ORIGINAL ARTICLE

Prospective multicentre cohort study on 9154 surgical procedures to assess the risk of postoperative bleeding – a DESSI study

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Abstract

Background To date, there is still a debate how to deal with patients receiving antithrombotic agents prior to surgical procedures on the skin.

Objective To prospectively assess complications after dermatosurgical interventions, especially bleeding, depending on anticoagulation therapy.

Methods Patients underwent surgery consecutively as scheduled, without randomization, whether or not they were currently taking anticoagulants. Nine institutions of the DESSI (DErmatoSurgical Study Initiative) working group documented patient data prospectively on a standardized study sheet prior to and after 9154 dermatosurgical interventions.

Results Bleeding complications were observed in 7.14% of cases (654/9154 surgeries). A severe bleed requiring intervention by a physician occurred in 83 surgeries (0.91%). In multivariate analysis, INR, length of the defect, perioperative antibiotic treatment, current treatment with anticoagulation therapy, age and surgery on hidradenitis suppurativa/acne inversa (HS/AI) were significant parameters independently influencing the risk of bleeding. Discontinuation of phenprocoumon therapy and subsequent switching to low molecular weight heparin was associated with the highest risk of bleeding (9.26%).

Conclusion Bleeding complications in skin surgery are generally rare. Even if slightly increased complication rates are found in patients taking anticoagulants during skin surgery, platelet inhibitors should not be stopped prior to surgery. If a surgical procedure in patients on a combination therapy of 2 or more antiplatelet cannot be postponed, it should be conducted with the patient remaining on combination therapy. Discontinuation of DOACs is recommended 24 h prior to surgery. Bridging of phenprocoumon should be terminated. In patients with a bleeding history, the INR value should be within the therapeutic range.

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Conflicts of interest

No conflicts of interest.

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Introduction

The incidence of skin cancer is rising, the population is ageing, and the number of people requiring treatment with anticoagulants is increasing.

The perioperative management of patients taking anticoagulation therapy is a challenge for all surgical specialties, and physicians are confronted with the decision of whether to continue or discontinue drugs.^{1–7}

The standard anticoagulation therapy after placement of coronary artery stents is clopidogrel and acetylsalicylic acid (ASA), which is also used for patients with unstable angina or after a non-ST-segment elevation myocardial infarction.^{8–10} Phenprocoumon or warfarin is often used after thrombosis or pulmonary embolism and may be combined with ASA for patients with mechanical heart valves.^{10–13} Discontinuation of these therapies is often contraindicated and associated with an increased risk of cardiovascular insults.

Kovich and Otley¹⁴ reported that the incidence of thrombotic events after discontinuation of warfarin was 1 in 6219 operations, which decreased to 1 in 21 448 if ASA was withheld.

Even bridging of warfarin discontinuation with heparin derivatives may increase the risk of thrombosis or embolism.^{10,15,16}

In a recent publication by Douketis *et al.*,¹² they described that forgoing bridging anticoagulation, after perioperative interruption of warfarin therapy, was non-inferior to perioperative bridging with low molecular weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.

Otley *et al.*¹⁷ also recommended continuing warfarin and aspirin perioperatively in excisional cutaneous surgery in most cases due to a minimal haemorrhagic risk but decreased risk of thromboembolic complications.

Up to now, only a few, mostly retrospective studies investigating the risk of bleeding in cutaneous surgeries in patients taking blood thinners have been published.

Large differences in the perioperative management of anticoagulant therapy during dermatosurgical procedures have been identified.⁴ There are only some practitioners who refer patients to a dermatologic surgeon without stopping anticoagulants, as the general knowledge still is that all blood thinners have to be stopped prior to any surgery. The aim of this large, prospective, multicentre data collection of 9154 interventions should reflect everyday reality in dermatologic surgery in Germany.

Therefore, the DESSI group (Dermatosurgical Study Initiative), a subgroup of the German Society of Dermatologic Surgery, has set up a prospective multicentre study to investigate the risk and need to discontinue anticoagulation therapy prior to skin surgery, especially focusing on patients taking combinations of multiple anticoagulants.

