antithrombotic regimes are administered (13–15). This is especially true in co-morbid patients with preexisting haemostatic defects of any kind. Such disorders may remain compensated, unless platelet function is not inhibited pharmacologically (12). Therefore, the benefit of the prevention from recurrent thrombotic or thromboembolic complications needs to outweigh the risk of severe haemorrhagic side-effects.

To translate this demand into clinical practice, several strategies and criteria for selecting the appropriate antithrombotic therapy should be considered to protect the individual patient from drug-induced bleeding. The core principle of this approach is a careful risk assessment and an individualized decision making for a given patient and a defined risk situation. Thus, apart from the acute or chronic clinical situation, a variety of distinct patient- and procedure-related risk factors have to be taken into account.

The individual risk profile is defined by patient characteristics such as age, co-morbidity (e.g., gastrointestinal disorders, chronic liver disease, renal failure, and diabetes mellitus), compliance, and co-medication. Patient-related risk factors for thrombosis include atrial fibrillation, mechanical heart-valve prothesis, cardiac thrombosis, a history of venous thromboembolism, and, as outlined above, genetically determined prothrombotic platelet receptor variants. Moreover, procedural risks along with PCI should be assessed, including vascular dissection, stent malposition, ostial stenting, long, multiple or overlapping stents (14). As the patient-related and the postprocedural risks may vary during the clinical course, re-assessment of the individual risk profile and adaption of the appropriate antithrombotic regimes are required (12). This refers to type, intensity, duration, and laboratory evaluation of the efficacy of antiplatelet therapy.

For high-risk patients (e.g., early after coronary stenting) who have to undergo urgent non-cardiac surgery with the mandatory need for interrupting the dual antiplatelet treatment, we (12) and others (14) have proposed a treatment algorithm that allows short-term discontinuation of oral antithrombotic therapy and i.v. administration of a GPIIb-IIIa receptor antagonist for bridging without increasing perioperative need for interrupting the dual antiplatelet therapy and i.v. administration of a GPIIb-IIIa receptor antagonist for bridging without increasing perioperative bleeding. Details of this algorithm using either tirofiban (Aggrastat®) or epitifibatide (Integrilin®) were presented recently in this Journal (12). For patients receiving clopidogrel or prasugrel who need elective or urgent non-cardiac surgery, an alternative to this regimen is now available by two newly designed direct platelet P2Y<sub>12</sub> antagonists, cangrelor and ticagrelor. Both agents have a reversible pharmacological effect on platelet function. Thus, cangrelor (which must be administered i.v.) and ticagrelor (which can be given orally) are associated with a rapid onset and reversal of platelet inhibition (60). As discussed below, recent findings of multicenter trials suggest that ticagrelor is superior in comparison to cangrelor (62–65). Thus, it appears reasonable to switch corresponding patients to ticagrelor 5 to 7 days before surgery (66).

**Decreased or defective platelet function**

In contrast to inherited platelet disorders such as Bernard Soulier syndrome, Glanzmann thrombasthenia, and congenital storage pool disease, acquired platelet function defects are much more frequent in clinical practice and therefore deserve special attention (15).

**Frequency of dysfunctional platelets and screening for defects in primary haemostasis**

Data on the rate of primary haemostatic defects are available from a prospective analysis by Koscielny et al (53) who studied 5649 consecutive patients (ranging in age between 17 and 87 years) prior to elective surgery. Aside from history and physical examination, the investigators used a bleeding history questionnaire and a standardized test panel for haemostatic screening, including in vitro bleeding time determined by platelet function analyzer (PFA-100). Patients with preexisting haemostatic disorders or anticoagulation therapy were primarily excluded from the analysis. Of the 5649 patients, bleeding history was negative in 5021 (88.8%); in the remaining group (11.2%) with a bleeding
history, screening for haemostatic defects was positive in 256 of the 628 patients (40.8%). Interestingly, diagnostic work-up of these 256 patients revealed platelet function defects in 73%, coagulation disorders in 0.8%, and combined haemostatic defects in 26.2% (including a predominant proportion of patients with von Willebrand disease). Among the 187 individuals with primary haemostatic defects, acquired platelet dysfunction was drug-induced in 162 patients (63.3%); among them, 147 were taking aspirin, ticlopidine, clopidogrel, or other nonsteroidal anti-inflammatory agents, while in 10 patients (6.2%) antibiotic treatment appeared to be the cause of platelet dysfunction. It is conceivable that this rate of antibiotics-induced bleeding diathesis may be even higher in other patient groups. Indeed, as reported on a smaller cohort of hospitalized patients with prolonged Ivy bleeding time, 54% were receiving large doses of antibiotics and 10% were taking aspirin or other nonsteroidal anti-inflammatory agents (54).

