Guideline

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S3 guideline: Management of anticoagulants and antiplatelet agents in cutaneous surgery

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Alexander Nast[1], Hans-Martin Häfner[2], Andreas Kolk[3], Jürgen Koscielny[4], Christian Kunte[5], Christoph Löser[6], Markus Meissner[7], Anna Pokrywka[8], Steffen Schirmer[9], Fabian David Scherer[1], Klaus Strömer[10], Tino Wetzig[11], Corinna Dressler[1]

(1) Division of Evidence-Based Medicine (dEBM), Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
(2) University Hospital for Dermatology, University Hospital Tübingen, Germany
(3) University Hospital for Oral and Maxillo-facial Surgery, Medical University of Innsbruck, Austria
(4) MVZ Coagulation Clinic with Hemophilia Center at Campus Charité Mitte, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
(5) Artemed Fachklinik München GmbH & Co. KG, Munich, Germany
Klinik und Poliklinik für Dermatologie und Allergologie, Ludwig-Maximilians Universität München
(6) Department of Dermatology and Center for Skin Tumors, Hospital Ludwigshafen, Germany
(7) Dermatology, Venereology and Allergology, University Hospital Frankfurt, Frankfurt am Main, Germany
(8) Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin
(9) Plastic, Esthetic and Reconstructive Microsurgery, Hand Surgery, St. Marien Hospital, Berlin, Germany
(10) Dermatological practice, Mönchengladbach, Germany
(11) Dermatology, Dermatosurgery and Allergology, ASKLEPIOS Hospital, Weißenfels, Germany

Professional Societies involved:

- Deutsche Dermatologische Gesellschaft (DDG, German Dermatological Society)
- Deutsche Gesellschaft für Dermatochirurgie (DGDC, German Society for Dermatosurgery)
- Berufsverband der Deutschen Dermatologen (BVDD, Professional Association of German Dermatologists)
- Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG, German Society for Oral and Maxillofacial Surgery)
- Deutsche Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen (DGPRÄC, German Society of Plastic, Reconstructive, and Esthetic surgeons)
- Gesellschaft für Thrombose und Hämostaseforschung (GTH, Society of Thrombosis and Hemostasis Research)

Preliminary remark

This guideline is an update; some sections have been adopted from the previous guideline issued in 2014 [1]. More detailed information on the methods can be found in the long version of this guideline at www.awmf.org.

Algorithm

This article does not include a comprehensive presentation of all contents of the guideline and serves only as an overview (Figures 1, 2).

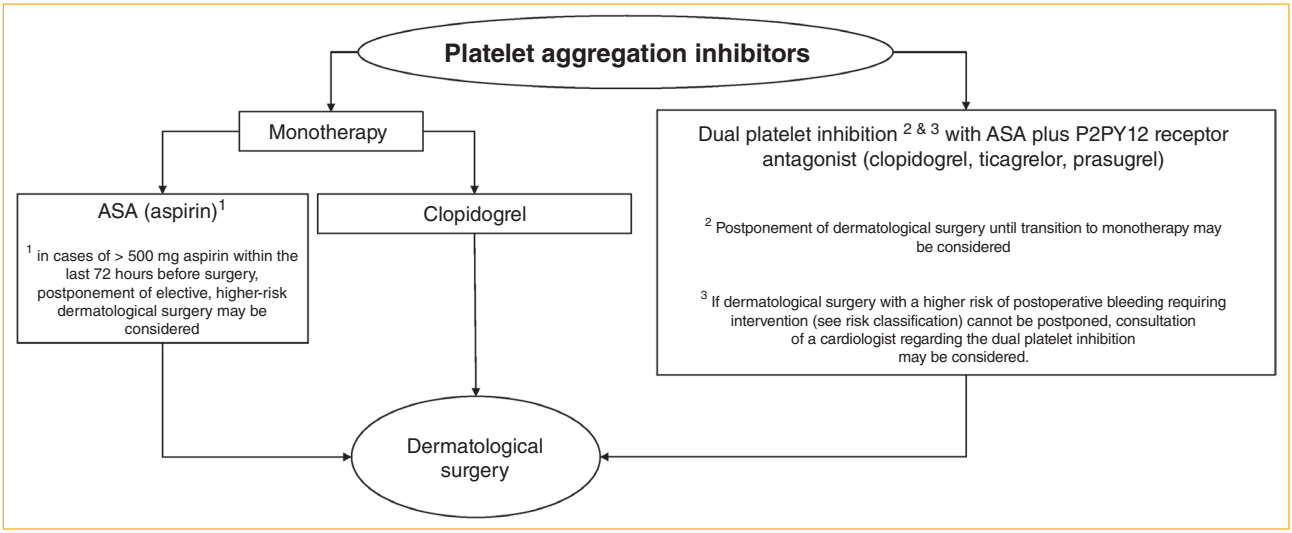

Figure 1 Management of antiplatelet agents.