Materials and methods

Patients were treated consecutively without randomization at nine institutions of the DESSI working group (Bochum, Darmstadt, Leipzig, Ludwigshafen, Mannheim, München, Münster, Münster-Hornheide, Tübingen). All centres documented patient data prospectively on a standardized study sheet. Approval was obtained from the appropriate ethics committee and data protection authority. Accrual time was January to November 2011. All data sheets were collected at the main study centre in Mannheim and scanned on an automated basis. Mild bleeding was defined as the need to change the dressing or place a pressure dressing on the surgical site. A physician's attendance was not required. Severe bleeding was defined as the need for intervention by a physician, e.g. electrocautery, surgical revision, blood transfusion or development of necrosis.

Data collection

The following data were documented on the standardized study sheet: Institution, ID number, gender, age, treatment or discontinuation with anticoagulant and type of anticoagulant, smoking, insulin-dependent diabetes, hypertension, clotting disorder, diagnosis treated (basal cell carcinoma, malignant melanoma, squamous cell carcinoma, other malignant or benign tumours, hidradenitis suppurativa/acne inversa (HS/AI), phlebological disorder), location of surgery (head/neck, upper extremity, trunk, lower extremity), days of hospitalization, perioperative antibiotic treatment, perioperative wound infection, necrosis of flap or transplant in %, multiple tumours, type of surgery, defect length, defect width, postoperative bleeding and action performed.

Statistics

Qualitative parameters are presented as absolute and relative frequencies. To compare two groups, the chi-square test, Fisher's exact test, two-sample *t*-test or Mann–Whitney *U*-test were performed, as appropriate. Furthermore, multiple logistic regression models were used to identify relevant parameters influencing the risk of bleeding using the forward selection method. A result was considered statistically significant if P < 0.05. All statistical calculations were performed using SAS software, release 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 6361 data sheets were included, from the nine institutions.

Patients' demographics and clinical characteristics are summarized in Table 1.

Most interventions were carried out to treat basal cell carcinoma, malignant melanoma or squamous cell carcinoma,

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Table 1 Study population

51 1		- 1	
	Yes	%	Missing data
Nicotine abuse	980	10.38	258
Diabetes	513	5.43	249
Hypertension	5685	60.14	247
Coagulation test	111	1.19	385
Perioperative antibiotic therapy	2526	26.96	329
Postoperative wound infection	439	4.82	595
Multiple tumours	3362	34.66	0
Flap necrosis	325	3.35	0
Necrotic area	Median 9.0% (1–99%)		9375
Diagnosis	Ν	%	Missing data n = 302
Basal cell carcinoma	4999	53.19	
Squamous cell carcinoma	1376	14.64	
Melanoma	1417	15.08	
Other malignant skin tumour	380	4.04	
Benign tumour	407	4.33	
Hidradenitis suppurativa/Acne inversa	168	1.79	
Phlebological diseases	83	0.88	
Other	568	6.04	
Localization	Ν	%	Missing data n = 319
Head/neck	6629	70.66	
Upper extremities	547	5.83	
Trunk	1403	14.96	
Lower extremities	802	8.55	
Surgery performed	Ν	%	Missing data n = 353
Open excision	3524	37.70	
Excision with wound closure	1034	11.06	
Closure by tissue expansion	1614	17.27	
Flap	1448	15.49	
Skin graft	536	5.73	
Sentinel node biopsy	307	3.28	
Contantor mode biopoly			
Complete lymph node dissection	60	0.64	
Complete lymph node	60 73	0.64	
Complete lymph node dissection			
Complete lymph node dissection Phlebosurgery	73	0.78	

Given are absolute and relative frequencies for qualitative factors or median and range for quantitative parameters. 5406 male (57.29%). 4030 female (42.71%). Missing data 264. Mean Age 69.0 years, median age 73.0 years, standard deviation 16.7 years (n = 9416, missing data 284).

followed by other malignant or benign tumours, HS/AI phlebological disorder or other diagnoses (Table 1). Accordingly, most of the surgeries were performed in the head and neck region (6629: 71%). In 546 of the surgeries, there was no documentation concerning bleeding complications. Therefore, only the remaining 9154 surgeries were suitable for statistical analysis concerning the risk of bleeding. In 654 of these, 9154 procedures (7.14%) postoperative bleeding occurred. Of these bleeds, 571 (87.5%) could be stopped just by changing the dressing or placing a pressure dressing onto the surgical site (Table 2). Severe bleeds, defined by the need for intervention by a physician, only occurred in 83 cases (12.5% of 654; 0.91% of 9154 surgeries). Of these, 68 (10.4% of 654) were stopped using electrocautery (82%). More severe bleeds occurred in 15 surgeries (2.2% of 654). In nine of these cases, surgical revision was necessary; in two cases, a blood transfusion had to be performed; and in four cases, necrosis occurred (Table 2).