In conclusion, the data reported by Koscienly et al (53) convincingly illustrate several important issues:

- Acquired platelet function defects are indeed more frequent in clinical practice than generally believed.
- In the majority of cases, platelet dysfunction is drug-induced,
- whereby the predominant proportion of antiplatelet agents should not lead to an underestimation of given inhibitory effects by antibiotics.
- Screening for primary haemostatic defects requires indeed appropriate laboratory techniques, as demonstrated by the PFA-testing. Thus, albeit trivial, the widespread practice of platelet counting and coagulation screening (by APTT and prothrombin time) is entirely inappropriate to identify individuals with platelet dysfunction(s).
- Finally, as also documented here (in 2 of 256 patients), ‘pure’ coagulation defects occur less frequently than generally assumed.

Clinical conditions associated with platelet dysfunction and bleeding

Platelet function may be adversely affected by drugs, foods, food additives, or spices and by haematologic and non-haematologic disorders. Overall, it appears important to have a balanced view on impaired or compromised platelet function. In the majority of affected individuals, the clinical significance of acquired qualitative platelet disorders is low in daily life. Thus, their manifestations are usually mild. However, there are relevant exceptions to this rule, particularly when platelet dysfunction is associated with other haemostatic defects and/or when affected subjects undergo surgery. Furthermore, clinical assessment of acquired qualitative platelet disorders can by problematic by difficulties in standardization and interpretation of laboratory tests such as Ivy bleeding time and platelet aggregometry. These tests appear more useful in diagnosing platelet dysfunction than in predicting the true risk of bleeding (55, 56).

Apart from pharmacological agents, certain pathological conditions are frequently associated with platelet dysfunction(s) and clinical bleeding. These include uremia, in which small toxic compounds such as guanidinosuccinic acid and phenolic acids are produced known to inhibit platelet aggregation; liver cirrhosis, in which severe bleeding occurs when low coagulation factor activities, dysfibrinogenemia, and thrombocytopenia are concomitantly present with platelet functional defects of multifactorial cause; myeloproliferative disorders, acute leukemias, and myeloplastic syndromes, in which dysfunctional platelet populations are being produced resulting from clonal abnormalities of megakaryocytes; monoclonal gammopathy and antiplatelet autoantibodies which are frequently being associated with impaired platelet function; and cardiopulmonary bypass and haemodialysis, in which platelets are exposed to artificial surfaces, resulting in activation and degranulation (“exhausted” platelets). Acquired storage pool disease may be also observed in autoimmune thrombocytopenias, disseminated intravascular coagulation and in acute or chronic rejection following renal transplantation (17, 57).

Some of the clinical conditions that are frequently associated with complex haemostatic defects and, consequently, can cause overt bleeding, but may provoke life-threatening haemorrhages when anti-thrombotic agents are administered, have been reviewed recently (12, 15).

Drug-induced platelet dysfunction

Pharmacological agents are the most common cause of acquired platelet function disorders in our overmedicated society. A prominent source of unexpected bleeding is represented by well-known prototypes of antiplatelet agents, including

- acetylsalicylic acid (Aspirin®) and numerous nonsteroidal anti-inflammatory drugs (NSAIDs),
- thienopyridines (ticlopidine: Tikkly®; clopidogrel: Iscover®, Plavix®; prasugrel: Efient®, cangrelor and ticagrelor),
- GPIIb-IIIa receptor antagonists (abciximab: ReoPro®; epifibatide: Integrim®, and tirofiban: Aggrastat®).

