Antiplatelet drugs and outcome in mixed admissions to an intensive care unit*

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LEARNING OBJECTIVES

After participating in this activity, the participant should be better able to:

1. Identify antiplatelet drugs.
2. Describe their use in patients admitted to the intensive care unit.
3. Use this information in a clinical setting.

Unless otherwise noted below, each faculty or staff's spouse/life partner (if any) has nothing to disclose.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: **Platelet activation has been implicated in microvascular thrombosis and organ failure. We tested the hypothesis that antiplatelet drugs favorably affect outcome in patients nonelectively admitted to an intensive care unit.**

Design: **Retrospective cohort study.**

Setting: **A 22-bed intensive care unit of a tertiary care center.**

Patients: **Six hundred fifteen consecutive patients admitted to an intensive care unit within 24 hrs after hospitalization were enrolled, approximately 25% of whom received antiplatelet drugs (acetylsalicylic acid, clopidogrel) for secondary prevention of vascular disease. Impact of antiplatelet drugs and established risk factors on mortality were assessed by logistic regression and 2 × 2 table analysis.**

Interventions: **None.**

Measurements and Main Results: **Patients on antiplatelet drugs were markedly older and presented higher Acute Physiology and Chronic Health Evaluation II scores on intensive care unit admission. There was no significant difference in injury severity scores in trauma patients with (21 [range, 13–29]) or without antiplatelet drugs (18 [range, 12–29]). Using logistic regression analysis, a significant reduction of mortality was estimated for the use of antiplatelet drugs in various subgroups of patients with normal or high bleeding risk (odds ratios, 0.04–0.34). Significant benefit was also estimated by 2 × 2 table analysis of Acute Physiology and Chronic Health Evaluation II-matched samples (Acute Physiology and Chronic Health Evaluation II >20) of internal medicine patients and/or patients receiving medical treatment. No significant benefit but also no harm of antiplatelet drugs was estimated in Acute Physiology and Chronic Health Evaluation II-matched samples of patients with increased bleeding risk: patients from surgery departments overall, patients with surgical treatment, trauma, active bleeding, or transfusion (odds ratios, 0.51–0.88).**

Conclusions: **Our data are consistent with prevention of organ dysfunction by antiplatelet drugs, which may be masked in some patients by concomitant bleeding risk. Antiplatelet drugs might offer a novel therapeutic option to prevent organ failure, at least in the absence of active bleeding. This hypothesis warrants testing in a prospective trial. (Crit Care Med 2010; 38:32–37)**

KEY WORDS: antiplatelet drugs; critical illness; fatal outcome; multiple organ failure; sepsis

***See also p. 298.**

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Sepsis and multiple organ failure are leading causes of death in critically ill patients. Activation of circulating blood platelets is a common feature of systemic inflammation and sepsis (1–3). Activation of platelets results in their sequestration in the microvasculature, and thrombocytopenia is a marker of poor outcome in critically ill patients (4). Platelets are not only one of the major players in hemostasis and thrombosis, but they are also considered inflammatory cells (5, 6). Platelets might not only contribute to organ failure by thrombotic microangiopathy and disseminated intravascular coagulation, but also by modulating inflammatory responses (1, 2, 7, 8). Thus, the question arises whether drugs that inhibit platelet activation such as acetylsalicylic acid or clopidogrel that are widely used in the secondary prevention of cardiovascular, cerebrovascular, and peripheral arterial thrombosis may have a benefit in critically ill patients. However, because antiplatelet drugs increase bleeding risk, they may counteract any potential benefit either on microcirculation or inflammation. Consistently, antiplatelet drugs are discontinued when patients are admitted to a surgical intensive care unit (ICU). The use of antiplatelet drugs in critically ill patients has scarcely been studied so far. There are only few reports on antiplatelet drugs in animal models of endotoxin-induced inflammatory responses and/or organ failure. Taylor et al (9) and Pu et al (10) have shown that infusion of antagonists of the platelet GPIIb/IIIa receptor, that is, the most powerful inhibitors of platelet aggregation (11), into baboons and rabbits decreases endotoxin-induced ischemic organ damage and lethality. Conflicting data have been reported on clopidogrel in endotoxinemia. Clopidogrel is an irreversible inhibitor of the platelet P2Y12 receptor and blocks the effect of ADP on platelet activation (12). No significant effects of clopidogrel on hemostatic and inflammatory responses were observed in pigs infused with *Escherichia coli* endotoxin (13), whereas in endotoxin-treated mice, clopidogrel reduced not only platelet activation, but also reduced platelet-mediated activation of neutrophils as well as endotoxin-induced tumor necrosis factor-α and interleukin-1β upregulation (14, 15). We are not aware of data on effects of acetylsalicylic acid (ASA), the most widely used antiplatelet drug (16, 17), in critical illness or models of endotoxemia. However, there are several reports indicating that even low doses of ASA inhibit inflammatory reactions such as increase in plasma levels of proinflammatory cytokines or C-reactive protein in patients with cardiovascular or cerebrovascular disease (18, 19). In an animal model of atherosclerosis, low-dose ASA was found to inhibit upregulation of nuclear factor κB, a central transcription factor in inflammation and cell death regulation, in the vessel wall (20).