The association between number of bleeds and anticoagulation therapies is shown in Table 3. A severe bleed occurred in 83 of 9154 surgeries (0.91%), and of those, whether the patients

Table 2 Bleeding complications

	Ν	%	Missing data <i>n</i> = 546
No bleeds	8500	92.86	
All bleeds	654	7.14%	
Required change of dressing	268	2.93	No severe bleed $n = 571$ (6.23% of all surgeries)
Required pressure dressing	303	3.31	
No severe bleeds	571	87.5%	
Electrocautery/suture	68	0.74	Severe bleeds n = 83 (0.91% of all surgeries)
Surgical revision	9	0.10	
Required blood transfusion	2	0.02	
Flap or transplant necrosis	4	0.04	
Severe bleeds	83	12.5%	

Table 3 Bleeding and anticoagulation therapy

Number of anticoagulants	Severe complicati	bleeding ion	Total
	Yes	No	
0	27 0.53%	5067 99.47%	5094
1	51 1.5%	3339 98.50%	3390
2	5 1.18%	419 98.82%	424
Total	83	8825	8908

Data missing = 246.

Chi-square, *P* < 0.0001.

were taking anticoagulants was documented in 8908 surgeries. Among this group of patients, 5094 were not taking any anticoagulant, and of them, 27 experienced a severe bleed (0.53%); 3390 patients were taking one anticoagulant of whom 51 experienced a severe bleed (1.5%) and 424 patients were taking two anticoagulants of whom five experienced a severe bleed (1.18%) (Table 3). Thus, the risk of severe bleeding was significantly higher in patients taking one anticoagulant (chi-square P < 0.0001).

In univariate analysis, gender, perioperative antibiotic treatment, surgery with a flap, coagulopathy, HI/AI, age (≤75 risk 0.67%; >75 risk 1.2%; P < 0.0001), international normalized ratio (INR) (≤ 1.3 risk 0.46%; >1.3 risk 3.7%; P < 0.0001) and size of the defect were found to be significant parameters influencing the risk of bleeding (Table 4). To assess whether the risk of bleeding is higher if defects were left open vs. any kind of closure, patients were divided into two groups. In the group undergoing surgery without wound closure (3315 patients), 43 (1.3%) experienced a bleeding complication, whereas in the group undergoing surgery with any kind of defect closure (5545 patients) 39 (0.7%) experienced a bleeding complication (P = 0.0046). In patients with HS/AI, there was no significant difference in the incidence of bleeds, whether the defects were left open after excision (four bleeding complications/99 patients) or immediately closed (one bleeding complication/51 patients).

Looking at patients not on anticoagulation during surgery, 26 of 4769 who had never received any anticoagulation therapy experienced a bleeding complication (0.55%), whereas patients who discontinued their anticoagulation therapy had no complications (phenprocoumon 0/71, clopidogrel 0/12, ASA and clopidogrel 0/2). Only one patient who was withholding his ASA therapy experienced a bleeding complication of 240 patients. The difference between those two groups was not significant.

Table 4	Bleedina	complications -	univariate	analvsis

Attribute	Test	P-value
Gender	Chi-square test	0.0391
Nicotine abuse		0.7406
Hypertension		0.1422
Perioperative antibiotic treatment		0.0112
Multiple tumours (yes/no)		0.7915
Localization of tumour		0.2839
Surgery – flap		0.0275
Diabetes	Fisher's exact test	0.0676
Coagulopathy		0.0022
Centre X		0.0521
Hidradenitis suppurativa/acne inversa		0.0027
Age	Two-sample t-test	0.0042
INR		0.0001
Multiple tumours number	Mann–Whitney U-test	0.9544
Size of defect in length		< 0.0001
Size of defect in width		< 0.0001

The risk of a bleeding complication in patients actually taking one anticoagulant was 1.4%. The highest risk was found for clopidogrel (3/105; 2.86%), followed by phenprocoumon at 2.28% (15/657), ASA at 1.42% (18/1267) and low molecular weight heparin at 0.6% (6/1014).

