Introduction

There has been a steady rise in the number of patients requiring therapy with anticoagulants or antiplatelet agents for various acute and chronic conditions. Perioperative management of these drugs continues to be a challenge in patients undergoing dermatologic surgery [1, 2]. Between 2013 and 2018 prescriptions of oral anticoagulants increased by 56 % in Germany [3]. However, this increase was not uniformly present in all classes of anticoagulants. Since 2013 prescriptions of phenprocoumon, a vitamin K antagonist, have been steadily declining – from 77 % to 32 % of all prescribed anticoagulants in 2018. In contrast, the use of factor Xa (rivaroxaban, apixaban, edoxaban) and thrombin (dabigatran) inhibitors, classified as direct oral anticoagulants (DOACs), almost quintupled [3]. Today, DOACs are the most frequently prescribed form of oral anticoagulation [3].

Furthermore, an ever longer life-expectancy is also forecasted to lead to substantial increases in incidence rates for both melanoma and nonmelanoma skin cancer in European countries over the coming decades [4]. Hence, the number of skin surgeries is expected to rise.

A survey from 2017 among hospital-based and office-based dermatologists in Germany found that there was significant heterogeneity with respect to the perioperative management of antithrombotic agents [5]. For example, for large excisions 63.9 % of hospital-based dermatologists continued phenprocoumon treatment, whereas 27.9 % bridged
it perioperatively with heparin and 6.6 % discontinued the anticoagulant around the time of the surgery. 57.8 % of office-based dermatologists continued acetylsalicylic acid (ASA) when performing large excisions, 26.5 % discontinued the antiplatelet therapy for such procedures and 12.2 % referred such patients to a colleague.

The aim of this systematic review was to evaluate whether (Question 1) the perioperative discontinuation in comparison to the continued use of antithrombotic agents and (Question 2) the bridging of vitamin K antagonists with heparin in comparison to their continued use during cutaneous surgery changes the risk of complications. We updated an existing systematic review [6] to inform the update of the German evidence-based (S3) guideline for the management of antithrombotic agents in cutaneous surgery [2].

Methods

The systematic review and meta-analyses were conducted in line with the Cochrane Handbook 6.0 [7]; for details, see Online Supplementary File 1. A protocol was registered (PROSPERO database ID: CRD42020167337) [8]. We reported in line with the PRISMA statements [9, 10], the Cochrane style manual [11, 12] and the advice of the Cochrane Consumer and Communication Group [13].

MEDLINE (Ovid), Embase (Ovid) and the Cochrane Library were systematically searched for potentially eligible studies (see protocol for search strategies). Two reviewers independently screened the identified records. The PICO/eligibility criteria for studies are shown in Table 1. We only included studies written in English, French, German, or Spanish. Data extraction was done independently by two reviewers. Table 2 shows the outcome definitions of perioperative bleeding complications. Study risk of bias assessments were performed (RoB 2 [14] and ROBINS-I [15] tool).

Meta-analysis was performed when two or more studies were available and I² was lower than 60 % [16]. I² is a measure of heterogeneity of the included studies [16]. Study results were pooled using a fixed-effect analysis model with the Mantel-Haenszel method using ReviewManager 5.4 [17]. The risk differences (RD) and risk ratios (RR) with corresponding 95 % confidence intervals (CI) were calculated.

The quality of evidence for each outcome was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [18] utilizing GRADEpro GDT [19]. The quality can be downgraded 1 or 2 levels due to “risk of bias, imprecision, inconsistency, indirectness, [or] publication bias” (p. 405) [20]. The final quality of evidence can be very low, low, moderate or high (e.g. very low means that “[t]he true effect is likely to be substantially different from the estimate of effect” (p. 404) [20]).

Results

Our searches identified 1,514 records for question 1 (Q 1) and 57 records for question 2 (Q 2). Twenty studies were included for Q 1 (1 randomized controlled trial [RCT], 19 prospective cohort studies) and 2 for Q 2 (1 RCT, 1 prospective cohort study; see Figure 1). See Online Supplementary File 2 for lists of included and excluded records with reasons for exclusion.

For Q 1 no studies were identified which compared the thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban, apixaban, or edoxaban against a control group not taking any antithrombotics perioperatively.