Among the thienopyridines, prasugrel appears to have a greater antiplatelet potency and a lower rate of ‘nonresponders’ as compared to clopidogrel (58, 59). Indeed, prasugrel has been shown to deliver 10- to 100-fold potency in the inhibition of platelet aggregation ex vivo and of thrombus formation in vivo, as compared to clopidogrel (60). The more consistent inhibition of platelet function induced by prasugrel should result in greater protection from acute vascular events in patients with atherothrombotic burden. This hypothesis was recently tested in the phase III trial TRITON TIMI-38, a randomized, double-blind, parallel-group multicenter trial that evaluated >13 600 patients with moderate-to-high-risk acute coronary syndromes who required percutaneous coronary intervention (61). Patients were randomized to receive prasugrel (a 60-mg loading dose followed by a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose followed by a 75-mg daily maintenance dose) for 6 to 15 months. Prasugrel was associated with significantly reduced rates of ischaemic events (prasugrel 9.9%; clopidogrel 12.1%; hazard ratio for prasugrel 0.83; 95% confidence interval: 0.70 to 0.99).
There are two newly designed direct platelet P2Y12 antagonists, cangrelor and ticagrelor, both of which have a reversible pharmacological effect on platelet function. Cangrelor (which must be administered i.v.) and ticagrelor (which can be given orally) are associated with a rapid onset and reversal of platelet inhibition. These properties make them attractive alternatives to the thienopyridines, especially when rapid inhibition of platelet functions or its reversal is required (60). Thus, together with these new drugs, a panel of different P2Y12 inhibitors should be now available that allow to tailor the most appropriate antiplatelet regimens to individual patients in given risk situations. However, as documented in two recent, double-blind large-scale international studies on >11,300 patients, the CHAMPION PCI trial and the CHAMPION PLATFORM trial, cangrelor was neither superior to an oral 600-mg loading dose of clopidogrel dose (62) nor to placebo (63) in reducing the composite endpoint of death, myocardial infarction, or ischemia-driven revascularization at 48 hrs. An editorial on the negative results for cangrelor was entitled “a champion lost in translation?” (64). By contrast, in the PLATO study, a multicenter, double-blind, randomized trial on >18,600 patients with acute coronary syndromes, treatment with ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding, as compared to treatment with clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) (65). However, ticagrelor was associated with more frequent bleeding not related to coronary-artery bypass grafting (ticagrelor 4.5%; clopidogrel 3.8%; p = 0.03) and new side effects (not seen with clopidogrel), including dyspepsia, bradycardia, and increased levels of uric acid and creatinine (65). Thus, therapy with ticagrelor is not recommended in patients with chronic obstructive pulmonary disease, hyperuricaemia, renal failure, or bradycardia (66).

Agents that increase intraplatelet cyclic adenosine monophosphate (cAMP), either by stimulation of its synthesis (prostaglandin E$_2$ (PGE$_2$); prostacyclin (PGI$_2$); Iloprost®) or by phosphodiesterase inhibition (dipyridamol; formerly Persantin®, today in combination with aspirin: Aggrenox®; theophylline; caffeine), may also impair platelet function. Nitric oxide (NO) donors can increase the bleeding time and may contribute to haemorrhage, specifically in uremic patients. Antibiotics, particularly those of the β-lactam type such as penicillins and cephalosporins, may cause a prolongation of the bleeding time even in normal volunteers. The mechanism whereby these antibiotics impair platelet function is currently not known, although it has been proposed that they bind to the platelet membrane and inhibit the interaction of agonists and von Willebrand factor or modify platelet receptors chemically (67). Differences in the antiplatelet effect (e.g., inhibition of aggregation) of various anti-biotics (such as carbencillin, penicillin G, ticarcillin, ampicillin, nafcillin, azlocillin, piperacillin, alpacin, or mezlocillin) probably relate to differences in blood levels and in drug potency. Adsorption and nonspecific binding to platelet membrane constituents are also discussed as mechanism by which volume expanders can impair platelet aggregation, however, interference of dextran or hydroxyethyl starch with GPIIb-IIIa and its ligands may be relevant clinically only in patients with a preexisting haemostatic defect (e.g., von Willebrand disease) (67).

In general, acquired platelet function defects secondary to drugs are mild and ubiquitous, considering, for example, the large number of individuals who take aspirin regularly and therefore have impaired platelet function due to irreversible inhibition of cyclo-oxygenase-1-dependent thromboxane A$_2$ formation. The effect of aspirin ingestion on the haemostatic competency of normal volunteers has been debated but appears to be of minor relevance. Nevertheless, individuals taking aspirin chronically report an increase in bruising and epistaxis. More importantly, the use of aspirin is associated with gastrointestinal blood loss and, rarely, with intracranial haemorrhage. For example, there was a slight, but statistically insignificant increase in haemorrhagic strokes in a group of otherwise healthy physicians who took aspirin chronically as primary prophylaxis against myocardial infarction (68). Besides aspirin, more than 250 pharmacological agents, foods (fish oils, black tree fungi) or diets (eicosapentaenoic acid), spices (onion, garlic, cumin), and vitamins have been reported to impair platelet function. For further information, the reader is referred to other review articles (50, 67, 69, 70).