Patients who continued taking one anticoagulation therapy while discontinuing another had a 2.59% risk of bleeding. Of those patients who discontinued their phenprocoumon therapy but continued taking low molecular weight heparin, the risk of a bleeding complication was 9.26% of all patients. All other patients just taking one anticoagulant had a 1.38% risk of a bleeding complication, showing a trend towards significance (P = 0.0785), and it is expected that this difference would be significant if the number of patients was higher. The risk of bleeding in patients taking two anticoagulants was 3.57% for ASA and clopidogrel, 2.13% for ASA and phenprocoumon and 1.32% for ASA and low molecular weight heparin.

To identify relevant parameters that influence the risk of bleeding, we performed multiple logistic regression analysis using two different models. In the first model, we included the parameter INR. As in 3601 data sheets the INR was missing, the number of data sets appropriate for this model was reduced to 5132 with 43 (0.84) surgeries involving a bleeding complication (Table 5). In this model, INR was the most important independent risk factor for bleeding [odds ratio (OR) 1.067, P < 0.0001]. The other significant parameters independently influencing the risk of bleeding were length of the defect (OR 1.004, P = 0.0013), perioperative antibiotic treatment (OR 2.582, P = 0.0028), current treatment with anticoagulation therapy (OR 3.116, P = 0.0031) and surgery on HS/AI (OR 4.645; P = 0.0214) (Table 5).

As so many data sets had to be eliminated, a second calculation was performed without taking INR into consideration. This allowed 7988 data sets to be used in Model 2 with 68 (0.85%) involving bleeding complications (Table 6). Among these, HS/ AI (OR 9.145, P = 0.0003) was the most important factor influencing the risk of bleeding. In contrast to Model 1, age was also a relevant factor influencing the risk of bleeding (P = 0.0521).

 $\label{eq:table_state} \begin{array}{l} \textbf{Table 5} & \text{Bleeding complications} - \text{multiple analysis using logistic} \\ \text{regression} - \text{Model 1} \end{array}$

Parameter	Characteristic	Odds ratio	P-value	Missing
INR		1.067	< 0.0001	3601
Length of defect	mm	1.004	0.0013	252
Perioperative antibiotic	yes – no	2.582	0.0028	259
Actual anticoagulation	yes – no	3.116	0.0031	246
Diagnosis Hidradenitis suppurativa/Acne inversa	yes – no	4.645	0.0214	273

Data set n = 5132; 43 (0.84%) with a bleeding complication (4020 data sets eliminated).

AUC = 0.795 (A perfect model reveals an AUC of 1, and in an unsuitable statistical model, the AUC is 0.5).

Additionally, the length of the defect, perioperative antibiotic treatment (P = 0.0327) and current anticoagulation therapy (P = 0.0013) were also statistically significant parameters influencing the risk of bleeding in Model 2.

One may assume that when these factors are found in both models, the risk of bleeding is likely to be significantly increased. To compare the viability of these two models, the area under the curve (AUC) is a suitable method. A perfect model reveals an AUC of 1, while in an unsuitable statistical model the AUC is 0.5. In Model 1, we obtained an AUC of 0.795, with a sensitivity of 88% and a specificity of 62% (optimal case; Fig. 1). In Model 2, we obtained an AUC of 0.711, with a sensitivity of 76% and a specificity of 59% (optimal case; Fig. 2). Despite the elimination of many data sets, Model 1, which includes the INR parameter, seems to be better, from a statistical point of view as well as from a clinical point of view. One must also consider that eliminating a large data set may lead to a study bias.