The aim of our present study was to test the hypothesis that antiplatelet drugs, that is, ASA or clopidogrel, as they are used in atherosclerotic patients, have an impact on the outcome in patients developing life-threatening conditions not necessarily associated with their underlying cardiovascular disease such as acute infection, emergency surgery, and trauma. Thus, as a first approach, we analyzed data from more than 600 consecutive emergency admissions of whom approximately 25% were either on low-dose ASA or clopidogrel. Because both drugs irreversibly inhibit platelet activity, we could expect to see their possible effects for at least 1 week even when the drugs were discontinued on admission.

PATIENTS AND METHODS

The design of this retrospective study that analyzed consecutive patients who were admitted over a period of 2 yrs to a 22-bed ICU of a tertiary care center was approved by the local ethical committee. Informed consent was obtained from patients or next of kin before any clinical and laboratory data from a patient record were evaluated. Only patients who were admitted to the ICU within 24 hrs after arrival in the hospital were included. Exclusion criteria were elective surgery, transfer from an ICU of another hospital, age <18 yrs, and pregnancy. According to these criteria, data from 615 patients could be evaluated. Three hundred sixty-one patients received only medical treatment and 254 patients underwent surgery.

Information regarding the use of antiplatelet drugs for secondary prevention of cardiovascular, cerebrovascular, or peripheral arterial diseases before hospitalization was obtained from the case histories of the patients. Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Injury Severity Scores (ISSs) were recorded on ICU admission. "Bleeding" was defined as any bleeding event documented in the patient files. Red blood cells, blood platelets, or fresh–frozen plasma were administered at the discretion of the physician in charge. Transfusion status (defined as administration of any blood product as specified previously), information on mechanical ventilation, catecholamine treatment, continuous venovenous hemodiafiltration, and infection were similarly assessed from the files.

The clinical end point of the study was death during ICU treatment (nonsurvivor) or discharge from the ICU.

Statistical analysis was performed with SPSS 13.0 for Windows (SPSS, Chicago, IL). If not otherwise indicated, data are presented as median with interquartile range given in brackets. Significance is developed at $p < .05$. Mann-Whitney U test was performed for comparing unpaired samples and chi-square test was used for comparing frequencies. Stepwise logistic regression was used to evaluate the impact of various variables on mortality. Forward and backward conditional selection of variables at significance levels of $p < .05$ and $p < .1$, respectively, led to identical results. Odds ratios were calculated either by logistic regression or by 2×2 table analysis (chi-square test).

RESULTS

Epidemiologic and Clinical Data. Seventy-one percent of the 615 patients were admitted to the ICU either primarily through the local emergency room (52%) or from general wards of the local internal and surgical departments (19%). The remaining 29% of patients who were first admitted to another hospital or medical center were secondarily brought to the unit within 24 hrs. Approximately two third of the patients had been allocated to the surgical departments and one third to the medical departments; one patient came from the department of gynecology (Table 2). One hundred seventy-five patients were admitted with trauma (ISS = 20 [12–29]), including 143 patients with craniocerebral injury and 115 patients with multiple trauma (ISS >16). Approximately 60% of all patients presented signs of active bleeding on admission or during the ICU stay; in 40% of patients, intracranial bleeding was diagnosed. Thirty-six percent of all patients needed transfusions. Three hundred sixty-one patients received only medical treatment, whereas 254 patients underwent surgery.