The included studies used different descriptions to report the bleeding complications. In order to group bleeding events for the meta-analyses, an attempt to match the different terms to the outcome definitions (Table 2) was made. The results of the outcome matching can be found in the Online Supplementary File 2. Table 3 shows an overview of all included studies.

Tables and figures displaying further study information, outcome data, the respective risk of bias assessments as well as GRADE evidence profiles and forest plots for all 16 comparisons can be found in the Online Supplementary File 2.

The following five comparisons were judged to have the highest clinical relevance. All studies included in the following comparisons are prospective cohort studies with the exception of Engheta et al. [21]. This study is an RCT assessing thromboembolic events comparing ASA versus no ASA.

Comparison: ASA versus no ASA

- Excessive intraoperative bleeding (Figure 2a): Two studies [22, 23] including 354 participants reported on this outcome. Continuing ASA perioperatively may increase the risk of excessive intraoperative bleedings (RD 0.07, 95 % CI 0.01 to 0.13; quality of evidence: very low).
- Uncontrollable intraoperative bleeding: No events occurred in either the ASA group (n = 40) or in the comparator group (n = 20) in the one study [23] reporting on this outcome. Due to imprecision, it is uncertain whether the perioperatively continued use of ASA increases the risk of uncontrollable intraoperative bleedings (RD 0.00, 95 % CI –0.07 to 0.07; quality of evidence: very low).
- Minor postoperative bleeding (Figure 2b): A meta-analysis of four studies [22–25] with 606 participants was conducted. Due to imprecision, it is uncertain whether the perioperative continuation of ASA increases the risk of minor postoperative bleedings (RD 0.003, 95 % CI –0.05 to 0.04; quality of evidence: very low).
- Significant postoperative bleeding (Figure 2c): Seven studies reported on this outcome. Two studies [26, 27], which did not report an event in either study arm, were not included in the meta-analysis (n = 280). Data collected
Table 1  Eligibility criteria for studies. The criteria were obtained from the German guideline for the management of antithrombotic agents in cutaneous surgery [36]. Abbr.: RCTs, randomized controlled trials.

| Patients | Inclusion: Any patients undergoing cutaneous surgery were considered. |
|----------|--------------------------------------------------------------------|
| Intervention | Inclusion:  
Question 1: Monotherapy or combination therapy with any of the following medications:  
– Platelet aggregation inhibitors: acetylsalicylic acid, clopidogrel, ticlopidine, ticagrelor, prasugrel, cilostazol, dipyridamole  
– Vitamin K antagonists: phenprocoumon, warfarin, acenocoumarol  
– Thrombin inhibitors: dabigatran, argatroban, desirudin, bivalirudin  
– 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  
– Factor Xa inhibitors: rivaroxaban, apixaban, edoxaban, fondaparinux  
At least one of the listed medications had to be taken by the participants prior to the operation without the perioperative thromboembolic prophylaxis having been the indication for said drugs. |
| Comparator | Inclusion:  
Question 1:  
– Placebo  
– No treatment  
– Perioperative discontinuation of one or more of the medications listed above  
– Comparison of any of the above mentioned interventions  
Question 2: Perioperative discontinuation of a vitamin K antagonist (phenprocoumon, acenocoumarol, warfarin) and bridging with unfractionated heparin (heparin sodium, heparin calcium) or with low molecular weight heparin (enoxaparin sodium, dalteparin sodium, nadroparin calcium, reviparin sodium, tinzaparin sodium, certoparin sodium) |
| Outcomes | Inclusion: Primary outcome measures  
– Proportion of patients with perioperative bleeding  
– Proportion of patients with a perioperative thromboembolic event  
Secondary outcome measures  
– Perioperative mortality  
– Proportion of patients with wound dehiscence, wound infection, skin graft or flap failure, and erythema  
– Cosmetic outcome as reported  
– Quality of life (Skindex, Dermatology Life Quality Index) and quality adjusted life years as reported  
At least one of the listed outcomes had to be reported. |
| Study design | Inclusion: RCTs; controlled clinical trials; prospective cohort studies with a comparison group; prospective interventional studies with a retrospectively matched control group  
Exclusion:  
Retrospective studies; case studies; case series; studies with less than 10 patients per study arm |
Table 2 Outcome definitions of perioperative bleeding complications.