Discussion

To date, there is no available standardized approach for dealing with patients receiving antithrombotic agents prior to surgical procedures on the skin,^{1–7} although the number of patients taking blood thinners is steadily increasing.¹³

Therefore, we initiated the largest prospective study investigating the risk of bleeding in anticoagulated patients undergoing dermatological surgeries.

The risk of postoperative bleeding is known to be low, especially with regard to severe bleeding.^{18,19} However, other studies have found the risk of bleeding and haematoma (15.4%) to be high, but they did not perform differentiation concerning the severity of bleeding.²⁰

In the present study, bleeding occurred in 654 of 9154 surgeries (7.1%). Included in this number are patients who required dressing changes or placing of pressure dressings, defined as mild bleeding. As 7.1% is a very high proportion, one must assume that changing dressings is not a real bleeding complication because the indication for changing dressings was not clearly defined in this study, nor was the time point for dressing changes. Thus, dressing changes might have been necessary for

Table 6 Bleeding complications - multiple analysis - Model 2

Parameter	Characteristic	Odds ratio	P-value	Missing
Diagnosis Hidradenitis suppurativa/Acne inversa	yes-no	9.145	0.0003	273
Actual anticoagulation	yes-no	2.397	0.0013	246
Length of defect	mm	1.003	0.0075	252
Perioperative antibiotic	yes-no	1.713	0.0327	259
Age	Years	1.020	0.0521	263

Data set n = 7988; 68 (0.85%) with a bleeding complication (1166 data sets eliminated).

AUC = 0.711 (A perfect model reveals an AUC of 1, and in an unsuitable statistical model, the AUC is 0.5).

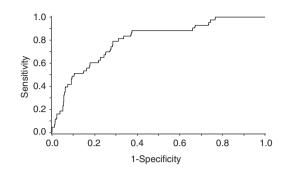


Figure 1 Multiple analysis Model 1. Area under the curve 0.795; Analysis with INR.

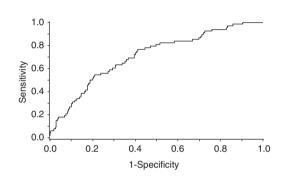


Figure 2 Multiple analysis Model 2. Area under the curve 0.711; Analysis without INR.

other reasons such as they were saturated, patients found them uncomfortable, or they got wet. In most of the cases, bleeding must have already stopped and there might have been just a slight postoperative oozing that is not a real complication and is self-limited.

Relevant postoperative bleeding complications in our study were defined as severe bleeds, requiring intervention by a physician. They occurred in 83 cases (0.91% of 9154 surgeries). In 68 cases, an electrocautery (0.74%) and in 15 surgeries a more demanding intervention (0.16%), such as a blood transfusion, were necessary.

Our data correspond to a recently published review and meta-analysis by Nast *et al.*,¹⁸ who found the risk of bleeding in dermatosurgical interventions in patients not taking anticoagulants to be approximately 1%. In our study, we found a 0.53% risk of bleeding in this group of patients.

In patients discontinuing their anticoagulation therapy and not taking another for bridging, we did not find any bleeding complication, except for ASA in one of 240 patients.

As well as in univariate analysis, INR (\leq 1.3 risk 0.46%; >1.3 risk 3.7%; *P* < 0.0001) was also found to be a significant factor influencing the risk of bleeding in multivariate analysis. This was a calculated risk that might possibly not be clinically relevant.

This is in contrast to the study of Blasdale and Lawrence who found this factor to be a poor predictor of postoperative bleed-ing²¹ and also found an 8% risk of bleeding in patients (n = 65) taking warfarin.²¹

