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A Practical Concept for Preoperative Identification of Patients with Impaired Primary Hemostasis

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Summary: The findings of a large prospective study designed to identify primary and/or secondary hemostatic disorders before surgical interventions are presented. A total of 5649 unselected adult patients were enrolled to identify impaired hemostasis before surgical interventions. Each patient was asked to answer a standardized questionnaire concerning bleeding history. Activated partial thromboplastin time (aPTT), prothrombin time (PT), and platelet counts (PC) including PFA-100 (platelet function analyzer): collagen-epinephrine (C/E), and collagen-ADP (C/ADP) were routinely done in all patients. Additional tests, bleeding time (BT), and von Willebrand factor (vWF: Ag) were performed only in patients with a positive bleeding history and/or evidence of impaired hemostasis; e.g., drug ingestion. The bleeding history was negative in 5021 patients (88.8%) but positive in the remaining 628 (11.2%). Impaired hemostasis could be verified only in 256 (40.8%) of these patients. The vast majority were identified with PFA-100: C/E (n=250; 97.7%). The other six patients with impaired hemostasis were identifiable solely based on the PT (n=2), PFA-100: C/ADP (n=2), and vWF: Ag (n=2). The PFA-100: C/ADP detected 199 patients (77.7%). The only abnormality found among patients with a negative bleeding history was a prolonged aPTT due to lupus anticoagulant in nine patients (0.2%). The sensitivity of the PFA-100: collagen-epinephrine was the highest (90.8%) in comparison to the other screening tests (BT, aPTT, PT, vWF: Ag). The positive predictive value of the PFA-100: collagen-epinephrine was high (81.8%), but the negative predictive value was higher (93.4%). The use of a standardized questionnaire and, if indicated, the PFA-100: C/E and/or other specific tests not only ensure the detection of impaired hemostasis in almost every case but also a significant reduction of the cost.

Key Words: Standardized questionnaire of bleeding history—Hemostatic screening tests—PFA-100—Bleeding time—Coagulation tests.

A thorough assessment of the bleeding history, including a physical examination, is doubtless the best tool for identifying patients with impaired hemostasis and/or an increased risk of bleeding complications during and after surgery (1–4). Several investigators have questioned the need for routine preoperative hemostatic screening of parameters such as the platelet count (PC), activated partial thromboplastin time (aPTT), prothrombin time (PT), and bleeding time (BT) (5–13). From a clinical viewpoint, conclusive diagnoses and therapeutic strategies are largely based on the results of hemostatic testing. However, a large number of the affected patients may escape identification with these testing procedures. Platelet dysfunctions including vWD (von Willebrand disease) are the most common and most important defects of hemostasis (14,15). Both of the routinely used parameters, PC and BT, are plagued by poor reliability and reproducibility (9,10,13). The platelet function analyzer (PFA-100) has meanwhile proven to be a reliable in vitro test for measurement of platelet adhesion and aggregation (16–21).

Because preoperative coagulation tests (PC, aPTT, PT) are still routinely performed at our hospital, we decided to compare the predictive value of these tests with that of a standardized questionnaire, tests of platelet function (PFA-100, bleeding time), and von Willebrand factor (vWF: Ag).

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METHODS

A total of 5649 (2631 females and 3018 males, ranging in age between 17 and 87 years) patients scheduled for elective vascular, thoracic, orthopedic, gynecology, urology, rhinolaryngology with head-neck or cranio-maxillofacial surgery were recruited into the study from January 2, 2000 to January 2, 2001 (Table 1).

Emergency surgeries and patients with preexisting hemostatic disorders and anticoagulation therapies were excluded. The study was approved by the local ethics committee. Informed consent was obtained from each participant.

On entry, hemostatic screening including PC, aPTT, and PT including PFA-100®: collagen-epinephrine and collagen-ADP (Dade-Behring, Liederbach, Germany) was done as a part of the preoperative tests ordered by the surgeons and/or anesthesiologists. Additionally, each patient underwent a complete history and physical examination by the anesthesiologist who also reviewed the reply of the patient to the bleeding history questionnaire (Table 2) given to him on admission. Based on previous studies (1,3,4) and our experiences, the questionnaire was designed to cover the most common symptoms of impaired hemostasis, and to supplement the history and physical examination. The need for further hemostatic testing was determined by the anesthesiologist and hemostatic experts. Patients who seemed (on the basis of history, clinical examination, or any question of the questionnaire) to have a impaired hemostasis were classified as having a positive bleeding history and/or evidence of impaired hemostasis; e.g., drug ingestion. If there was no evidence for the presence of a bleeding tendency, patients were classified as having a negative bleeding history.