| Outcome term                        | Outcome definition                                                                                                                                 |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Excessive intraoperative bleeding   | “Significant [intraoperative] bleeding that was difficult to control” (p. 757) [21]                                                                  |
| Uncontrollable intraoperative bleeding | “Severe [intraoperative] bleeding necessitating termination of procedure” (p. 253) [22]                                                             |
| Minor postoperative bleeding        | Postoperative bleeding that was managed by patients themselves [23]                                                                                |
| Significant postoperative bleeding  | Postoperative bleeding that “require[ed] some form of professional medical help […] or compromis[ed] the surgical outcome” (p. 215) [23] |
| Any postoperative bleeding          | Any kind of postoperative bleeding                                                                                                                   |

by Eichhorn et al. [28] could not be pooled because they reported bleedings per procedure (n = 176). Four studies [22, 24, 29, 30] with 4037 participants were pooled for meta-analysis. Due to imprecision, it is uncertain whether the perioperative continuation of ASA increases the risk of significant postoperative bleedings (RD 0.004, 95 % CI −0.003 to 0.019; quality of evidence: very low).

– Thromboembolic events: One study including 73 participants reported zero thromboembolic events [21]. Details on how these were monitored were not provided. Due to imprecision, it is uncertain whether continuing ASA perioperatively increases the risk of thromboembolic events (RD 0.00, 95 % CI −0.05 to 0.05; quality of evidence: very low).

Comparison: Clopidogrel versus no clopidogrel
– Significant postoperative bleeding (Figure 2d): Three studies [27, 29, 30] including a total of 1,593 participants were pooled. Due to imprecision, it is uncertain whether continuing clopidogrel perioperatively increases...
Table 3  Overview of included studies (ASA, acetylsalicylic acid).

| Author (Year)      | Study arms                  | Number of participants | Outcomes as matched to our categories (see Table 2) |
|--------------------|-----------------------------|------------------------|--------------------------------------------------|
| Alcalay (2001)     | Warfarin, Control           | 16, 77                 | Excessive intraoperative bleeding, Any postoperative bleeding |
| Bartlett (1999)    | ASA, Control                | 52, 119                | Minor postoperative bleeding, Significant postoperative bleeding, Any postoperative bleeding |
| Billingsley (1997) | ASA, Warfarin, Control      | 81, 12, 213            | Excessive intraoperative bleeding, Minor postoperative bleeding, Significant postoperative bleeding |
| Blasdale (2007)    | Warfarin, Control           | 65, 92                 | Excessive intraoperative bleeding, Uncontrollable intraoperative bleeding, Minor postoperative bleeding, Significant postoperative bleeding, Any postoperative bleeding |
| Bordeaux (2011)    | ASA and clopidogrel, ASA and warfarin, Control | 50, 37, 1027          | Any postoperative bleeding |
| Dixon (2007)       | ASA, Warfarin, Control      | 334, 11, 67, 1982     | Any postoperative bleeding |
| Eichhorn (2014)    | ASA, Control                | 91, 85                 | Significant postoperative bleeding |
| Engheta (2016)     | ASA, Placebo                | 38, 38                 | Any postoperative bleeding, Thromboembolic events |
| Gowrishankar (2017)| Rivaroxaban, Warfarin       | 15, 44                 | Minor postoperative bleeding, Significant postoperative bleeding, Any postoperative bleeding |
| Harbottle (2014)   | Warfarin, Control           | 86, 87                 | Minor postoperative bleeding, Significant postoperative bleeding, Any postoperative bleeding |
| Kargi (2002)       | ASA, Warfarin, Control      | 37, 21, 44             | Minor postoperative bleeding |
| Koenen (2017)      | ASA, ASA and clopidogrel, ASA and phenprocoumon, Clopidogrel, Discontinued ASA, Discontinued clopidogrel, Discontinued phenprocoumon, Phenprocoumon, Phenprocoumon bridged with heparin, Control | 1267, 28*, 47*, 105, 240, 12, 71, 657, 54*, 4769 | Significant postoperative bleeding |

Continued
the risk of significant postoperative bleedings (RD 0.02, 95 % CI –0.02 to 0.05; quality of evidence: very low).