One hundred fifty-four of the 615 patients were on antiplatelet drugs at the time of admission to the hospital. One hundred twenty-nine patients were on ASA (maximum dosage 160 mg/day), 10 had received clopidogrel (maximum dosage 75 mg/d), and 15 a combination of ASA plus clopidogrel. As a result of the low numbers of patients receiving clopidogrel or ASA + clopidogrel, we did not perform subgroup analyses.

Patients using antiplatelet drugs were markedly older by approximately 16 yrs and had higher APACHE II scores at admission when compared with patients not using such medication (Table 1). The differences in the APACHE II score were not only the result of the difference in age, but also the result of higher values of the acute physiology score and chronic health points. No differences were observed in the Glasgow Coma Scale. Despite the marked differences in age and APACHE II score, patients receiving antiplatelet drugs had the same mortality as those without such pre-existing medication (37 vs. 38%; Table 1). There were also no differences between patients with and without antiplatelet drugs in respect to the length of ICU stay (6 [2–18] vs. 6 [2–18] days), the frequency of infections (53% vs. 48%), sepsis (both 45%), mechanical ventilation (86% vs. 84%), continuous venovenous hemodiafiltration (14% vs. 9%), or treatment with catecholamines (56% vs. 50%).

In all subgroups of patients stratified according to allocation to departments (internal medicine, surgery), type of treatment (medical or surgical), traumatic injuries, or presence of active bleeding, the pre-existing medication with antiplatelet drugs was associated with markedly higher APACHE II scores, but there were no significant differences in mortality (Table 2).

Although not significantly different, trauma patients with antiplatelet drugs had slightly higher ISSs when compared with patients without such pre-existing medication (21 [13–29] vs. 18 [12–29]). This was also true for patients with multiple trauma (28 [18–40] vs. 26 [19–36]) or craniocerebral injury (ISS: 25 [17–43] vs. 20 [14–29]).

Time Course of Platelet Count. An effect of the premedication with antiplatelet drugs could be clearly demonstrated by differences in the time course of the platelet count after ICU admission (Fig. 1). The initial drop in platelet count with a nadir at day 3 after ICU admission as well as the recovery, which started to surmount the initial values at day 8 to 10, was blunted in patients with antiplatelet drugs when compared with control subjects.

Logistic Regression Analysis. As a result of the large differences in age and APACHE II score but no differences in mortality between patients with and without pre-existing medication with antiplatelet drugs, logistic regression was applied to evaluate the influence of antiplatelet drugs on outcome. In a first step with outcome (survival/nonsurvival) as the dependent variable and age, gender, APACHE II score, and pre-existing medication with anti-platelet drugs as independent variables, only gender was found to have no significant effect on mortality. Pre-existent medication with antiplatelet drugs reduced the odds ratio for mortality by a factor of approximately 5, whereas an increase of APACHE II score

Table 1. Age, gender, APACHE II score, and mortality in patient with and without pre-existing medication with antiplatelet drugs

	Antiplatelet Drugs		
	No	Yes	*p*
n	461	154	
Age, yrs	56 [41–71]	72 [63–79]	≤.0001
Male/female, %	57.0/43.0	57.4/42.6	.835
APACHE II score	19 [13–19]	25 [19–32]	≤.0001
Acute physiology score	9 [6–13]	13 [8–16]	≤.0001
Chronic health points	0 [0–0]	5 [0–5]	≤.0001
Glasgow Coma Scale score	5 [0–10]	5 [1–10]	≤.359
Age points	3 [0–5]	5 [3–6]	≤.0001
Intensive care unit mortality, %	38.4	36.8	.760

APACHE, Acute Physiology and Chronic Health Evaluation.