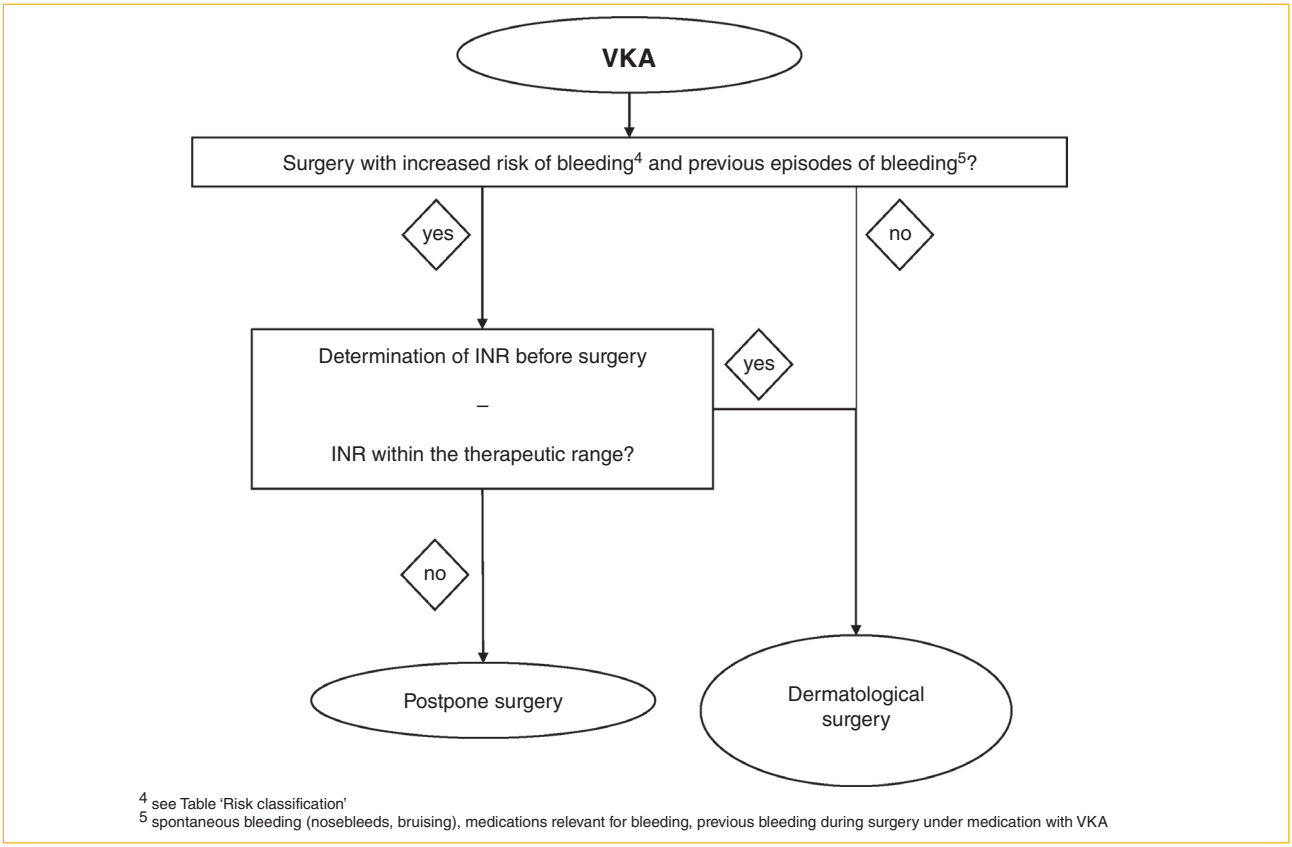

Figure 2 Management of vitamin K antagonists.

Clinical introduction

Current health care situation and aims of this guideline

In the perioperative management of surgical patients, medication with oral anticoagulants (OAC) and platelet aggregation inhibitors (PAI) remains a challenge. In dermatology, but also in other specialties, there are large differences in the perioperative management of antithrombotic drugs [2–4]. The first version of this guideline has already led to a more unified approach in managing aspirin (acetylsalicylic acid, ASA) and vitamin K antagonists (VKA) [1, 5, 6].

Within the context of a repeated cross-sectional study in Germany on the management of anticoagulants and platelet aggregation inhibitors, a strong heterogeneity in care was still apparent, most recently in 2017, in particular with regard to the perioperative management of direct oral anticoagulants (DOAC) [4, 5]. The aim of this guideline is to update the recommendations of the previous guideline, taking into account new study data, newly gained experience within the expert panel, and data from the health services research study.

Treatment with antithrombotic drugs

In the last few years, prescriptions of antithrombotic drugs have shifted significantly in Germany, with an increase in the prescriptions of DOAC by 360 % between 2013 and 2018 [7]. Figure 3 offers an overview on available antithrombotic drugs. In patients receiving treatment with vitamin K antagonists (VKA), the coagulation status must be monitored by measuring thromboplastin time ('Quick test'). Its results are usually reported in percent. Since thromboplastin reagents may show varying sensitivity, the INR value (International Normalized Ratio) has been recommended since 1986 to improve comparability. A standardized method comparing the marketed measuring methods with a standard reagent and applying a formula for calculation ensures that the result is independent of the reagent used, and coagulation values can be compared. "Normal" plasmatic coagulation corresponds to an INR of 1.0.

Table 1 offers an overview of the therapeutic goals in various indications. As opposed to VKA, monitoring of the anticoagulant effect is usually unnecessary in patients treated with DOAC.

Assessment of bleeding risk

Risk classification		Consent
Procedures with an increased risk of postoperative bleeding requiring intervention include: – Procedures involving additional layers (such as fascia, muscle, periosteum, cartilage, bone) – Tissues well supplied with blood in the head and neck region (such as the scalp, nose, lips, periorbital region) as well as the genital area, also surgery on metastases – Procedures with impaired overview of the operation site (such as liposuction, sweat gland curettage, phlebosurgery, proctosurgery, lymph node surgery) – Extensive* multi-stage procedures – Extensive* ablative procedures (such as dermabrasion, laser ablation) – Extensive* skin transfers (such as local, pedicled, or microvascular flap grafts, skin transplants) *> 4 cm^2	Statement	Strong Consensus (100 %)