Comparison: ASA & clopidogrel versus neither ASA nor clopidogrel

– Significant postoperative bleeding (Figure 3a): Pooled analysis of the two studies [29, 30] reporting on this outcome included 6,048 participants. Due to imprecision, it is uncertain whether continuing this dual antiplatelet therapy perioperatively increases the risk of significant postoperative bleedings (RD 0.01, 95 % CI –0.02 to 0.03; quality of evidence: very low).

Comparison: Phenprocoumon versus no phenprocoumon

– Significant postoperative bleeding (Figure 3b): One study [30] with 728 participants reported on this outcome. Continuing phenprocoumon perioperatively may increase the risk of significant postoperative bleedings (RD 0.02, 95 % CI 0.00 to 0.05; quality of evidence: very low).
**Figure 2** Forest plots. ASA versus no ASA – Excessive intraoperative bleeding (a); ASA versus no ASA – Minor postoperative bleeding (b); ASA versus no ASA – Significant postoperative bleeding (c); Clopidogrel versus no clopidogrel – Significant postoperative bleeding (d).

*Abbr.*: ASA, acetylsalicylic acid; M-H, Mantel-Haenszel; 95% CI, 95% confidence interval.
Comparison: Bridging phenprocoumon with heparin versus phenprocoumon

- Significant postoperative bleeding (Figure 3c): One study [30] with 711 participants reported on this outcome. Bridging phenprocoumon with heparin perioperatively may increase the risk of significant postoperative bleedings when compared to its continuation (RD 0.07, 95% CI 0.01 to 0.22; quality of evidence: very low).

No studies were identified that compared the perioperative continuation with the discontinuation of direct oral anticoagulants in patients undergoing cutaneous surgery.

Four studies reported the occurrence of bleeding complications per procedure [28, 31, 34, 35]. Therefore, they could not be pooled with studies reporting event rates per patient. One exception was the data for uncontrollable intraoperative bleeding for the comparison warfarin versus no warfarin because no events occurred in either study arm [34]. Another exception was Dixon et al. [31] because outcome data was also reported as number of bleeds on first procedures and was therefore treated as “per patient” data.

Discussion

We conducted a systematic review of the literature regarding the perioperative risk of complications due to antithrombotic agents in cutaneous surgery. We included two RCTs and 19 prospective cohort studies. Despite the fact that the correct perioperative management of antithrombotic agents is a frequent clinical decision in cutaneous surgeries, the evidence available to guide these decisions is still surprisingly sparse.
In an exercise to rank the importance of the different outcomes in the course of the development of the German guideline for the management of anticoagulants and antiplatelet agents in cutaneous surgery, the outcomes “excessive intraoperative bleeding”, “uncontrollable intraoperative bleeding”, “significant postoperative bleeding”, and “thromboembolic events” were determined to be of critical importance [36]. “Minor postoperative bleeding” was deemed as important.

For ASA, the included studies suggest an increased rate of excessive intraoperative bleedings.

It is uncertain whether, compared to its discontinuation, continuing ASA perioperatively increases the risk of either uncontrollable intraoperative bleeding, minor postoperative bleeding, significant postoperative bleeding, or thromboembolic events as no differences were found. Limited evidence and imprecision hamper any strong conclusions.

For clopidogrel with or without ASA versus no use/interrupted use, no difference was found regarding the rates of significant postoperative bleedings, again based on very low quality evidence.

Continuing phenprocoumon perioperatively versus no use/interrupted use, may lead to an increase in the risk of significant postoperative bleedings (quality of evidence: very low). The observed increase in the risk justifies particular attention in these patients and further studies are needed. In particular, as Koenen et al. point out, a higher INR (International Normalized Ratio) might lead to more bleeding complications [30]. They note that an INR > 1.3 was found to significantly increase the rate of bleeding complications when compared to an INR ≤ 1.3.

When compared to the continued use of phenprocoumon the formerly common procedure of bridging phenprocoumon with heparin was found to increase the rate of significant postoperative bleedings (quality of evidence: very low).

Our findings with regard to bridging of vitamin K antagonists with heparin are in line with findings in previous reviews [37, 38]. The complete lack of evidence with regard to DOACs hints at a relevant research gap, especially when taking into account the strong increase in the number of patients taking these medications [3].