Table 2. Characterization of patients with and without pre-existing medication with antiplatelet drugs according to place of primary admission, allocation to treatment specialization, trauma injury, bleeding, and type of treatment

		Without Antiplatelet Drugs			With Antiplatelet Drugs		
Patient Characteristics	n	n, %	APACHE II	Mortality, %	n, %	APACHE II	Mortality, %
Primary admission from							
Local emergency room	321	77	19 (13–25)	35	23	26 (21–33)[a]	39
Local wards	118	61	22 (14–26)	45	39	28 (19–33)[c]	39
Other hospitals/medical centers	176	81	19 (13–24)	41	19	23 (19–30)[b]	48
Allocation to departments							
Internal medicine	222	65	24 (17–30)	46	35	27 (21–33)[c]	36
General surgery	61	66	18 (13–24)	35	34	24 (18–34)[d]	38
Trauma surgery	89	89	14 (8–20)	9	11	24 (16–33)[c]	40[d]
Neurosurgery	242	81	19 (13–23)	46	19	25 (18–30)[a]	38
Gynecology	1						
Trauma	181	88	16 (10–22)	19	12	25 (18–30)[a]	27
Multiple trauma (Injury Severity Score >16)	117	87	18 (12–24)	25	13	27 (20–31)[a]	33
Craniocerebral injury	144	87	17 (12–22)	21	13	26 (20–31)[a]	21
Active bleeding	378	82	18 (12–24)	37	18	26 (19–31)[a]	43
With transfusion	163	76	19 (13–24)	28	24	27 (20–31)[a]	36
Intracranial bleeding	245	78	19 (14–23)	44	19	25 (19–39)[a]	41
Type of treatment							
Conservative/medical	361	72	21 (15–27)	50	28	26 (21–33)[a]	40
Surgical	254	79	17 (12–22)	23	21	24 (18–31)[a]	31

APACHE, Acute Physiology and Chronic Health Evaluation.
Significant differences between patient without and with antiplatelet drugs: [a]$p < .0001$; [b]$p < .001$; [c]$p < .01$; [d]$p < .05$.

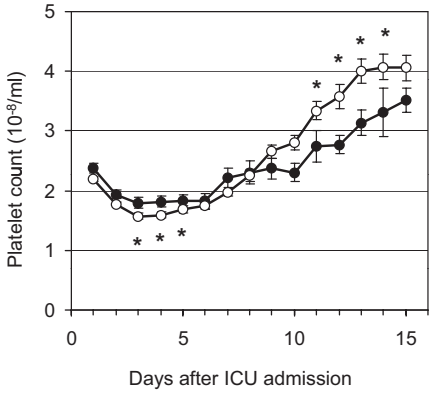

Figure 1. Time course of platelet count (mean ± SEM) on admission to the intensive care unit (*ICU*) in patients without (*open circles*) and with antiplatelet drugs (*filled circles*). Days with a significant difference ($p < .05$) are indicated by an asterisk.

Table 3. Odds ratio for mortality in all patients[a]

Variable	Odds Ratio	95% Confidence Interval
Age	1.04	1.03–1.06
APACHE II	1.16	1.12–1.19
Antiplatelet drugs	0.19	0.12–0.33

APACHE, Acute Physiology and Chronic Health Evaluation.

[a]The model of stepwise logistic regression included age, gender, APACHE II score, and pre-existing medication with antiplatelet drugs as independent variables.

by 1 point or age by 1 year was associated with an increase in odds ratio by 16% and 4%, respectively (Table 3). Because patients who died within the first 24 to 48 hrs after ICU admission may introduce a bias to the effects of antiplatelet drugs on mortality, we repeated the analysis excluding the 185 patients with a stay of less than 48 hrs. Compared with the entire cohort, the effect of the pre-existing medication on mortality was only slightly increased (odds ratio, 0.19 [0.12–0.33] vs. 0.22 [0.12–0.40]).

Next we tested the effect of antiplatelet drugs on outcome in subgroups of patients with special focus on patients with high bleeding risk. Patients who were allocated to surgery (general, trauma, or neurosurgery) had even a more favorable effect of antiplatelet drugs compared with internal medicine patients (odds ratios, 0.26 [0.13–0.53] vs. 0.15 [0.07–0.32]). The benefit in the surgical patients resulted from the large cohort of neurosurgical patients for whom a mortality odds ratio as low as 0.12 (0.04–0.30) was calculated (Table 4).