Focusing on cutaneous surgery in the head and neck region with continued phenprocoumon therapy, Eichhorn et al. found a 9% risk of bleeding in 171 surgeries performed on 55 patients (control: 211 surgeries in 89 patients).²² The bleeding risk was significantly higher for the nose than for other regions of the head and neck area (21% vs. 6%).²² Syed et al.²³ reported the risk of bleeding to be 60% in patients with an INR >3.5% and 27% for those with an INR <3.5. In our 83 patients with a bleeding complication, we could not see a direct relation between bleeding risk and arithmetically increased INR values. Dixon et al.²⁴ found a bleeding risk of 2.5% in patients taking warfarin, which corresponds to our data (15/657 patients; 2.28%). In three published meta-analyses, the risk of bleeding in patients taking warfarin was found to be 2.4%, 5.7% and 12.1%, respectively.^{18,25,26} Phenprocoumon is mainly used in Europe, whereas in other parts of the world warfarin is more common. Most of the published data were from studies conducted in patients taking warfarin, which might be the reason for the differences between published data and our study. We found a 2.28% risk of bleeding in patients on phenprocoumon (15/657 patients). To reduce the risk of bleeding in patients taking phenprocoumon, it is common to discontinue the treatment and bridge with heparin. In our study, we found the highest bleeding risk in this group of patients (9.26%) compared with just 2.28% in patients continuing to take phenprocoumon. In a large systematic review, Siegal et al.¹⁶ concluded that bridging was associated with an increased risk of bleeding in 13 studies (odds ratio 5.4) and major bleeding in five studies (odds ratio 3.6). There was also an increased risk of overall bleeding with full vs. prophylactic heparin bridging (odds ratio 2.28). On the other hand, Douketis et al. performed a randomized, double-blind, placebocontrolled trial in patients with atrial fibrillation trial in which, after perioperative interruption of warfarin therapy, patients were randomly assigned to receive bridging anticoagulation therapy with low molecular weight heparin or matching placebo administered subcutaneously twice daily. Warfarin was stopped 5 days before surgery. They found a decreased risk of major bleeding and no increased risk of arterial thromboembolism in the group of patients just interrupting warfarin without bridging.12

Hence, we recommend continuing phenprocoumon therapy prior to skin surgery. It carries a slightly higher risk of bleeding as compared to patients not taking anticoagulants, but the risk is still much lower than that associated with bridging with heparin which, in some studies, also carries an increased hazard of thromboembolic events.^{10,15,16} In case of the development of spontaneous haematoma, treatment with other drugs which enhance the risk of bleeding, or history of intense bleeding in a prior surgery, the INR value should be determined. Surgery may be performed if the INR is within the therapeutic range of the underlying disease.⁷

Cook-Norris *et al.* found severe bleeding complications in 11 of 363 surgical sites in 10 patients taking clopidogrel (220 patients, 363 procedures on 268 occasions).²⁷ Patients taking clopidogrel-containing drugs have a 28-fold higher risk of severe bleeding than patients not on anticoagulation therapy and a six-fold higher risk than patients taking ASA.²⁷ There was no statistically significant difference between patients taking clopidogrel monotherapy and control subjects not taking anticoagulants (24). A possible bias in this study might be that patients experiencing severe complications were more likely to have larger post-operative surgical sites (P < 0.001) (24). In our study, patients taking clopidogrel had only a slightly increased risk of bleeding (2.86%; 3/105 patients) compared with 9% described by Cook-Norris *et al.* (24). Patients not treated with an anticoagulant had a risk of 0.55% in our study.

Postoperative bleeds have been described in patients taking ASA (severe bleeding in 2–3% of patients).^{18,27} We found only a slightly increased risk of bleeding in patients taking ASA (1.42%). Other authors could not confirm an increased bleeding risk in patients treated with ASA compared with controls.^{24,28} The recommendation is not to discontinue patients on monotherapy with antiplatelet drugs.

Six of 1024 of our patients treated with low molecular weight heparin as monotherapy experienced a bleeding complication.

To date, there has been no large study investigating the risk of postoperative bleeding in patients undergoing dermatologic surgery while taking combinations of anticoagulants. The risk of bleeding in our patients on dual antiplatelet therapy (ASA and clopidogrel) was 3.57%, which means just a slightly increased risk in contrast to a clopidogrel monotherapy, while for the combination with phenprocoumon the risk was 2.13% and for low molecular weight heparin it was 1.32%. Cook-Norris *et al.*²⁷ found that a severe complication of Mohs surgery was eight times more likely in patients taking ASA and clopidogrel (10/258 cases: 3.9%) compared with the ASA control group (2/395 cases: 0.5%). Other authors confirmed an increase in bleeding complications in patients taking more than one anticoagulant.²⁹

In our study, gender, perioperative antibiotic treatment, surgery with a flap, coagulopathy, surgery on HS/AI, age, INR and size of the defect were found to be significant parameters influencing the risk of bleeding in univariate analysis.