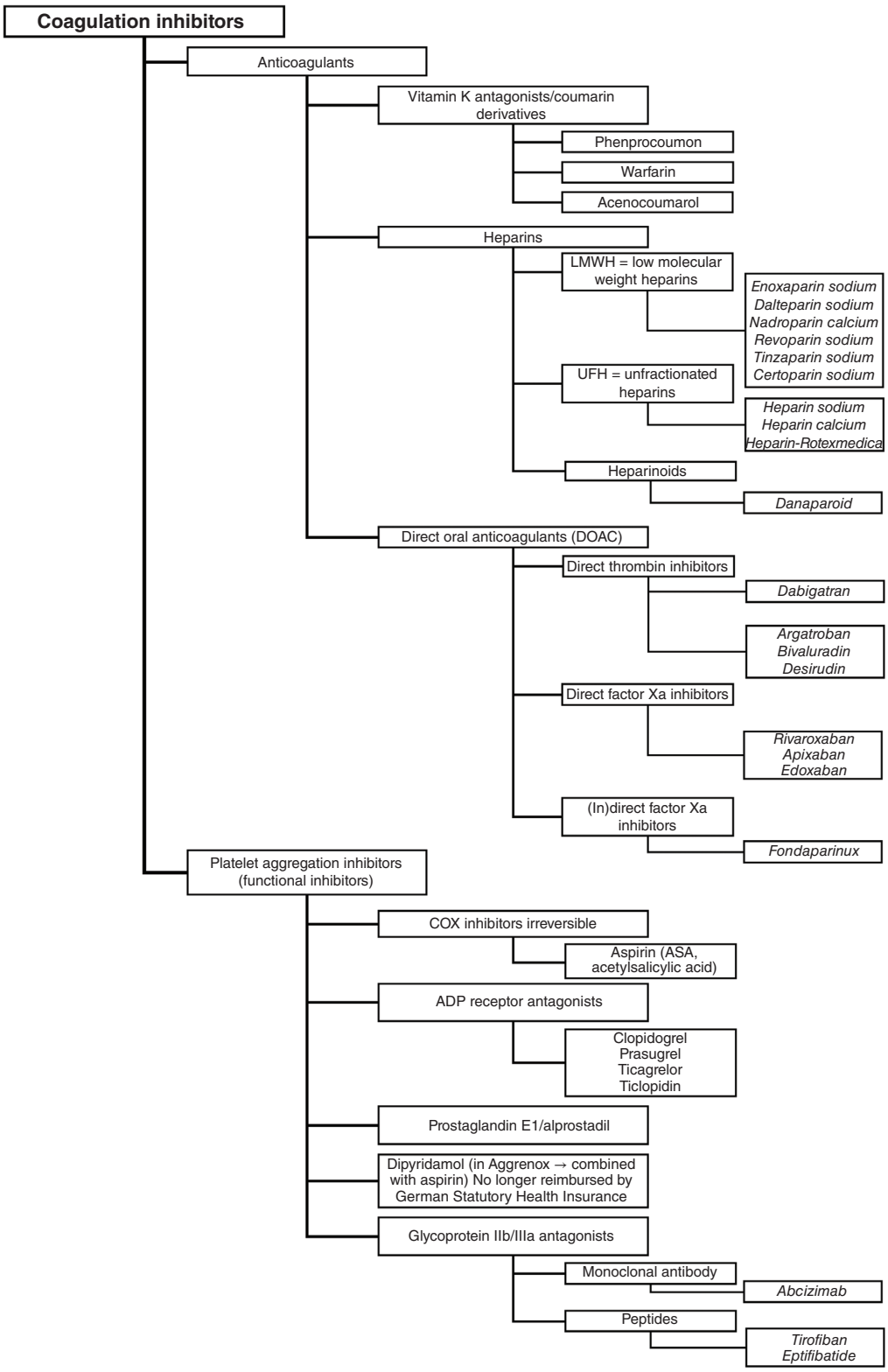

Figure 3 Antithrombotic drugs.

Table 1 INR target ranges for anticoagulant therapy.

Indication	INR
Normal value	1.0 (0.90–1.25)
Atrial fibrillation/atrial flutter (if anticoagulation is indicated)	2.0–3.0
Deep vein thrombosis/pulmonary embolism (patients with antiphospholipid syndrome may require higher INR)	2.0–3.0
Mechanical cardiac valves, bioprostheses	2.0–3.5 (up to 4.5 in some cases)

Recommendations on the perioperative management of antithrombotic drugs in skin surgery

Anticoagulants

Vitamin K antagonists (Phenprocoumon)

Recommendation "preoperative INR analysis"	Strength	Consent
For dermatological surgery with an increased risk of postoperative bleeding requiring intervention (see risk classification) and a positive history of bleeding episodes*, it is **suggested** that preoperative INR assessment be performed. *Spontaneous bleeding (nosebleeds, bruises), medications that affect bleeding, previous bleeding events associated with surgery on phenprocoumon [7].	↑	Strong Consensus (100 %)

Recommendation "perioperative management of VKA with INR within the therapeutic range"	Strength	Consent
It is recommended to continue VKA medication when dermatological surgery is performed.	↑↑	Strong Consensus (100 %)

Recommendation "perioperative management of VKA"	Strength	Consent
Dermatological surgery should not be performed in patients with a positive history of bleeding episodes if the surgery entails an increased risk of postoperative bleeding that itself would require intervention* (see Table on risk classification) and the INR is above the therapeutic range. *Spontaneous bleeding (nosebleeds, bruises), medications that affect bleeding, previous bleeding events associated with surgery on phenprocoumon [7].	↓	Strong Consensus (100 %)

Evidence "Management of VKA"

The review by Scherer et al. [8] reported on a prospective study on phenprocoumon versus no phenprocoumon, with the outcome of "significant postoperative bleeding" be, see Table 2.

Recommendation "Switching from VKA to heparin *(Bridging)*"	Strength	Consent
Switching from VKA to heparin (*Bridging*) is **not recommended** for dermatological surgery.	↓↓	Evidence and consensus-based recommendation, see *Evidence to Decision (EtD) Framework* 2 Strong Consensus (100 %)

Evidence "Switching from VKA to heparin"

The systematic review by Scherer et al. [8] included two comparative studies:

1. Bridging phenprocoumon with heparin, versus continued phenprocoumon treatment (cohort study) (Table 3).
2. Bridging warfarin with heparin, versus warfarin (randomized controlled trial [RCT]) (Table 4).