When patients were grouped according to the actual treatment (medical or surgical) irrespective of the department to which they were allocated or any other indications of increased bleeding risk such as trauma, signs of active bleeding, or need for transfusion, a pre-existing medication with antiplatelet drugs was associated with a slightly more favorable odds ratio for mortality in patients with medical treatment when compared with those with surgical treatment (Table 4).

Using logistic regression, a very high benefit from a pre-existing medication with antiplatelet drugs was also estimated for patients with trauma, that is, odds ratios as low as 0.04 to 0.06 were calculated irrespective of medical or surgical treatment. Such benefit was also observed in patients with multiple trauma and/or craniocerebral injuries (Table 4). As mentioned, patients with antiplatelet drugs had slightly higher ISS when compared with those without such medication.

Even for patients with signs of active bleeding, including intracranial bleeding, or those needing transfusion, a significant benefit of antiplatelet drugs was estimated by logistic regression (Table 4).

Two × Two Table Analysis in Subgroups of Patients According to APACHE II Scores. As a second approach to evaluate a possible benefit of a pre-existing medication with antiplatelet drugs, we divided all patients into subgroups according to the quartiles of APACHE II scores to better match patients without and with pre-existing medication with antiplatelet drugs. Odds ratios for mortality of approximately 1.0 were obtained when either all patients or patients with low APACHE II scores (first and second quartiles) were considered. However, when disease was more pronounced, that is, APACHE II scores at admission were ≥15, odds ratios <0.5 were observed indicating a benefit of antiplatelet drugs on outcome (Fig. 2).

In analogy to the stepwise logistic regression as described in Table 4, we performed 2 × 2 table analyses with corresponding APACHE II-matched subgroups with low and high bleeding risk. We used a cutoff of APACHE II >20 to get nearly matched groups, 207 without and 110 with antiplatelet drugs, and APACHE II scores of 26 (23–30) and 29 (25–35), respectively ($p < .00001$). In this analysis, internal medicine patients had a significant benefit of a pre-existing medication with antiplatelet drugs that was slightly lower when compared with the odds ratio obtained with logistic regression (Table 4). In contrast to logistic regression, the 2 × 2 table analysis failed to provide a significant benefit of antiplatelet drugs in patients from the surgery departments (Table 4). However, a still significant benefit was estimated for neurosurgery patients with an odds ratio of 0.32 (0.12–0.84). We did also not observe significant effects (benefit or harm; odds ratios ranging from 0.42–0.88) in the APACHE II-matched subgroups of patients with trauma, active bleeding, and/or transfusion and surgical treatment. However, a highly significant benefit was calculated for patients with medical treatment irrespective of any risk factors of bleeding (Table 4).

DISCUSSION

In the present study, we performed a retrospective analysis on the effect of a pre-existing medication with antiplatelet drugs on the mortality in critically ill patients who were submitted to the ICU within 24 hrs after hospitalization. Six hundred fifteen patients were enrolled and approximately 25% of them were on antiplatelet drugs because they had atherosclerotic cardiovascular, cerebrovascular, or peripheral arterial occlusive disease. Such vascular diseases have a high prevalence in elderly subjects. Consistently, patients with antiplatelet drugs were approximately 16 yrs older than those without antiplatelet drugs. The higher age as well as the advanced atherosclerosis may be the main reasons for the higher APACHE II score of patients with antiplatelet drugs at the time of ICU admission when compared with their control cohort; nevertheless, patients with antiplatelet drugs had both higher chronic and acute APACHE II subscores.

The two types of antiplatelet drugs that had been given to the present patient cohort, that is, ASA and clopidogrel, inhibit irreversibly platelet functions. Clopidogrel interacts with the purinergic P_2Y_{12} receptor, and this receptor plays a crucial role in platelet activation (11, 12, 21). There is also some evidence that P_2Y_{12} receptors should be involved in the function of neuronal cells (21). ASA preferentially inhibits cyclo-oxygenase-1, which is constitutively expressed in platelets as well as gastric mucosa cells and has much less effect on cyclo-oxygenase-2 that is upregulated in various cell types during inflammation (17, 22).