We used two models to identify independent factors influencing the risk of bleeding. These were INR, defect length, perioperative antibiotic treatment, current anticoagulation therapy and surgery on HS/AI in Model 1 and additionally age in Model 2 which did not take INR into account. As could be expected, larger defects (such as in HS/AI) were more likely to bleed. Dixon *et al.* performed a prospective study of 5959 skin lesions excised in 2394 patients. They were able to identify four independent factors associated with the risk of bleeding: age of 67 years or older, warfarin therapy, surgery on or around the ear and closure with a skin flap or graft.^{24,27}

The limitations of the present study are the lack of data concerning new drugs such as factor Xa inhibitors and direct thrombin inhibitors. Future studies are necessary to evaluate the risk of bleeding in patients undergoing dermatological surgeries while taking or discontinuing these drugs. On the other hand, these new drugs have a much shorter half-life and currently it is recommended to stop this anticoagulation therapy 24 h prior to surgery and continue 1 h after surgery.⁷ For some of these drugs, renal function also needs to be monitored.

This study reveals that the perioperative management of anticoagulated patients still is quite variable among German dermatologic surgeons.

To summarize, bleeding complications in skin surgery are generally rare. If patients are taking antiplatelet agents, like ASA or clopidogrel, surgeries may be performed. In patients taking a combination therapy (clopidogrel + other antiplatelet agents), it should be ascertained whether postponement of a cutaneous surgical procedure is possible until the patient has been switched to monotherapy. If a surgical procedure of the skin cannot be postponed, it should be conducted with the patient remaining on combination therapy.⁷

Discontinuation of DOACs is recommended 24 h prior to surgery and it may be resumed no earlier than 1 h postoperatively. An adjustment of discontinuation might be necessary in impaired renal function.⁷

An interruption of therapy in patients taking VKAs in low bleeding risk procedures and high bleeding risk procedures with no positive bleeding history is not necessary.⁷

In patients taking VKAs planning to undergo a high bleeding risk procedure with a positive bleeding history (e.g. spontaneous bleeding, intraoperative bleeding in prior surgeries), a preoperative INR test is recommended. If the INR value is without the therapeutic range for the underlying disease, surgery should be postponed until the therapeutic range is reached.⁷

The widely practised method of bridging discontinued phenprocoumon therapy was accompanied by the highest bleeding rates in our study and should therefore be terminated.

A follow-up study could investigate whether bleeding complications can even be reduced if all involved surgeons adhere to common guidelines.

References

- Kirkorian AY, Moore BL, Siskind J, Marmur ES. Perioperative management of anticoagulant therapy during cutaneous surgery: 2005 survey of Mohs surgeons. *Dermatol Surg* 2007; 33: 1189–1197.
- 2 Kovich O, Otley CC. Perioperative management of anticoagulants and platelet inhibitors for cutaneous surgery: a survey of current practice. *Dermatol Surg* 2002; **28**: 513–517.
- 3 Otley CC. Perioperative evaluation and management in dermatologic surgery. J Am Acad Dermatol 2006; 54: 119–127.