The following parameters were additionally assessed in all patients with a positive bleeding history and/or evidence of impaired hemostasis, e.g. drug ingestion: bleeding time (Surgicutt®, New Jersey, USA) and vWF: Ag (STA LIATEST® vWF, Boehringer Mannheim, Germany).

The PFA-100 device simulates primary hemostasis by aspirating citrate-anticoagulated whole blood (3.2%; 106 mM) and high shear (5000–6000/s) through a 150-μm aperture membrane coated with collagen and either ADP or epinephrine (22). The reference range of PFA-100: collagen-epinephrine was 82 bis 150 sec. The collagen-ADP test had a reference range between 62 and 100 sec. The blood samples for the PFA-100 were processed within 1 hour after sample collection. The variation coefficient for collagen-epinephrine was 5.9% from day to day (same proband) compared to 5.7%, respectively, for collagen-ADP.

Von Willebrand factor (vWF): Ag was measured using the particle immunoassay (STA LIATEST® vWF, Boehringer Mannheim, Germany).

TABLE 1. Demographic Data and Distribution of Patients

Patients*	(n)	Hemostasis Normal (n)	Impaired (n)
Total	5649 (100%)	5393 (100%)	256 (100%)
Female	2631 (47%)	2506 (46%)	125 (49%)
Male	3018 (53%)	2887 (54%)	131 (51%)
Orthopedic surgery	1298 (23%)	1230 (23%)	68 (27%)
Gynecology	1245 (22%)	1189 (22%)	56 (22%)
General and vascular surgery	1143 (20%)	1093 (21%)	50 (20%)
Thoracic surgery	607 (11%)	562 (10%)	45 (18%)
Craniomaxillofacial surgery	499 (9%)	485 (9%)	14 (5%)
Rhinolaryngology, head-neck surgery	463 (8%)	451 (8%)	12 (4%)
Urology	394 (7%)	383 (7%)	11 (4%)

*Age (range in years): all patients: 54 (17–87), patients with normal hemostasis: 54 (17–87), and patients with impaired hemostasis: 46 (17–81).

TABLE 2. Questionnaire for the Detection of an Increased Risk for Bleeding

1. Have you ever experienced strong nose bleeding without prior reason?
   _____
2. Did you ever have—without trauma—"blue spots" (hematoma) or "small bleedings" (at the torso or other unusual regions of the body)?
   _____
3. Did you ever have bleeding of the gums without apparent reason?
   _____
4. How often do you have bleedings or "blue spots" (hematoma): more than 1 or 2 times a week or 1 to 2 times a week?
   _____
5. Do you have the impression that you have prolonged bleedings after minor wounds (e.g., razor cuts)?
   _____
6. Did you have prolonged or grave bleedings after or during operations (e.g., tonsillectomy, appendectomy or during labor)?
   _____
7. Did you ever have prolonged or grave bleedings while after a tooth extraction?
   _____
8. Did you ever recieve blood packs or blood products during an operation? If so, please define the operation(s):
   _____
   _____
9. Is there a history of bleeding disorders in your family?
   _____
10. Do you take analgesic drugs or drugs against rheumatic disease? If so, please specify:
    _____
    _____
11. Do you take other drugs? If so, please specify:
    _____
    _____
12. Do you have the impression that you have prolonged menstruation (> 7 days) and/or a high frequency of tampon change (to be answered only by women)?
    _____

The cutoff values used to define abnormal and suspected vWF values were less than 50% and 50% to 70%, respectively. The vWF multimeric analyses were performed in the follow-up period according to a luminographic procedure (23). The classification followed the guidelines provided by the "Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis" (24).