Comparison of our findings with existing systematic reviews is limited by relevant differences in the methods. Most published systematic reviews summarize the results narratively and do not attempt to perform meta-analysis. Our findings are corroborated by previous systematic reviews looking into the same subject. Differences are due to different methodological approaches. A systematic review by Isted et al. found no difference in bleeding risk when continuing ASA perioperatively [39]. We have found a potential increase of excessive intraoperative bleedings in our meta-analysis. Our other findings (no increased risk with ASA) are in line with Isted et al. [39]. They reported “conflicting” (p. 464) evidence regarding warfarin and clopidogrel (“are both likely associated with a small increase in rate of bleeding complications” (pp. 465–466)) [39]. Our study confirms the very low quality of the available evidence. On the contrary, our study results highlight that it is uncertain whether continuing clopidogrel perioperatively increases the risk of bleeding complications. Direct comparison of the results for vitamin K antagonists are not possible as our review focused on phenprocoumon (as it is the medication used in the German healthcare setting) whereas Isted et al. [39] only included studies with warfarin cohorts.

In Germany, recommendations for the management of antithrombotic agents in cutaneous surgery have first been published in 2015 [2]. The expert group recommended the perioperative continuation of phenprocoumon in low-risk operations or in patients without a positive bleeding history. It is recommended to preoperatively measure the INR in patients undergoing skin surgeries with an increased bleeding risk. If the INR is above the therapeutic range, they recommend to not proceed with the operation. In addition, they advised against the perioperative discontinuation of ASA and clopidogrel. Similarly, the American College of Chest Physicians suggests that vitamin K antagonists and ASA should be continued perioperatively in patients undergoing minor dermatologic procedures [40]. Furthermore, the European Heart Rhythm Association recommends that non-vitamin K antagonist oral anticoagulants should not be interrupted for small dermatologic excisions or when hemorrhages are readily manageable [41].

With the notable exception of the German evidence-based (53) guideline [2] and its update [36], there are no guidelines available focusing on the management of antithrombotic agents during cutaneous surgery that we are aware of.

Limitations

The quality of evidence for all outcomes across all comparisons was judged to be very low. No study sufficiently controlled for potential confounders (e.g. comorbidities, age, or sex) and only one cohort study [25] reported blinding of outcome assessors. Missing outcome data in six studies [21, 22, 30–33] led to a higher risk of bias rating.

Different follow-up times for postoperative bleeding complications introduced methodological heterogeneity (range: from 24 hours [21, 22] up to 30 days [27]), but clinically the majority of bleeding complications occur during the first 24 hours postoperatively. Therefore, the quality of evidence was not downgraded due to inconsistency.

Imprecision was judged to be serious to very serious across all analyzed outcomes. The confidence intervals were generally very wide and often included both no difference between treatment groups as well as large absolute risk
increases. The “optimal information size (OIS)” (p. 582) for a meta-analysis describes the number of participants required to find a clinically relevant risk difference with sufficient power and sensitivity [42]. When the events of interest are rare, the OIS needs to be larger than when the analyzed events are more common. Bleeding complications in cutaneous surgery are relatively rare events. Therefore, no meta-analysis reached the OIS if calculated with the clinical decision thresholds used for the GRADE assessment.

Reporting on perioperative thromboembolic events was limited to the two included RCTs [21, 43], while none of the included cohort studies reported such outcomes. It might have been advantageous to define different patient population for bleeding versus thromboembolic complications [44]. On the one hand, the risk of bleeding complications is influenced by the invasiveness of the surgery. For bleeding outcomes, it is therefore reasonable to only look at patients undergoing cutaneous surgery. On the other hand, the risk of thromboembolic complications due to the interruption of any antithrombotic medication is less dependent on the kind of surgery undertaken.

Only Engheta et al. [21], Koenen et al. [30], Lam et al. [43], and Sun et al. [26] included comparison groups in which participants under regular antithrombotic therapy discontinued their medications perioperatively. All other studies included in this review had comparison groups which did not regularly take any antithrombotic drugs. Studies using the former kind of group address the clinical questions of this review more appropriately. Furthermore, comparison groups, who had not been under regular antithrombotic therapy preoperatively, tended to have lower levels of comorbidity (e.g. hypertension) [32, 45], included a higher proportion of women [27, 28, 32, 34, 45, 46], and often significantly younger participants [27, 32, 34, 45, 46] relative to other study arms in their respective trials in which drug therapy was continued perioperatively.