Additional evidence from two other systematic reviews [10, 11] was included for the comparison of bridging VKA with heparin versus continued VKA. The thromboembolic event rates of the two management strategies did not differ. Bridging was, however, associated with an increased risk of perioperative bleeding. The studies included in the systematic reviews were mostly performed with the VKA acenocoumarol and warfarin.

Table 2 Phenprocoumon vs. no phenprocoumon, outcome "significant postoperative bleeding".

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with no phenprocoumon	Risk difference with phenprocoumon (95 % CI)
Significant postoperative bleeding	728 (1 PCS)	⊕◯◯◯ VERY LOW[a,b]	Not estimable	0 per 1,000	*23 more per 1,000* (from 0 fewer to 45 more)

Abbr.: CI, confidence interval; PCS, prospective cohort study.
[a]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9700 documented operations.
[b]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) once.

Table 3 Heparin bridging vs. continuous phenprocoumon, outcome "significant postoperative bleeding".

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with phenprocoumon	Risk difference with bridging phenprocoumon with heparin (95 % CI)
Significant postoperative bleeding	711 (1 PCS)	⊕◯◯◯ VERY LOW[a,b]	*RR 4.06* (1.53 to 10.73)	23 per 1,000	*70 more per 1,000* (from 12 more to 222 more)

Abbr.: CI, confidence interval; PCS, prospective cohort study; RR, relative risk.
[a]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9700 documented operations.
[b]The optimal information size was not reached. The width of the confidence interval for the risk difference exceeds twenty percentage points.

Table 4 Heparin bridging vs. continuous warfarin.

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with warfarin	Risk difference with bridging warfarin with heparin (95 % CI)	Comments (quotes)
Excessive intraoperative bleeding	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	–	–	–	"No excessive intraoperative-bleeding [...] in either of [the] study groups" [9]
Any postoperative bleeding	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	–	–	–	"[T]here were no statistically significant differences in the rate of postoperative bleeding complications (P = 0.48 at the operative site and P = 0.59 at the donor site)" [9]
Thromboembolic event	26 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	–	–	–	"No [...] thromboembolic complications in either of [the] study groups" [9]

Abbr.: CI, confidence interval; RCT, randomized controlled trial.
[a]No information about randomization process. No information about the methods used to measure the outcome. No sufficient information to judge the appropriateness of the conducted analysis.
[b]No confidence interval was estimable. The optimal information size was not reached.

Direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban)

The systematic search did not reveal any relevant data on bleeding risk with apixaban, dabigatran, rivaroxaban, or edoxaban (Scherer et al. [8]). Thus, the recommendations could be developed and agreed upon solely based on expert opinion, as well as on the guidelines issued by other medical specialties.

The cross-sectional study to evaluate current management strategies found significant heterogeneity in the perioperative management of DOAC during skin surgeries [5]. This heterogeneity was also reflected within the guideline panel. Our recommendations therefore represent a corridor for action. More research is needed.

The highest concentrations of apixaban, dabigatran, edoxaban, or rivaroxaban are reached between 30 minutes and 4 hours after intake. It is therefore prudent to avoid surgery during this period since the bleeding risk for surgical procedures is at its highest [12–15].

Differences in the biological half-life of the various substances and altered pharmacokinetics in patients with renal insufficiency need to be considered [12].

Recommendation on "DOAC"	Strength	Consent
In cases of small-scale curettage and punch biopsies of the skin **it is suggested** that DOAC medication be continued.	↑	Strong Consensus (100 %)

Recommendation on apixaban and dabigatran in procedures without an increased risk of postoperative bleeding requiring intervention	Strength	Consent
Apixaban and dabigatran are usually administered twice a day. For dermatological surgery without an increased risk of postoperative bleeding requiring intervention, **it may be considered** to either continue intake as normal, or observe an interval of 12 hours between the last intake and the surgical procedure. The latter means that one regular dose is omitted (Figures 4, 5).	O	Strong Consensus (100 %)
It is suggested that treatment be subsequently continued with the regular evening dose.	↑	Strong Consensus (100 %)
Recommendation on apixaban and dabigatran – increased risk	**Strength**	**Consent**
Apixaban and dabigatran are usually administered twice a day. For dermatological surgery with an increased risk of postoperative bleeding requiring intervention, **it may be considered** to either continue intake as normal, or observe an interval of 12–24 hours between the last intake and the surgical procedure. The latter means that one or two regular doses are omitted (Figures 4, 5).	O	Strong Consensus (100 %)
It is suggested that treatment be subsequently continued with the regular evening dose.	↑	Strong Consensus (100 %)

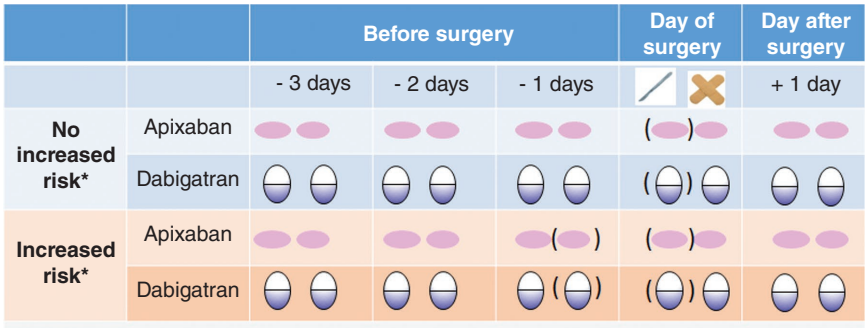

Figure 4 Management of apixaban and dabigatran in single-stage skin surgery (adapted from [12]).