If vWD and drug ingestion were excluded, the following tests were done to confirm the diagnosis of hereditary thrombopathies: platelet morphology, mean platelet volume (distribution of platelets), platelet aggregation using Born`s turbidometric method (ristocetin, ADP, collagen,

arachidon acid), flow cytometry using glycoprotein-specific monoclonal antibodies CD 41a, CD 42b, CD 61, CD 62, CD 63 (PLATELET Gp kit®; Biocytex, Marseille), before and after TRAP 6-stimulation (thrombocyte-receptor activating peptid 6, Bechem, Heidelberg).

The Mann-Whitney test was used to compare abnormal spot checks. The difference was considered to be significant at a level of p less than 0.05 ("statistical view-4.5" software). The level of significance was adjusted as recommended by Bonferoni (25). Specifity, sensitivity, and predictive values (26,27) are used accordingly. The effect of changes in the cutoff value on the test performances; i.e., sensitivity and specifity, was determined by using a receiver operating characteristic (ROC) curve.

RESULTS

Complete data sets were obtained for a total of 5649 patients (3018 male and 2631 female) ranging in age from 17 to 87 years (mean: 53 ± 15) and 17 to 87 years (mean: 54 ± 14), respectively (Table 1).

The bleeding history was negative in 5021 patients (88.8%) and positive in the remaining 628 (11.2%). Only nine (0.2%) of the former patients had abnormal aPTTs due to lupus anticoagulant; their prothrombin times and platelet counts were normal (Fig. 1). A total of 256 (40.8%) of the patients with a positive bleeding history and/or evidence of impaired hemostasis; e.g., drug ingestion, exhibited abnormalities in at least one of the hemostatic tests. The affected patients were most frequently identified by PFA-100: collagen-epinephrine (97.7%) followed by PFA-100: collagen-ADP (77.7%) and BT (73.4%). All patients with abnormal bleeding times had abnormal PFA-100 on both types of cartridges. Only two of the patients with abnormal PFA-100: collagen-ADP had normal PFA-100: collagen-epinephrine. Both patients had hereditary thrombocytopathies. The routine screening tests only infrequently (aPTT) or rarely (PT) detected the impaired hemostasis (Fig. 1). Regarding the patients with von Willebrand disease (vWD; n=54), prolonged closure times were detected with PFA-100 epinephrine in 52 cases and with PFA-100 ADP in 42 cases. The remaining two patients were identified with particle immunoassay only. At least one of the routine coagulation tests and one of the platelet function tests was abnormal in 21 patients of the 256 patients with impaired hemostasis. Two patients exhibited abnormalities only in the "routine" tests: One patient with congenital dysfibrinogenemia that has been confirmed by family studies, and one with hereditary factor VII deficiency whose family could not be studied. None of the tests used reflected abnormalities in the remaining 372 (59.2%) patients with a positive bleeding history and/or evidence of impaired hemostasis; e.g., drug ingestion. However, the bleeding history was not highly suggestive in the majority of these patients. For example, the bleeding tendency was often related to an underlying disease rather than to a "true" bleeding disorder, e.g. nosebleeds in 59 patients with hypertension, gumbleeds in 45 patients with periodontitis, and profuse menstruation in 18 patients with uterine myomas. On the other hand, the PFA-100 did not detect platelet dysfunction in 43 patients receiving antiplatelet drugs.

The reasons for impaired hemostasis were largely related to acquired platelet dysfunction due to drug use (Fig. 2). Congenital platelet dysfunction was observed in only 18 patients. In addition, family studies could be done in 14 of 18 cases. Hereditary thrombocytopathies could be confirmed in all studied cases. The remaining patients exhibited von Willebrand disease (n=54), liver cirrhosis (n=13), congenital dysfibrinogenemia (n=1), and hereditary factor VII deficiency (n=1).

The most reliable questions (Table 3) were those related to: 1) bleeding of minor wounds (sensitivity: 85.5%), 2) frequent bruising (sensitivity: 73.8%), and 3) use of nonsteroidal antiinflammatory drugs or platelet function antagonists (sensitivity: 67.2%). The positive predictive value was said to be greater than 99% if four questions were answered in the affirmative. Interestingly, 14 of the 162 patients (8.6%) with drug-induced platelet dysfunction initially failed to report their outpatient medication. Antiplatelet drug use was suspected after testing and confirmed upon requestioning.