- 4 Nast A, Ernst H, Rosumeck S, Erdmann R, Sporbeck B, Fluhr JW. Management of anticoagulation during dermatosurgical procedures in Germany - results from a cross-sectional study. J Dtsch Dermatol Ges 2013; 11: 52–59.
- 5 Palamaras I, Semkova K. Perioperative management of and recommendations for antithrombotic medications in dermatological surgery. *Br J Dermatol* 2015; **172**: 597–605.
- 6 Amici JM. Don't stop antithrombotics for cutaneous surgery: just do it now!. Br J Dermatol 2015; 172: 555–556.
- 7 Sporbeck B, Georges Bechara F, Hafner HM et al. S3 guidelines for the management of anticoagulation in cutaneous surgery. J Dtsch Dermatol Ges 2015; 13: 346–356.
- 8 Chassot PG, Delabays A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. *Br J Anaesth* 2007; **99**: 316–328.
- 9 Korte W, Cattaneo M, Chassot PG et al. Peri-operative management of antiplatelet therapy in patients with coronary artery disease: joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (OGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). Thromb Haemost 2011; 105: 743–749.
- 10 Nishimura RA, Otto CM, Bonow RO *et al.* 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2438–2488.
- 11 Douketis JD, Spyropoulos AC, Spencer FA et al. Perioperative management of antithrombotic therapy: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e326S-e350S.
- 12 Douketis JD, Spyropoulos AC, Kaatz S *et al.* Perioperative bridging anticoagulation in patients with atrial fibrillation. *N Engl J Med* 2015; **373**: 823–833.
- 13 Hein L. Antithrombotika und Antihämorrhagika. In: Schwabe U, Paffrath D, eds. Arzneiverordnungs-Report 2012. Springer Medizin Verlag, Berlin Heidelberg, 2012: 425–445.
- 14 Kovich O, Otley CC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. J Am Acad Dermatol 2003; 48: 233–237.
- 15 Spyropoulos AC, Turpie AG, Dunn AS et al. Perioperative bridging therapy with unfractionated heparin or low-molecular-weight heparin in patients with mechanical prosthetic heart valves on long-term oral anticoagulants (from the REGIMEN Registry). Am J Cardiol 2008; 102: 883–889.
- 16 Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. *Circulation* 2012; **126**: 1630–1639.
- 17 Otley CC. Continuation of medically necessary aspirin and warfarin during cutaneous surgery. *Mayo Clin Proc* 2003; 78: 1392–1396.
- 18 Nast A, Ernst H, Rosumeck S, Erdmann R, Jacobs A, Sporbeck B. Risk of complications due to anticoagulation during dermatosurgical procedures: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2014; 28: 1603–1609.
- 19 Amici JM, Rogues AM, Lasheras A *et al.* A prospective study of the incidence of complications associated with dermatological surgery. *Br J Dermatol* 2005; **153**: 967–971.
- 20 Alam M, Ibrahim O, Nodzenski M *et al.* Adverse events associated with Mohs micrographic surgery: multicenter prospective cohort study of 20,821 cases at 23 centers. *JAMA Dermatol* 2013; 149: 1378– 1385.
- 21 Blasdale C, Lawrence CM. Perioperative international normalized ratio level is a poor predictor of postoperative bleeding complications in

dermatological surgery patients taking warfarin. Br J Dermatol 2008; 158: 522–526.

- 22 Eichhorn W, Barsukov E, Al-Dam A *et al.* Postoperative bleeding risk for cutaneous surgery in the head and neck region with continued phenprocoumon therapy. *J Craniomaxillofac Surg* 2014; **42**: 608–611.
- 23 Syed S, Adams BB, Liao W, Pipitone M, Gloster H. A prospective assessment of bleeding and international normalized ratio in warfarin-anticoagulated patients having cutaneous surgery. J Am Acad Dermatol 2004; 51: 955–957.
- 24 Dixon AJ, Dixon MP, Dixon JB. Bleeding complications in skin cancer surgery are associated with warfarin but not aspirin therapy. *Br J Surg* 2007; 94: 1356–1360.
- 25 Alcalay J, Alkalay R. Controversies in perioperative management of blood thinners in dermatologic surgery: continue or discontinue? *Dermatol Surg* 2004; **30**: 1091–1094; discussion 1094.
- 26 Lewis KG, Dufresne RG Jr. A meta-analysis of complications attributed to anticoagulation among patients following cutaneous surgery. *Dermatol Surg* 2008; 34: 160–164; discussion 164–165.
- 27 Cook-Norris RH, Michaels JD, Weaver AL et al. Complications of cutaneous surgery in patients taking clopidogrel-containing anticoagulation. J Am Acad Dermatol 2011; 65: 584–591.
- 28 Billingsley EM, Maloney ME. Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin, and nonsteroidal antiinflammatory agents. A prospective study. *Dermatol Surg* 1997; 23: 381– 383; discussion 384–385.
- 29 Shimizu I, Jellinek NJ, Dufresne RG, Li T, Devarajan K, Perlis C. Multiple antithrombotic agents increase the risk of postoperative hemorrhage in dermatologic surgery. J Am Acad Dermatol 2008; 58: 810– 816.