Taken together, for almost all agents interfering with platelet reactivity, antagonizing platelet activation, or inhibiting platelet function, data are limited to abnormal platelet aggregation studies in vitro or prolonged bleeding time which necessarily do not reflect the ‘true’ bleeding risk and therefore may have minor or questionable clinical importance. By contrast, treatment with antiplatelet agents can cause or aggravate severe haemorrhage in patients with pre-existing haemostatic defects of any kind. This is particularly true for certain clinical settings (sepsis, polytrauma, disseminated intravascular coagulation), or conditions (cardiopulmonary bypass surgery, liver transplantation), haematologic or systemic diseases that affect platelet function or are associated frequently with bleeding disorders (renal failure, liver cirrhosis, systemic lupus erythematosus, myeloproliferative disorders, acute leukemias, myelodysplastic syndromes, and myeloma). In this context, it will be prudent to avoid the use of the new P2Y$_{12}$ inhibitors, prasugrel and ticagrelor, both of which appear to have a higher platelet inhibitory potency than clopidogrel, in patients with a history of transient ischaemic attack or stroke, or symptoms of an increased bleeding risk (presumably due to multiple haemostatic defects along with various underlying disorders) (66).

**Bleeding risks associated with antiplatelet therapy**

To date, major bleeding is the most-feared and also most important complication of
treatment in patients on antiplatelet treatment (71). Numerous randomized controlled trials (RCTs) and subsequent meta-analyses of RCTs have provided valid and reliable data on the incidence of bleeding in selected study populations using antiplatelet agents.

In 2002, the Antithrombotic Trialists’ (ATT) Collaboration analyzed 287 studies involving 135 000 patients in comparisons of antiplatelet therapy versus control (195 trials) and 77 000 in comparisons of different antiplatelet regimens (92 trials) (10). These ATT data were recently reviewed in this Journal (12). Overall, allocation to antiplatelet therapy was effective by reducing “serious vascular events” with 10 to 20 such events avoided for each year of treatment among high-risk patients. In each of the risk categories (non-fatal myocardial infarction, non-fatal stroke, and vascular mortality), “the absolute benefits of antiplatelet therapy substantially outweighed the absolute risks of major extracranial bleeding” (10). More detailed information, taken from the ATT Collaboration, is depicted in Table 1. Among patients at high risk of immediate coronary occlusion, short-term addition of an intravenous GPIIb-IIIa receptor antagonist to aspirin prevented a further 20 vascular events per 1000 (p < 0.001) but caused 23 major (but rarely fatal) extracranial bleeds per 1000.

In a more recent meta-analysis of 18 randomized trials, comprising almost 130 000 patients and comparing single and dual antiplatelet regimens, major, minor, fatal and intracranial bleedings were evaluated (72). For each endpoint, relative risk (RR) and 95% confidence intervals (CI) were calculated. Dual antiplatelet therapy was associated with a significantly increased risk of major (RR 1.47, CI 1.36–1.60) and minor bleeding (RR 1.56, CI 1.47–1.66) compared to single agent therapy. By contrast, no significant differences were found in fatal (RR 1.10, CI 0.87–1.40) or intracranial bleedings (RR 1.07, CI 0.85–1.35). However, the numbers in these subgroups were too small to make definitive assessments. As discussed previously (12), conclusions from this meta-analysis are limited: inclusion criteria of the trials were clinical follow-up for at least one month and the presence of data on bleeding complications during this time interval.

Overall, patients treated with dual antiplatelet therapy appear to have an approximately 40 to 50% increase in risks of major or minor bleedings compared to those receiving single agent therapy. The magnitude of this excess risk is close to the approximately 60% increase documented in trials comparing single antiplatelet agents to placebo. This significant risk should be considered when selecting the optimal antiplatelet strategy for long-term treatment of patients with a history of occlusive vascular events or those at high risk of developing cardiovascular or occlusive arterial disease.