Table 4. Effects of antiplatelet drugs on outcome in subgroups of patients[a]

Subgroups of Patients	Stepwise Logistic Regression			2 × 2 Table Analysis		
	N	OR	95% CI	N	OR	95% CI
Allocation to departments						
Internal medicine	78/144	0.26	0.13–0.53	61/93	0.36	0.18–0.75
General surgery	21/40	0.24	0.04–1.31	13/17	0.87	0.15–5.00
Trauma surgery	10/79	0.92	0.06–13.6	6/17	3.67	0.38–42.1
Neurosurgery	46/196	0.12	0.04–0.30	30/79	0.32	0.12–0.84
Trauma	22/159	0.06	0.01–0.35	15/47	0.51	0.51–2.02
Multiple trauma (Injury Severity Score >16)	15/102	0.04	0.01–0.35	11/35	0.56	0.11–2.63
Craniocerebral injury	19/125	0.04	0.01–0.32	14/40	0.56	0.13–2.40
Active bleeding	68/319	0.23	0.12–0.47	48/128	0.71	0.34–1.48
With transfusion	39/124	0.34	0.12–0.90	49/72	0.82	0.20–2.20
Intracranial bleeding	46/191	0.13	0.05–0.34	32/82	0.42	0.16–1.05
Type of treatment						
Medical	101/260	0.20	0.11–0.36	77/145	0.32	0.17–0.59
Surgical	54/200	0.24	0.10–0.61	32/62	0.88	0.34–2.26

APACHE, Acute Physiology and Chronic Health Evaluation; OR, odds ratio; CI, confidence interval.

[a]Odds ratios of mortality were calculated either by a stepwise model of logistic regression with age, gender, APACHE II score, and pre-existing medication with antiplatelet drugs as independent variables or by 2 × 2 table analysis in APACHE II-matched subgroups of patients. n = numbers of patients with/without antiplatelet drugs.

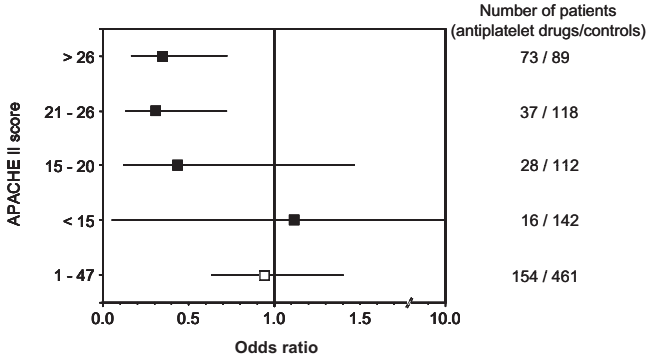

Figure 2. Effects of antiplatelet drugs on outcome (odds ratios of mortality) in all patients (□) and in subgroups of patients according to the quartiles of Acute Physiology and Chronic Health Evaluation (*APACHE*) II scores (■).

Platelets are anucleated cells and have a very limited capacity of protein synthesis. Thus, even after withdrawal of antiplatelet medication, an inhibition of platelet function by either ASA or clopidogrel is maintained for at least 1 week, whereas other cells that may be affected by the inhibitors can quickly overcome an inhibition by either drug as a result of *de novo* synthesis of enzyme and receptor proteins (17, 22). This was the rationale for the present analysis and is consistent with the time course of platelet count as shown in Figure 1. Critical illness with systemic inflammatory response is known to result in a drop in platelet count, which is followed in case of patient survival by a recovery with a maximum that exceeds the basal values (4). We could show here that a pre-existing medication with antiplatelet drugs diminishes both the drop as well as the maximum after recovery of the platelet count. The observed blunting of this phenomenon is compatible with the long-lasting effect of both ASA and clopidogrel on platelet function.