The results of hemostatic testing used are summarized in Table 4. All three screening tests for platelet function showed significant differences in the medians for the patients with positive bleeding histories or impaired hemostasis compared with those of the prospective control group. In contrast, none of the routine tests revealed any significant differences. In contrast, none of the routine tests revealed any significant differences.

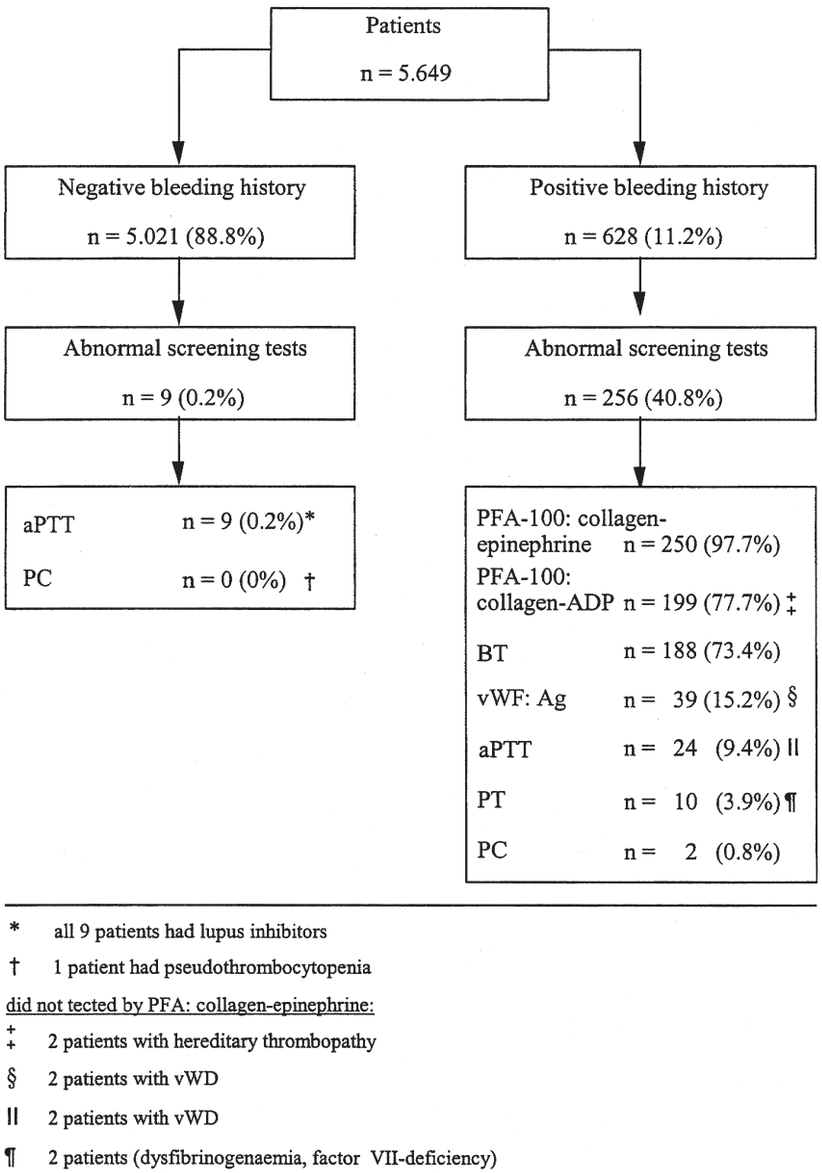

FIG. 1. Abnormal laboratory results in patients with negative bleeding history and positive bleeding history and/or evidence of impaired hemostasis, e.g., drug ingestion.

The sensitivity (Fig. 3) of the PFA-100: collagen-epinephrine was the highest (90.8%) in comparison to the other screening tests (BT, aPTT, PT, vWF: Ag). The sensitivity of the PFA-100: collagen-ADP was too low (47.7%) in comparison to the other screening tests (BT, aPTT, PT, vWF: Ag). However, both PFA-100 tests used achieved high specifities (PFA-100: collagen-epinephrine: 86.6%; PFA-100: collagen-ADP: 93.5%). In addition, the highest prevalence of impaired hemostasis (39.8%) was reflected by the PFA-100: collagen-epinephrine (Fig. 1). Based on these data, the calculated positive predictive value of impaired hemostasis was 81.8% for the PFA-100: epinephrine-collagen and 77.3% for the PFA-100: ADP-collagen, and the negative predictive values were 93.4% and 79.4%, respectively.