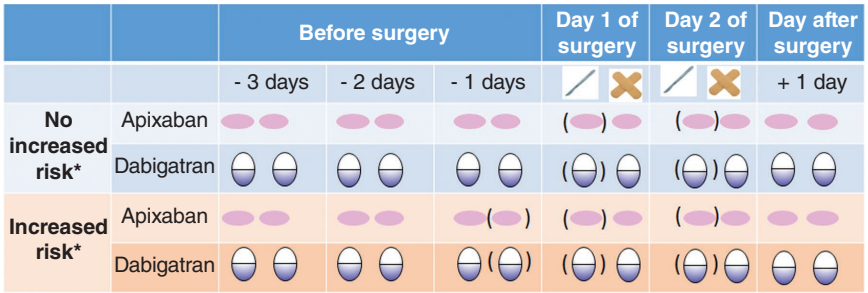

Figure 5 Management of apixaban and dabigatran in multi-stage skin surgery (adapted from [12]).

Recommendation on edoxaban and rivaroxaban	Strength	Consent
For dermatological surgery, **it may be considered** to either continue intake as normal, or observe an interval of 24 hours between the last intake and the surgical procedure. The latter means that if the regular daily dose is taken in the evening, this will be omitted. If the regular daily dose is taken in the morning, this will be delayed until one hour after surgery (Figure 6).	O	Strong Consensus (100 %)

Recommendation on "management of DOAC for dermatological surgery in cases of increased risk and renal insufficiency"	Strength	Consent
For dermatological surgery with an increased risk of postoperative bleeding requiring intervention (see risk classification) in patients with renal insufficiency, **it may be considered** to observe longer intervals between DOAC doses: – Apixaban, edoxaban, or rivaroxaban in patients with a *creatinine clearance* of 15–29 ml/min: at least 36 hours. – Dabigatran in patients with a *creatinine clearance* of 50–79 15–ml/min: at least 36 hours. – Dabigatran in patients with a *creatinine clearance* of 30–49 ml/min: at least 48 hours.	O	Strong Consensus (100 %)

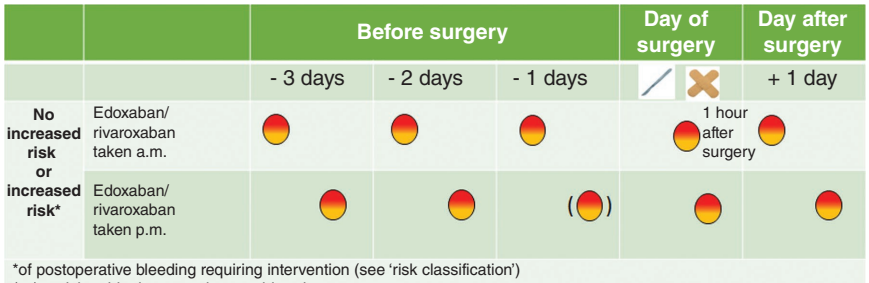

Figure 6 Management of edoxaban and rivaroxaban in single-stage skin surgery (adapted from [12]).

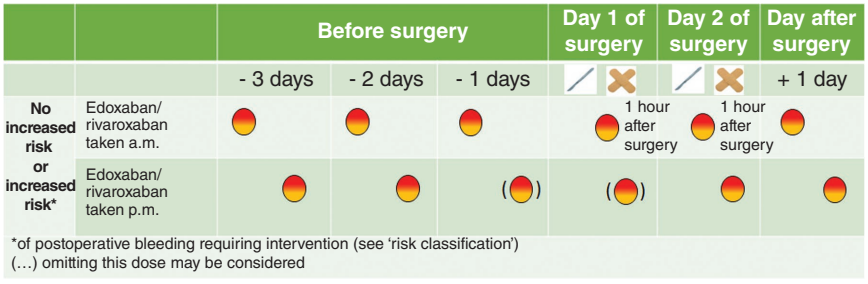

Figure 7 Management of edoxaban and rivaroxaban in multi-stage skin surgery (adapted from [12]).

Platelet aggregation inhibitors

Aspirin (acetylsalicylic acid, ASA)

Recommendation on "aspirin"	Strength	Consent
It is recommended that medically necessary aspirin medication be continued in cases of dermatological surgery.	↑↑	Evidence and consensus based recommendation, see *EtD Framework* 1 Strong Consensus (100 %)
If higher doses (> 500 mg ASA) have been taken within the last 72 hours before surgery, postponement of elective dermatological surgery with an increased risk of postoperative bleeding requiring intervention (see risk classification) **may be considered**.	O	Strong Consensus (100 %)

Evidence on aspirin

The systematic review included data on six different outcomes extracted from ten cohort studies and one RCT, comparing "aspirin" with "no aspirin" (Table 5).

Clopidogrel

Recommendations on "Clopidogrel"	Strength	Consent
In most cases, there is an absolute indication for continuing clopidogrel medication for cardiovascular protection.	Statement	Strong Consensus (100 %)
Therefore, clopidogrel medication **should not** be changed due to dermatological surgery.	↓	Evidence and consensus based recommendation, see *EtD Framework* 1 Strong Consensus (100 %)

Evidence on clopidogrel versus no clopidogrel

Relevant outcomes were extracted from four cohort studies (Table 6).

Combination treatment (aspirin + P2Y12 receptor antagonist [clopidogrel, ticagrelor, prasugrel])

Recommendation on "aspirin + P2Y12 receptor antagonist (clopidogrel, ticagrelor, prasugrel)"	Strength	Consent
In most cases, there is an absolute indication for continuing medication with aspirin plus a P2Y12 receptor antagonist (clopidogrel, ticagrelor, prasugrel) for cardiovascular protection over a certain period of time.	Statement	Strong Consensus (100 %)
Postponement of dermatological surgery until after the switch to monotherapy **may be considered**.	O	Evidence and consensus based recommendation, see *EtD Framework* 1 Strong Consensus (100 %)
If dermatological surgery cannot be postponed, **it is suggested** to perform the procedure without changing the medication with aspirin plus a P2Y12 receptor antagonist (clopidogrel, ticagrelor, prasugrel).	↑	Evidence and consensus-based recommendation, see *EtD Framework* 1 Strong Consensus (100 %)
If dermatological surgery with an increased risk of postoperative bleeding requiring intervention (see risk classification) cannot be postponed, consultation with an angiologist or cardiologist regarding a switch to monotherapy **may be considered**.	O	Strong Consensus (100 %)

Evidence on combination therapy

The systematic review combined the results of two cohort studies comparing aspirin plus clopidogrel combination therapy with "no aspirin" or with "no clopidogrel" (Table 7).