The retrospective analysis clearly indicated that critically ill patients had a benefit when they were on antiplatelet drugs before the event that caused hospitalization and ICU treatment. This benefit is at least obvious as long as ICU survival is considered. To establish the benefit, we used two approaches: 1) stepwise logistic regression with the use of antiplatelet drugs and age, gender as well as APACHE II score as established mortality risk factors as independent variables; and 2) direct comparison of APACHE II-matched patients without and with antiplatelet drugs, that is, we included only patients with an APACHE II score >20. In both approaches, the premedication with antiplatelet drugs was associated with a marked reduction in mortality as indicated by the estimated odds ratios.

An important aim of our study was to evaluate whether patients with increased bleeding risk have also a benefit of a pre-existing medication with antiplatelets. Therefore, we paid special interest to patients with trauma and/or surgery as well as patients with active bleeding and/or a need for transfusion. Using logistic regression with all patients of the respective subgroups, we observed significant benefits in all subgroups of patients. Surprisingly, patients allocated to surgery departments, in particular neurosurgery patients, as well as patients with trauma, including multiple and/or craniocerebral trauma, or patients with intracranial bleeding had the highest benefit from a pre-existing medication with antiplatelet drugs. However, one has to consider that the benefit of anti-platelet drugs in some of the subgroups of patients could be overestimated as a result of a bias caused by rather small numbers of patients with antiplatelet drugs and the enormous differences in age and APACHE II scores between patients with and without antiplatelet drugs. Thus, results obtained by a direct comparison of APACHE II-matched subgroups of patients might provide a more realistic figure. Two × 2 table analysis that included only patients with an APACHE II score >20 did not reveal any significant effect of antiplatelet drugs in patients allocated to surgery departments but a favorable effect maintained in neurosurgery patients. There was also no sig-

nificant effect in patients with trauma, active bleeding, or surgical treatment. However, it is important to note that in neither of these subgroups was an odds ratio >1.0 observed, indicating that the pre-existing medication with antiplatelet drugs may not worsen the outcome. In accordance with the logistic regression performed in subgroups of the entire cohort, 2 × 2 table analyses provided a significant benefit not only in internal medicine patients and/or patients who received only medical therapy, but also in neurosurgery patients who are considered to have a high risk of bleeding. The benefit in neurosurgery patients may be in accordance with the observation of a strong trend of benefit in APACHE II-matched patients presenting intracranial bleeding (odds ratio, 0.42 [0.16–1.05]).

Both statistical analyses that were applied to evaluate an effect of a pre-existing medication with antiplatelet drugs on the ICU survival of critically ill patients provided good evidence that two groups of patients may have a substantial benefit: 1) internal medicine patients and/or patients who did not undergo any surgical treatment; and 2) neurosurgery patients. Considering the results of both analyses, it is also obvious that neither of the subgroups of patients who may be at increased risk for bleeding as defined in our study have a significant disadvantage of a pre-existing medication with antiplatelet drugs.

With respect to a reduction of organ failure and mortality in critically ill patients by a pre-existing medication, it remains to be elucidated whether such benefit is only the result of a reduced prothrombotic potential of platelets or whether it is also the result of modulation of the systemic inflammatory response. Platelets are known to modulate inflammatory reactions, including gene expression of inflammation-relevant genes in monocytes (5, 6, 23, 24), and it was recently reported that inhibition of platelets by clopidogrel reduces neutrophil activation and cytokine production in endotoxin-treated mice (14, 15). In a similar animal model, we could show that clopidogrel not only reduces the formation of microthrombi in lungs, but also modulates the gene expression in blood leukocytes as assessed by DNA microarray technique (25).

It seems to be worth mentioning again that the benefit of the pre-existing medication with antiplatelet drugs was also evident in patients with high bleeding risk such as in neurosurgery patients. Thus, the contribution of an antiplatelet therapy to unfavorable bleeding may have been overestimated in the past. Such conclusion is in line with a recommended perioperative continuation of an antiplatelet medication. The risk for a cardiovascular or cerebrovascular event resulting from withdrawal of the drugs is considered to be superior to bleeding complications when medication is continued (26, 27).

In light of these results, the current practice to discontinue antiplatelet drugs should be tested in a prospective trial. Furthermore, antiplatelet drugs might offer novel therapeutic options to prevent organ failure.

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