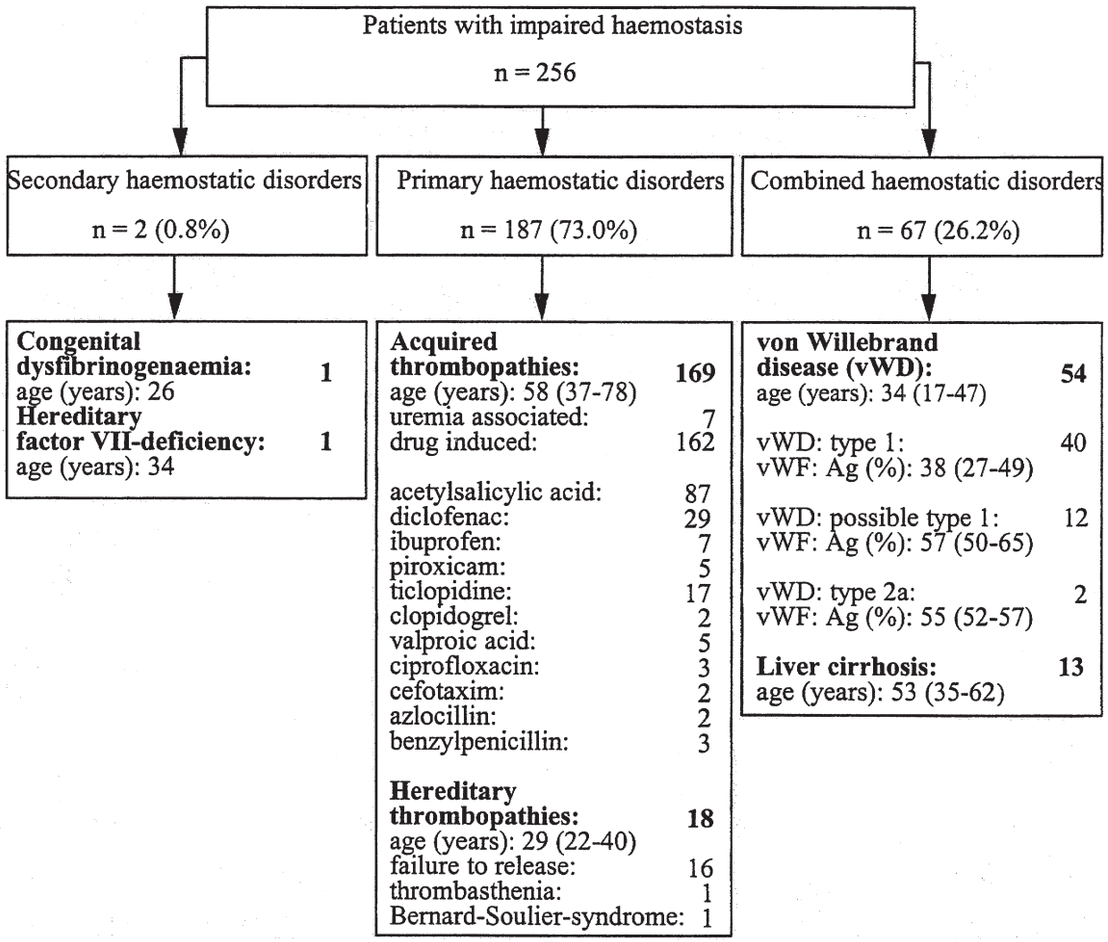

FIG. 2. Patients with impaired hemostasis.

DISCUSSION

In agreement with the results of previous studies, our study clearly shows that primary hemostatic disorders are much more common than secondary disorders. The vast majority of patients at increased risk for bleeding complications could not be identified by routine screening for PC, PT, and aPTT. These tests did not identify a single patient without previous suspicion of impaired hemostasis (positive bleeding history and/or evidence of impaired hemostasis, e.g. drug ingestion). PC and PT were normal in all patients with a negative bleeding history, and all recognizable aPTT abnormalities in these patients were related to lupus inhibitors, that reflected in our patients an increased risk of thrombosis and not of bleeding complications. Moreover, only two patients with a positive bleeding history and/or evidence of impaired hemostasis, e.g. drug ingestion, (0.3%) had plasma disorders that were detectable only with PT (one patient with dysfibrinogenemia, and one with hereditary factor VII deficiency). Similarly, the aPTT and PC did not provide any additional information. The former test was abnormal in 24 of 39 patients with vWD who also showed platelet dysfunction in 37 cases. Only two patients with vWD were undetectable by both types of PFA-100. The PC was significantly decreased in two patients with liver cirrhosis, both of whom also had detectable platelet dysfunction. Even if the