Table 5 ASA vs. no ASA, multiple outcomes.

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with no ASA	Risk difference with ASA (95 % CI)
Excessive intraoperative bleeding	354 (2 PCS)	⊕◯◯◯ VERY LOW[a,b]	Not estimable	39 per 1,000	*70 more per 1,000* (from 7 more to 133 more)
Uncontrollable intraoperative bleeding	60 (1 PCS)	⊕◯◯◯ VERY LOW[c,d]	Not estimable	0 per 1,000	*0 fewer per 1,000* (from 73 fewer to 73 more)
Minor postoperative bleeding	606 (4 PCS)	⊕◯◯◯ VERY LOW[e,f]	Not estimable	61 per 1,000	*3 fewer per 1,000* (from 46 fewer to 41 more)
Significant postoperative bleeding	4,037 (4 PCS)	⊕◯◯◯ VERY LOW[g,h]	*RR 1.48* (0.64 to 3.41)	8 per 1,000	*4 more per 1,000* (from 3 fewer to 19 more)
Any postoperative bleeding (prospective cohort studies)	4,830 (4 PCS)	⊕◯◯◯ VERY LOW[i,j]	*RR 0.96* (0.43 to 2.18)	6 per 1,000	*0 fewer per 1,000* (from 4 fewer to 8 more)
Any postoperative bleeding (randomized controlled trial)	73 (1 RCT)	⊕◯◯◯ VERY LOW[k,l]	Not estimable	0 per 1,000	*29 more per 1,000* (from 46 fewer to 103 more)
Thromboembolic event	73 (1 RCT)	⊕◯◯◯ VERY LOW[k,m]	Not estimable	0 per 1,000	*0 fewer per 1,000* (from 52 fewer to 52 more)

Abbr.: CI, confidence interval; RCT, randomized controlled trial; PCS, prospective cohort study.
[a]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 10 of 332 participants in Billingsley 1997.
[b]The confidence interval for the risk difference crosses the clinical decision threshold (20 per 1,000) once.
[c]No control for likely confounders. No blinding of outcome assessors reported.
[d]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1,000) twice.
[e]No control for likely confounders. Three studies did not report any blinding of outcome assessors. Missing outcome data for 10 of 332 participants in Billingsley 1997.
[f]The confidence interval for the risk difference crosses the clinical decision threshold (20 per 1,000) twice.
[g]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9,700 documented operations in Koenen 2017 and for 10 of 332 participants in Billingsley 1997.
[h]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1,000) once.
[i]No control for likely confounders. No blinding of outcome assessors reported. Exclusion of approximately one percent of participants in Dixon 2007 after beginning of study period.
[j]The optimal information size was not reached.
[k]No information about allocation sequence concealment. No intention-to-treat analysis (6 of 38 participants from the intervention group not included in analysis). No pre-specified protocol available.
[l]The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1,000) twice.
[m]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1,000) twice.

Limitations of this guideline

The identified studies on the risk of bleeding associated with skin surgery in patients on treatment with anticoagulants or platelet aggregation inhibitors remain quite limited in terms of quality and quantity. Therefore, this guideline cannot offer clear recommendations especially not on management of DOAC. In comparison with the previous version of the guideline, our recommendations have been opened up based on expert experience and will need to be re-evaluated after a few years. The evidence on thromboembolic events is even worse, so again the available evidence limited the possibilities of an evidence-based consensus.

Need for more research

The evidence we found on all questions addressed in this guideline was of low quality, there is an urgent need for

Table 6 Clopidogrel vs. no clopidogrel, multiple outcomes.

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with no clopidogrel	Risk difference with clopidogrel (95 % CI)
Significant postoperative bleeding	1,593 (3 PCS)	⊕◯◯◯ VERY LOW[a,b]	Not estimable	2 per 1,000	*15 more per 1,000* (from 22 fewer to 52 more)
Any postoperative bleeding	2,105 (1 PCS)	⊕◯◯◯ VERY LOW[c,d,e]	*RR 43.19* (7.47 to 249.72)	1 per 1,000	*59 more per 1,000* (from 9 more to 348 more)

Abbr.: CI, confidence interval; PCS, prospective cohort study.
[a]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9700 documented operations in Koenen 2017.
[b]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1,000) twice.
[c]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 9 of 32 participants in the intervention group.
[d]In the intervention group 7 out of 32 participants took ASA & clopidogrel.
[e]The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1,000) once. The width of the confidence interval for the risk difference exceeds twenty percentage points.

large studies comparing perioperative discontinuation of DOAC with continued treatment [8].

Notes on how to use guidelines

Guidelines represent systematically developed tools for clinically relevant counseling and decision settings. The development of a guideline can only reflect a limited number of standardized clinical situations. The recommendations in clinical guidelines are not legally binding; deviations from the recommendations may and should occur in specific circumstances. Implementation of guideline recommendations in any given clinical situation must always be analyzed in view of all relevant conditions (such as comorbidities, co-medications, contraindications).

Medical science is in constant flux. Users of the guideline need to be aware of new developments occurring after publication of the guideline. Users of this guideline are also urged to verify, by carefully examining the information and taking into account the product information provided by the manufacturers, whether the recommendations given are complete and up to date with regard to the way in which the interventions are carried out, contraindications to be considered, drug interactions, etc., as well as with regard to the approval and reimbursement situation.

Scope, target group, and aims of the guideline

This guideline is intended for physicians working in hospitals and practices who are involved in the perioperative management of patients undergoing skin surgery. The aims of the guideline are:

– Recommendations to ensure patient safety during dermatological surgery

Table 7 Clopidogrel + ASA vs. neither ASA nor Clopidogrel, outcome "significant postoperative bleeding".