More recently, the ATT Collaborators have assessed the benefits and risks of antiplatelet agents in primary prevention (11). Serious vascular events (myocardial infarction, stroke, or vascular death) and major bleeds were analyzed in 6 primary prevention trials (95 000 individuals at low-average risk; 660 000 person-years; 5554 serious vascular events) and 16 secondary prevention trials (17 000 patients at high-average risk; 43 000 person-years; 3306 serious vascular events) that compared long-term aspirin versus control. In the primary prevention trials, aspirin yielded a 12% proportional reduction in serious vascular events (0.51% aspirin vs. 0.57% control per year, p = 0.0001). Concomitantly, aspirin allocation increased major gastrointestinal and extracranial bleeds (0.10 vs. 0.07% per year, p < 0.0001). In the secondary prevention trials, aspirin allocation was associated with a greater absolute reduction in serious vascular events (6.7% vs. 8.2% per year, p < 0.0001), with a non-significant increase in haemorrhagic stroke but reduction of about a fifth in total stroke (2.08% vs. 2.54% per year, p = 0.002) and in coronary events (4.3% vs. 5.3% per year, p < 0.0001). The ATT Collaborators concluded that, for primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive vascular events needs to be weighed against any increase in major bleeds (11). This conclusion is also in accord with the large-population study of low-dose aspirin (100 mg every other day) in the primary prevention of cardiovascular disease enrolling more than 39 800 women (73). The initially healthy individuals (45 years or older) were randomly as-

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**Tab. 1** Effects of antiplatelet therapy on fatal and non-fatal major extracranial bleeds; data taken from (10)

<table>
<thead>
<tr>
<th>category of trial</th>
<th>number of fatal + number of non-fatal major bleeds / number of patients (combined %)*</th>
<th>stratified odds ratio (SE)</th>
<th>adjusted absolute excess risk/1000 (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>antiplatelet groups</td>
<td>adjusted controls†</td>
<td></td>
</tr>
<tr>
<td>previous MI</td>
<td>1 + 2 / 672 (0.45)</td>
<td>1 + 2 / 668 (0.45)</td>
<td></td>
</tr>
<tr>
<td>acute MI</td>
<td>2 + 26 / 9,134 (0.31)</td>
<td>3 + 20 / 9,136 (0.25)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>previous stroke and TIA</td>
<td>15 + 65 / 8,276 (0.97)</td>
<td>7 + 32 / 8,289 (0.47)</td>
<td>2.0 (0.3)</td>
</tr>
<tr>
<td>acute stroke</td>
<td>60 + 135 / 20,195 (0.97)</td>
<td>43 + 73 / 20,178 (0.57)</td>
<td>1.7 (0.1)</td>
</tr>
<tr>
<td>other high risk</td>
<td>17 + 212 / 8,881 (2.58)</td>
<td>17 + 135 / 8,897 (1.71)</td>
<td>1.5 (0.1)</td>
</tr>
<tr>
<td>total</td>
<td>95 + 440 / 47,158 (1.13)</td>
<td>71 + 262 / 47,168 (0.71)</td>
<td>1.6 (0.1)§</td>
</tr>
</tbody>
</table>

*only trials with systematic recording of all major extracranial bleeds (and that recorded at least one such bleed) included; † percentage adjusted for unbalanced randomization (10); ‡ p < 0.001; § p < 0.0001; ¶ χ² for heterogeneity = 2.6, df = 4, not significant (10)

MI: myocardial infarction; TIA: transient ischemic attack

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Management of patients at risk of decreased platelet function

In management of patients at risk of decreased platelet function, several strategies should be considered in order to prevent and protect the individual patient from bleeding due to antiplatelet therapy. These strategies include:

1. **Assessment of past and present history, including complete evaluation of medical history and laboratory testing.** Appropriate diagnostic investigations are essential to reduce the incidence of iatrogenic hazards of interruption of drug use for other relevant variables that need to be considered. The expanding use of laboratory testing has resulted in an increased proportion of drug-related bleeding episodes in patients with a history of bleeding, in particular due to antithrombotic therapy. This is particularly true for patients who are using antithrombotic drugs in the long-term.

2. **Evaluation of post and pre-surgical history, in particular the clinical course, re-assessment of the individual risk profile and adaption of the antiplatelet therapy.** The primary objective of any modus operandi is to prevent and protect the individual patient from bleeding due to antiplatelet therapy. As per the clinical course, re-assessment of the individual risk profile and adaption of the antiplatelet therapy are crucial in order to manage the risk from massive proportional (case-by-case analysis): patients with a history of bleeding, in particular due to antithrombotic therapy, should be differentiated in clinical practice.