TABLE 3. Positive Response, Sensitivity, Specificity, and Predictive Value of the 12 Questions Regarding the Bleeding History for Detection of Impaired Hemostasis in 5649 Patients

Question-Number*	Positive Response (%)	Sensitivity (%)	Predictive Value (%)	Specificity (%)
5	5.7	85.5	68.2	98.1
4	5.1	73.8	65.4	98.1
10	3.6	67.2	83.9	99.3
7	5.9	52.7	40.7	96.3
2	3.4	51.9	68.9	98.8
3	4.7	51.9	49.8	97.5
8	3.3	39.5	53.7	98.4
6	2.2	33.6	67.7	99.2
1	2.8	30.5	49.4	98.5
12	2.1	29.0	65.5	99.2
9	1.6	28.1	79.1	99.6
11	0.4	6.6	73.9	99.8

*For details see Table 1.

TABLE 4. Comparison of the Results (Medians Including 2.5% and 97.5% Percentiles) of Hemostatic Screening Tests in Patients With and Without Impaired Hemostasis

		Patients with	
Hemostatic Tests	Negative Bleeding History (n=5021)	Positive Bleeding History* (n=628)	Impaired Hemostasis (n=256)
PFA-100: C/E [sec]	129 (75/141)	133 (105/224)	181 (145/237)
		n.s.	$p < 0.01$
PFA-100: C/ADP [sec]	74 (62/96)	99 (72/141)	112 (85/144)
		n.s.	$p < 0.01$
BT [min]	n.p.	5.0 (2.6/8.8)	8.7 (5.2/10.5)
			n.s.
vWF: Ag [%]	n.p.	96 (51/123)	95 (40/144)
			n.s.
aPTT [sec]	35 (28/37)	35 (30/39)	36 (32/39)
		n.s.	n.s.
PT [%]	88 (74/111)	88 (78/108)	87 (74/104)
		n.s.	n.s.
PC [$10^3/\mu L$]	221 (157/325)	211 (177/313)	221 (166/329)
		n.s.	n.s.

p, level of significance, Bonferoni-adjusted for comparison (Mann-Whitney-test) with the group of impaired hemostasis; n.p., not performed; n.s., not significant; C/E, collagen-epinephrine; C/ADP, collagen-ADP.

*Positive bleeding history: positive bleeding history and/or evidence of impaired hemostasis, e.g. drug ingestion.