The findings of this systematic review are only generalizable to patients undergoing Mohs micrographic or excisional skin cancer surgery in the head and neck region because participants of included studies mainly underwent these kinds of surgeries. Hence, further large trials focusing on the perioperative management of antithrombotic medication in different types of surgeries with a high risk of bleeding complications should be conducted. Additionally, further prospective studies with a focus on the now commonly used factor Xa and thrombin inhibitors are needed.

Conclusions

The perioperative discontinuation of any antithrombotic agent can cause potentially life-threatening thromboembolic complications. Additionally, no clear indications of major or life-threatening risks for bleedings when continuing antithrombotic agents perioperatively in minor cutaneous surgeries were identified in this review. Therefore, the possible harm of such adverse effects generally outweighs the risk of manageable intra- and postoperative bleeding complications in minor skin surgeries.

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References

1. Nast A, Ernst H, Rosumeck S et al. Management of anticoagulation during dermatosurgical procedures in Germany – results from a cross-sectional study. J Dtsch Dermatol Ges 2013; 11(0): 52–9.
2. Sporbeck B, Bechara FG, Hafner HM et al. S3 guidelines for the management of anticoagulation in cutaneous surgery. J Dtsch Dermatol Ges 2015; 13(4): 346–56.
3. Hein L, Wille H. Antithrombotika und Antihämorrhagika. In: Schwabe U, Paffrath D, Ludwig WD, Klauber J: Arzneiverordnungs-Report 2019. Berlin, Heidelberg: Springer, 2019: 531–55.
4. Leiter U, Eigentler T, Garbe C. Epidemiology of Skin Cancer. In: Reichrath J: Sunlight, Vitamin D and Skin cancer. 2nd edition. New York: Springer, 2014: 120–40.
5. Gaskins M, Dittmann M, Eiser L et al. Management of antithrombotic agents in dermatologic surgery before and after publication of the corresponding German evidence-based guideline. J Dtsch Dermatol Ges 2018; 16(3): 297–305.
6. Nast A, Ernst H, Rosumeck S et al. Risk of complications due to anticoagulation during dermatosurgical procedures: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2014; 28(2): 1603–9.
7. Higgins JPT, Thomas J, Chandler J et al.: Cochrane Handbook for Systematic Reviews of Interventions, Version 6.0,
Cochrane, 2020, available from www.training.cochrane.org/handbook [Last accessed January 29, 2021].

Scherer FD, Dressler C, Nast A. Perioperative management of anticoagulants and antiplatelet drugs in patients undergoing cutaneous surgery: a systematic review and meta-analysis. PROSPERO 2020. Available from www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020167337 [Last accessed January 29, 2021].

Moher D, Liberati A, Tetzlaff J et al. preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; J Clin Epidemiol 2009; 62(10): 1006–12.

Page MJ, McKenzie J, Bossuyt P et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. Syst Rev 2021; 10(1): 89.

Cochrane Style Manual Working Group. Cochrane Style Manual. Available from www.community.cochrane.org/style-manual [Last accessed on January 29, 2021].

Cochrane Style Manual Working Group. Cochrane Style Basics. April 2019. Available from www.community.cochrane.org/style-manual/cochrane-style-basics [Last accessed January 29, 2021].

Cochrane Consumers and Communication La Trobe University, Ryan R, Synnot A, Hill S. Describing results. Version 2.0. Published December 1, 2016. Available from cccrg.cochrane.org/author-resources [Last accessed January 29, 2021].

Sterne JAC, Savovic J, Page MJ et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Sterne JAC, Hernan MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919.

Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J et al.: Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0. Cochrane, 2019. Available from www.training.cochrane.org/handbook [Last accessed January 29, 2021].

Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

Guyatt G, Oxman AD, Akl EA et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011; 64(4): 383–94.

GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). Available from wwwGRADEpro.org [Last accessed January 29, 2021].

Bals hem H, Helfand M, Schü nemann HJ et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4): 401–6.

Engheta A, Hadadi Abianeh S, Atri A, Sanatkarfar M. Aspirin use and bleeding volume in skin cancer patients undergoing surgery: a randomized controlled trial. Daru 2016; 24(1): 20.

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(3): 381–3.

Lawrence C, Sakuntabhai A, Tilling-Grosse S. Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. J Am Acad Dermatol 1994; 31(6): 988–92.