3. **Avoid unnecessary exposure to blood products.** Mild bleeding episodes in patients on antiplatelet therapy may be only considered as a therapeutic option. However, interruption of antiplatelet therapy is required in case of bleeding episodes of minor importance.

4. **Minimize the risk from massive proportional bleeding.** The risk from massive proportional bleeding can be managed by withdrawing the antiplatelet therapy. This is evident when comparing the results obtained from well-controlled patients with the findings of clinical trials with the results obtained from patients in real life surveys. For example, as discussed in the prothrombotic effects of both options. To date, recombinant factor VIIa treatment for their cardio- or cerebrovascular risk, present with de- creased platelet function.

5. **Balancing of the benefit-risk estimation.** To achieve the objective and to apply the individualized decision making and a thorough clinical assessment of the benefit-risk estimation with regard to the fact that patients with preexisting bleeding disorders and those with acquired platelet dysfunction (e.g., von Willebrand disease) are often diverse from the core principle, two groups of patients with different clinical picture, and the application of a staged protocol of investigations. The expanding use of laboratory testing has resulted in an increased proportion of drug-related bleeding episodes in patients with a history of bleeding, in particular due to antithrombotic therapy. This is particularly true for patients who are using antithrombotic drugs in the long-term.

6. **Case-by-case analysis: patients with a history of bleeding, in particular due to antithrombotic therapy, should be differentiated in clinical practice.** The primary objective of any modus operandi is to prevent and protect the individual patient from bleeding due to antiplatelet therapy. As per the clinical course, re-assessment of the individual risk profile and adaption of the antiplatelet therapy are crucial in order to manage the risk from massive proportional bleeding.

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10. **Case-by-case analysis: patients with a history of bleeding, in particular due to antithrombotic therapy, should be differentiated in clinical practice.** The primary objective of any modus operandi is to prevent and protect the individual patient from bleeding due to antiplatelet therapy. As per the clinical course, re-assessment of the individual risk profile and adaption of the antiplatelet therapy are crucial in order to manage the risk from massive proportional bleeding.

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17. **Balance the benefit-risk estimation with regard to the fact that patients with preexisting bleeding disorders and those with acquired platelet dysfunction (e.g., von Willebrand disease) are often diverse from the core principle, two groups of patients with different clinical picture, and the application of a staged protocol of investigations.** The expanding use of laboratory testing has resulted in an increased proportion of drug-related bleeding episodes in patients with a history of bleeding, in particular due to antithrombotic therapy. This is particularly true for patients who are using antithrombotic drugs in the long-term.

18. **Case-by-case analysis: patients with a history of bleeding, in particular due to antithrombotic therapy, should be differentiated in clinical practice.** The primary objective of any modus operandi is to prevent and protect the individual patient from bleeding due to antiplatelet therapy. As per the clinical course, re-assessment of the individual risk profile and adaption of the antiplatelet therapy are crucial in order to manage the risk from massive proportional bleeding.
VIIa (NovoSeven®) has been increasingly used in patients with unexpected major bleeds (78). Again, the thrombotic potential of activated factor VIIa has to be considered, specifically in patients prone to occlusive vascular complications.

Less specific treatments that enhance haemostasis and coagulation or inhibit fibrinolysis include desmopressin (DDAVP, Minirin®), epsilon aminocaproic acid (EAAC) and tranexamic acid (Cyklokapron®). Aprotinin (Trasylol®) was shown to be effective in reducing major bleeding, and thereby the need for transfusions of red cell concentrates, during and following cardiac surgery. However, serious concerns regarding the safety of this drug were made. Recently, a significantly reduced long-term survival among patients who received aprotinin compared with those who received EACA, tranexamic acid, or no haemostatic medication was documented (79). This report led to the withdrawal of aprotinin.

Apart from treatment of von Willebrand disease, the evidence base for therapy with desmopressin (DDAVP) is most developed in patients with platelet storage pool disorders (80). However, it remains to be demonstrated that shortening of abnormally bleeding time following administration of DDAVP in patients with qualitative platelet disorders really translates into reduced clinical bleeding.

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Conflict of Interests

R.E.S. is a consultant to Bayer HealthCare and receives funding from Baxter Deutschland. H.S. and M.M.R. declare that they have no conflict of interests.

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