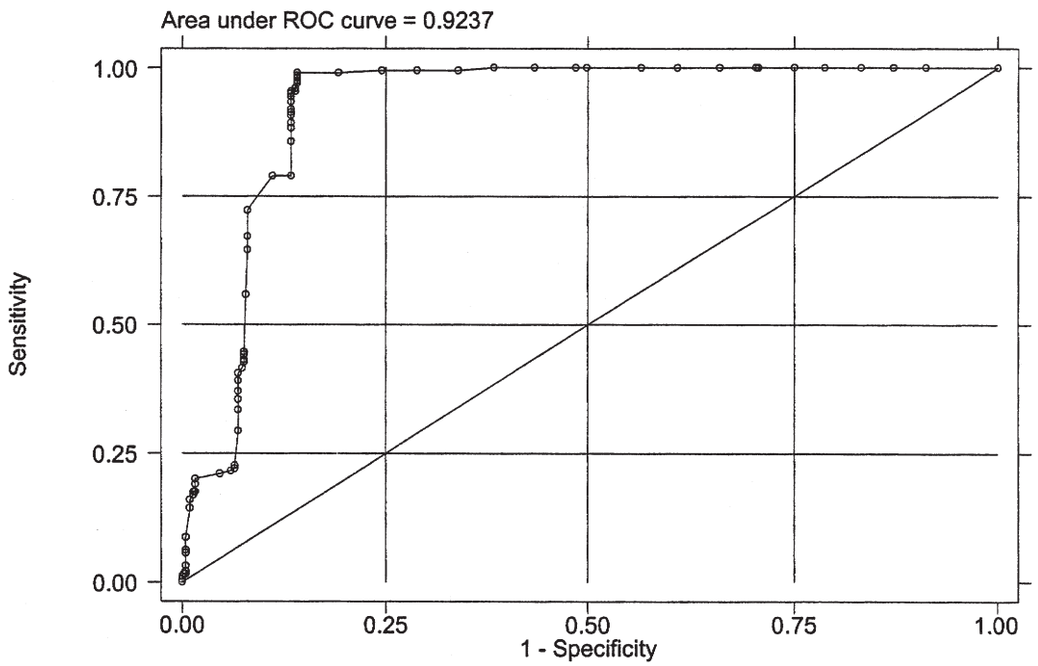

FIG. 3. Receiver operator characteristic (ROC) curve for the PFA-100: collagen-epinephrine in comparasion to other screening-tests (BT, aPTT, PT, vWF: Ag) in a total of 628 patients (with positive bleeding history and/or evidence of impaired hemostasis, e.g. drug ingestion) PFA-100: collagen-epinephrine: sensitivity: 90.8%; specifity: 86.6%.

bleeding time were added to the routine preoperative screening tests, approximately 20% to 30% of the patients with an increased risk of bleeding complications would escape detection by all these testing procedures (Fig. 1). Thus, as has previously been suggested by others (2,6,8,11–13), these tests should only be used in cases where indicated. In contrast, the bleeding history assessment using a standardized questionnaire and tests of platelet function were highly predictive. Both methods seem to supplement each other. All patients with positive bleeding histories related to primary or combined hemostatic disorders could be identified using PFA-100: collagen-epinephrine and/or PFA-100: collagen-ADP. It is also worth mentioning that the platelet function tests detected abnormalities in 14 patients who initially failed to report antiplatelet drug use. On the other hand, many patients reported a history of bleeding, but did not appear to have a hemostatic disorder (n=372). None of the laboratory tests revealed any abnormalities, and none of these patients developed bleeding that could be attributed to a hemostatic disorder.

In agreement with the findings of other groups (16,18–21), the PFA-100 is clearly superior to the bleeding time (BT). In addition, both PFA-100 tests showed high positive predictive values, and high negative predictive values (81.8% and 93.4% for the PFA-100: collagen-epinephrine, and 77.3% and 79.4% for the PFA-100: collagen-ADP). The sensitivity of the epinephrine technique was slightly superior to that of collagen-ADP. A similar discordance was recently reported by other investigators (20,21,28). This discrepancy was related either to aspirin ingestion (n=87 vs. 46) or vWD (n=52 vs. 42).

Based on all these findings, the following recommendation can be made. Patients with an increased risk of bleeding complications can best be identified using a standardized questionnaire

and, if indicated, the PFA-100: collagen-epinephrine test, von Willebrand-factor (vWF), PT, and aPTT. Hemostatic disorders that may escape this testing procedure are extremely rare and may include hypofibrinogenemia or dysfibrinogenemia and factor XIII deficiency. Thus, the so-called routine preoperative coagulation tests could be completely eliminated. Actually, the costs for testing are: PT and aPTT 2 (Euro) each, PC and BT 1 each, vWF: Ag 20 , and PFA-100 7 each. Suggesting that hemostatic testing including PC, PT, aPTT, and PFA-100: collagen-epinephrine would be done in indicated cases (11.2%) only, and approximately 5 million elective operations are made in Germany per 1 year (29), at least $16.3 million (14.2 million) would be saved in this diagnostic area, even when more affected patients would be identified by the use of PFA-100: collagen-epinephrine test. Based on our experiences, this test is important not only for the diagnosis of impaired primary hemostasis, but also for assessing the therapeutic efficacy of drugs such as aspirin and desmopressin acetate (DDAVP) (29,30). Newly developed "cone and platelet analyzer" (CPA) (31) might also be used for the detection of primary impaired hemostasis. The question of whether therapeutic intervention in affected patients may help in preventing bleeding complications is discussed in the therapeutic part of this study (32).

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