Bartlett GR. Does aspirin affect the outcome of minor cutaneous surgery? Br J Plast Surg 1999; 52(3): 214–6.

Kargi E, Babuccu O, Hosnuter M et al. Complications of minor cutaneous surgery in patients under anticoagulant treatment. Aesthetic Plast Surg 2002; 26(6): 483–5.

Sun Y, Wang Y, Li L et al. Continuous aspirin use does not increase bleeding risk of split-thickness skin transplantation repair to chronic wounds. J Cutan Med Surg 2017; 21(4): 316–9.

Shipkov H, Irthum C, Seguin P et al. Evaluation of the risk of post-operative bleeding complications in skin cancer surgery without interruption of anticoagulant/antithrombotic medication: A prospective cohort study. J Plast Surg Hand Surg 2015; 49(4): 242–6.

Eichhorn W, Kluwe L, Heiland M, Grobe A. Lack of evidence for increased risk of postoperative bleeding after cutaneous surgery in the head and neck in patients taking aspirin. Br J Oral Maxillofac Surg 2014; 52(6): 527–9.

O’Neill JL, Taheri A, Solomon JA, Pearce DJ. Postoperative hemorrhage risk after outpatient dermatologic surgery procedures. Dermatol Surg 2014; 40(7): 74–6.

Koenen W, Kunte C, Hartmann D et al. Prospective multicentre cohort study on 9154 surgical procedures to assess the risk of postoperative bleeding – a DESSI study. J Eur Acad Dermatol Venereol 2017; 31(4): 724–31.

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(11): 1356–60.

Kramer E, Hadad E, Westreich M, Shalom A. Lack of complications in skin surgery of patients receiving clopidogrel as compared with patients taking aspirin, warfarin, and controls. Am Surg 2010; 76(1): 11–4.

Syed S, Adams BB, Liao W et al. A prospective assessment of bleeding and international normalized ratio in warfarin-anticoagulated patients having cutaneous surgery. J Am Acad Dermatol 2004; 51(6): 955–7.

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(3): 522–6.

Harbottle M, Telfer M, Hunjan PS et al. Bleeding complications in cutaneous surgery for patients on warfarin who have skin cancer of the head and neck. Br J Oral Maxillofac Surg 2014; 52(6): 523–6.

Nast A, Häfner HM, Kolk A et al. 53-Leitlinie: Umgang mit Antikoagulatien und Thrombozytenaggregationshemmern bei Operationen an der Haut. J Dtsch Dermatol Ges 2021; 19(10): 1531–47.

Kuo HC, Liu FL, Chen JT et al.: Cochrane Handbook for Systematic Reviews of Interventions. Chapter 10: Analysing data and undertaking meta-analysis. J Clin Epidemiol 2009; 62(10): 1006–12.
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review and partial meta-analysis. Curr Pharm Des 2013; 19(22): 4014–23.

39 Isted A, Cooper L, Colville RJ. Bleeding on the cutting edge: A systematic review of anticoagulant and antiplatelet continuation in minor cutaneous surgery. J Plast Reconstr Aesthet Surg 2018; 71(4): 455–67.

40 Douketis JD, Spyropoulos AC, Spencer FA et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141(2): e326S–e350S.

41 Steffel J, Verhamme P, Potpara TS et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018; 39(16): 1330–93.

42 Pogue JM, Yusuf S. Cumulating evidence from randomized trials: Utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials 1997; 18(6): 580–93.

43 Lam J, Lim J, Clark J et al. Warfarin and cutaneous surgery: a preliminary prospective study. Br J Plast Surg 2001; 54(4): 372–3.

44 Peryer G, Golder S, Junqueira D et al. Chapter 19: Adverse effects. In: Higgins JPT, Thomas J, Chandler J et al.: Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0. Cochrane, 2019. Available from www.training.cochrane.org/handbook [Last accessed January 29, 2021].

45 Shalom A, Wong L. Outcome of aspirin use during excision of cutaneous lesions. Ann Plast Surg 2003; 50(3): 296–8.

46 Shalom A, Klein D, Friedman T, Westreich M. Lack of complications in minor skin lesion excisions in patients taking aspirin or warfarin products. Am Surg 2008; 74(4): 354–7.