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95 % CI)	Risk with neither ASA nor clopidogrel	Risk difference with ASA & clopidogrel (95 % CI)
Significant postoperative bleeding	6,048 (2 PCS)	⊕◯◯◯ VERY LOW[a,b]	Not estimable	5 per 1,000	*8 more per 1,000* (from 18 fewer to 33 more)

Abbr.: CI, confidence interval; PCS, prospective cohort study.
[a]No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9700 documented operations in Koenen 2017.
[b]The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1,000) twice.

Table 8 Ranking of outcomes.

Outcomes	Definition of outcome [8].	Importance (Median; mean)
Excessive intraoperative bleeding	Significant intraoperative bleeding that was difficult to control	CRITICAL (7; 6.2)
Uncontrollable intraoperative bleeding	Severe intraoperative bleeding necessitating termination of procedure	CRITICAL (9; 7.7)
Minor postoperative bleeding	Postoperative bleeding that was managed by patients themselves	IMPORTANT (4; 4.1)
Significant postoperative bleeding	Postoperative bleeding that required some form of professional medical help or compromised the surgical outcome	CRITICAL (7.5; 6.9)
Any postoperative bleeding	Any kind of postoperative bleeding	OF LIMITED IMPORTANCE (3.5; 3.8)
Thromboembolic event	Perioperative thromboembolic complication leading to relevant morbidity or causing death	CRITICAL (9; 8.2)

- Optimizing quality of life, effort and cost for patients associated with the perioperative management of dermatological surgery
- Reduction of health care costs involving consultation of physicians, prescription of drugs, laboratory investigations, and referrals
- Reduction of effort in clinical care by medical staff
- Decreased divergence in patient care
- Decrease of uncertainties/greater standardization of information available to patients, physicians, and experts on the perioperative management of anticoagulants and platelet aggregation inhibitors

Users of this guideline are dermatologists/dermatosurgeons, plastic surgeons, oro-maxillofacial surgeons, and other physicians from related or interested specialties. The target group of this guideline covers patients treated with anticoagulants and/or platelet aggregation inhibitors who undergo dermatological surgery in an in-patient or out-patient setting.

Methods

Selection of key questions and relevant outcomes

The key questions were selected at the 'Kick-off' meeting in December 2019.

1. How high is the risk of complications during dermatological surgery in patients receiving anticoagulants/platelet aggregation inhibitors?
2. Does the perioperative interruption of direct oral anticoagulants, as compared to their continued use, reduce perioperative complications associated with dermatological surgery?
3. Does the perioperative interruption of vitamin K antagonists with a switch to heparin, as compared to continued use, reduce perioperative complications associated with dermatological surgery?

A list of various endpoints was generated via a systematic review, see Scherer et al. [8]. To better evaluate study results or meta-analyses, all experts were asked to assess the relevance of individual endpoints on a scale of 1 to 9, employing the recommendations of the GRADE working group [16]. This was performed separately for all six outcomes via an anonymous online survey. All experts participated. Table 8 shows the results of this assessment.

Literature search, selection and evaluation of evidence

The PICO model was used for systematic research of the abovementioned key questions (KQ). Inclusion and exclusion criteria were also developed; see below.

Step 1 was the specific search for guidelines addressing the key questions. We focused our search on dermatological and cardiological guidelines, We searched the websites of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF), the Guidelines International Network (GIN), the National Institute of Clinical Excellence (NICE), and the websites of cardiological associations in Germany, Europe, and the USA. The search

was performed in January 2020. No guidelines specifically addressing dermatological surgery were identified. We therefore widened our search to include other types of surgery. Ultimately, e.g. the 2018 European Heart Rhythm Association Practical Guide was used [12].

KQ 1:

Patients	Included: Patients undergoing dermatological surgery

Intervention	Included:
	Monotherapy or combined treatment with the medications listed below
	– Heparins:
	  – Low-molecular-weight heparins: enoxaparin sodium, dalteparin sodium, nadroparin calcium, reviparin sodium, tinzaparin sodium, certoparin sodium
	  – unfractionated heparins: heparin sodium, heparin calcium
	  – Heparinoids: danaparoid sodium
	– Vitamin K antagonists: phenprocoumon, acenocoumarol, warfarin
	– Thrombin inhibitors: dabigatran, argatroban, desirudin, bivalirudin
	– Factor Xa inhibitors: rivaroxaban, apixaban, edoxaban, fondaparinux
	– Platelet aggregation inhibitors: aspirin (ASA, acetylsalicylic acid), clopidogrel, ticlopidine, ticagrelor, prasugrel, cilostazol, dipyridamol

Comparison	Included: Placebo, no treatment, comparison of the abovementioned interventions, break in the intake of one or more of the abovementioned medications
Outcomes	Included: *At least one of the following outcomes must be reported:* – perioperative complications (percentage of patients): bleeding (as reported, classification of bleeding severity – minor, moderate, severe – will be performed later if not stated), wound dehiscence, wound infection, loss of skin graft or flap, erythema – Quality of life (such as SKINDEX, DLQI), quality-adjusted life years (QALYs) (as reported) – Cosmetic result (as reported) – Thromboembolic events (percentage of patients) – perioperative mortality
Study design	Included: RCT, clinical control trials (CCT), prospective cohort studies with comparison group, prospective interventional studies with retrospectively assigned matched controls Excluded: retrospective studies, case reports, case series, studies with less than ten subjects per group

KQ 2:

Patients	Included: Patients treated with direct oral anticoagulants (DOAC) such as dabigatran, argatroban, rivaroxaban, apixaban, or edoxaban who underwent dermatological surgery
Intervention	Included: Perioperative break of intake in patients treated with direct oral anticoagulants (DOAC) such as dabigatran, argatroban, rivaroxaban, apixaban, edoxaban
Comparison	Included: Continued treatment with direct oral anticoagulants (DOAC) such as dabigatran, argatroban, rivaroxaban, apixaban, edoxaban
Outcomes	Included: *At least one of the following outcomes must be reported:* – perioperative complications (percentage of patients): bleeding (as reported, classification of bleeding severity – minor, moderate, severe – will be performed later if not stated), wound dehiscence, wound infection, loss of skin graft or flap, erythema – Quality of life (such as SKINDEX, DLQI), quality-adjusted life years (QALYs) (as reported) – Cosmetic result (as reported) – Thromboembolic events (percentage of patients) – perioperative mortality
Study design	Included: RCT, CCT, prospective cohort studies with comparison group, prospective interventional studies with retrospectively assigned matched controls Excluded: retrospective studies, case reports, case series, studies with less than ten subjects per group

KQ 3:

Patients	Included: Patients treated with a vitamin K antagonist (VKA) such as phenprocoumon, acenocoumarol, or warfarin, who underwent dermatological surgery
Intervention	Included: Perioperative interruption of a VKA such as phenprocoumon, acenocoumarol, or warfarin, with switch to heparin (heparins: *(1.)* Low-molecular-weight heparins: enoxaparin sodium, dalteparin sodium, nadroparin calcium, reviparin sodium, tinzaparin sodium, certoparin sodium; *(2.)* unfractionated heparins: heparin sodium, heparin calcium)
Comparison	Included: Continued treatment with a VKA such as phenprocoumon, acenocoumarol, or warfarin
Outcomes	Included: *At least one of the following outcomes must be reported:* – perioperative complications (percentage of patients): bleeding (as reported, classification of bleeding severity – minor, moderate, severe – will be performed later if not stated), wound dehiscence, wound infection, loss of skin graft or flap, erythema – Quality of life (such as SKINDEX, DLQI), quality-adjusted life years (QALYs) (as reported) – Cosmetic result (as reported) – Thromboembolic events (percentage of patients) – perioperative mortality
Study design	Included: systematic reviews, meta-analyses, RCT, CCT, prospective cohort studies with comparison group, prospective interventional studies with retrospectively assigned matched controls Excluded: retrospective studies, case reports, case series, studies with less than ten subjects per group

Since no guidelines could be found, a systematic review was performed to update an existing review [6] that had been prepared in 2014 during the development of the first guideline "Management of anticoagulants in dermatological surgery". Detailed reporting on the procedure can be found in Scherer et al. [8]. The protocol of this systematic review was published on PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=167337

The review identified data on all three key questions. Two "Evidence to Decision" frameworks describing the results of the systematic review were prepared (see online supplement). Both frameworks were made available to the members of the expert panel. The most important GRADE-Summary-of-Findings-Tables [17] were then incorporated into this guideline (permission received).

Since our search for key question 3 returned very few hits, an additional search for systematic reviews was conducted that was no longer limited to dermatological surgery. The search was performed on February 13, 2020. A total of 882 hits were generated: 199 in CENTRAL, 0 in CDSR 0, 254 in MEDLINE Ovid, and 429 in Embase Ovid. Selection was performed according to the abovementioned criteria. 13 hits were included from the title/abstract screening. Seven systematic reviews were included in the final selection and subsequently evaluated via the SIGN checklist [18]. Reviews that did not assess the included primary studies were excluded. Ultimately, two systemic reviews were included. These were summarized for the group with regard to the relevant outcomes [10, 11].

Generating recommendations/ consensus conference

During an online consensus conference on 7th October 2020, agreement on the proposed recommendations was achieved utilizing the nominal group technique. The structured consensus finding process was facilitated by Professor Alexander Nast. After presentation of the recommendations which needed to be agreed upon, each group member commented on the draft. Dissenting suggestions were noted. This was followed by discussion, preliminary voting, debate/discussion, and final voting. Every member of the expert panel had one vote. Strong consensus (> 95 % agreement) was the general goal. If this was not achieved even after discussion, a "consensus" decision (> 75 % agreement) was an option. In our case, all recommendations were agreed upon with strong consensus. The strength of consensus was documented in each case.

Strength of recommendation, wording and symbols

An overview of wording, symbols, and notes regarding the interpretation of the strength of recommendations can be found in Table 9.

Table 9 Strengths of recommendation – wording, symbols and interpretation (modified from Kaminski-Hartenthaler et al., 2014 [19]).

Strength of recommendation	Wording	Symbol	Interpretation
Strong recommendation *in favor* of an approach	"... **recommended** ..."	↑↑	We consider that *all or almost all informed individuals would take this decision. Clinicians do not have to spend large amounts of time in deciding on the right decision together with the patient.* In most clinical situations, this recommendation can be adopted as a general approach.
Weak recommendation *in favor* of an approach	"... **suggested** ..."	↑	We consider that *most informed individuals would take this decision, but a substantial segment would not. Clinicians and other health professionals need to spend more time* to make sure that the chosen approach including possible consequences reflects the individual patient's values and preferences. Decision processes in the health care system require in-depth discussion and inclusion of many stakeholders.
Open recommendation as to approach	"... **may be considered** ..."	o	At this point in time, no recommendation for or against a certain approach can be given, due to certain circumstances (for example no available evidence, unclear or unfavorable risk-benefit ratio, etc.)
Weak recommendation *against* an approach	"... **should not** ..."	↓	We consider that most informed individuals would take this decision, but a substantial segment would not.
Strong Recommendation *against* an approach	"... **not recommended** ..."	↓↓	We consider that all or almost all informed individuals would take this decision.

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Conflict of interest

Please refer to the long version of this guideline at www.awmf.org for our declaration on conflicts of interest.

Correspondence to

Prof. Dr. med. Alexander Nast
Department of Dermatology, Venereology and Allergology
Division of Evidence-Based Medicine (dEBM)
Charité – Universitätsmedizin Berlin
Charitéplatz 1

10117 Berlin
Germany

E-mail: debmo1@charite.de

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