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Does Aspirin Increase Risk of Bleeding in Patients Undergoing Skin Lesion Excision: A Systematic Review and Meta-Analysis

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Background: Aspirin is a commonly prescribed medication, which impairs the action of platelets. This also results in a higher risk of bleeding. Cutaneous lesion excision is frequently performed for diagnosis and treatment of malignancies, as well as for aesthetic or functional benefits. We must balance the risk of bleeding against the risk of discontinuing aspirin. We conducted a systematic review, and meta-analysis, in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines to evaluate the evidence of postoperative bleeding risk conferred by continuation of aspirin in cutaneous surgery.

Methods: A systematic search of the literature was performed. Included studies evaluated the incidence of hemorrhage or hematoma in adults undergoing cutaneous surgery. The following participant characteristics were noted: age, sex, surgical site, and type of wound closure performed. A random-effects model was chosen to calculate the effect size—expressed as odds ratio (OR) with a 95% confidence interval—for bleeding of any severity, moderate severity, severe severity, infection, and wound dehiscence (outcomes).

Results: A total of 26,860 procedures were included from 20 studies. A statistically significant increase in odds of bleeding of any severity (16,748 procedures included) OR 1.39 (1.02–1.90) and for bleeding of severe severity (12,311 procedures included) OR 2.46 (1.53–3.95) was identified. Moderate severity bleeding (1629 procedures included) OR 0.92 (0.46–1.81), infection OR 0.60 (0.28–1.28), and wound dehiscence OR 0.92 (0.41–2.06) effect size results did not attain statistical significance.

Conclusions: Our analysis identified a statistically significant increase in postoperative bleeding risk for patients taking aspirin and undergoing cutaneous surgery.
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INTRODUCTION

The incidence of cutaneous malignancy in England exceeded 184,000 cases in 2020.[1] Skin lesion excision is the gold standard for diagnosis and treatment. Additional indications include cosmesis and relieving functional impairments.

Aspirin is an antiplatelet medication prescribed at low doses (<350 mg once daily) for the prevention of thrombosis. In the United States, 1 in 3 adults older than 40 years report using it.[2] Its therapeutic effects are primarily mediated by irreversible acetylation of the cyclooxygenase enzymes. Platelets synthesize thromboxane A2, a prothrombotic prostaglandin, whereas endothelium primarily produces prostaglandin I_2, which is vasodilatory and antithrombotic.[3] Endothelial cells can upregulate the synthesis of cyclooxygenase to overcome its inhibition, but anucleate platelets are incapable of this. The net result is

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more than 80% reduction of thromboxane A2, whereas the levels of beneficial prostaglandins are sustained.

The most common indication for aspirin is secondary prevention of cardiovascular events.[4] Platelets are principally involved in primary hemostasis, and naturally, we must consider how aspirin interferes with this process and augments the risk of bleeding.[5] The "washout period" of aspirin is a product of its half-life (15–20 min) and the time it takes to replace the circulating platelet pool (approximately 7–10 d).[6] In an otherwise healthy patient, a 10% restoration per day in platelet function can be expected.[7] Most clinicians suggest cessation 5 days before a procedure, as platelet aggregation has been sufficiently restored by this time.[8]

Based on the evidence available, The British Society of Dermatological Surgery recommends continuation of aspirin before skin lesion excision.[9] Bleeding adversely affects the patient and healthcare providers. A hematoma can precipitate a surgical site infection or wound dehiscence. Conversely, an infection can also impair wound healing and predispose to wound dehiscence.

Cutaneous surgery encompasses a heterogenous group of procedures and reconstructive techniques. Variables that influence the risk of complications include mode of healing (secondary intention, direct closure, local flap reconstruction and skin grafting), surgical site, comorbidities, age, sex, and closure technique. We must be mindful that we lack a model that can unify these determinants quantitatively to predict risk in an individual.

In our systematic review and meta-analysis, we review published evidence to ascertain the bleeding risk in patients who have undergone cutaneous surgery and are established on low-dose aspirin.

Takeaways

Question: We conducted this review to figure out whether patients who are regularly taking aspirin and need to have surgery to remove a skin growth are at an increased risk of bleeding due to their use of aspirin.

Findings: A total of 26,860 procedures were included from 20 studies. We calculate an increased risk of any severity bleeding odds ratio 1.39 (1.02–1.90) and severe bleeding odds ratio 2.46 (1.53–3.95). We highlight that most studies utilize an imperfect control group (nonusers of aspirin).

Meaning: Our findings show that there is a statistically significant increase in the risk of bleeding of any severity and severe bleeding when continuing aspirin.

MATERIALS AND METHODS

Our review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist.[10] A literature search to date was performed on May 1, 2024 using MEDLINE, Embase, Ovid and Health Management Information Consortium. (**See table, Supplemental Digital Content 1**, which displays the search strategy, **http://links.lww.com/PRSGO/E32**.)

Our study population included adults undergoing minor surgery for excision of a skin lesion on any part of their body. Sentinel lymph node biopsies were not included. We included only comparative studies with an intervention and control arm. We defined the intervention arm as aspirin monotherapy. The control arm is no anticoagulation or antiplatelet agent. For the control, we included patients who were not established on regular aspirin and those who discontinued aspirin at least 5 days before the procedure. Additional criteria are listed in Table 1.

Screening

Results were manually filtered to exclude unrelated studies. Remaining articles were evaluated by 2 independent reviewers against our inclusion/exclusion criteria. Cohen

Table 1. Inclusion and Exclusion Criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Study design	Full text available in English	Non-English language publications, case reports, studies including fewer than 5 patients in their analysis
Population	Patients established on regular, systemic low-dose (<350 mg once daily) aspirin therapy Patients undergoing an excision of a benign or malignant skin lesion on any part of the body Studies including patients who undergo an excisional biopsy or Mohs micrographic surgery	Studies including procedures involving complex reconstruction requiring a free flap and studies that include patients with a bleeding diathesis
Interventions	Studies including patients established on regular, systemic low-dose (<350 mg once daily) aspirin therapy	Studies in which outcomes for an aspirin monotherapy group were not available, studies that exclusively included curettage procedures, studies that exclusively evaluated patients established on nonsystemic formulations of aspirin, and studies in which outcomes for an aspirin monotherapy group were not available
Comparators	Patients are either not established on aspirin as a control or have discontinued aspirin at least 5 d before their procedure	
Outcome	Studies with outcomes that measure the incidence of bleeding or hematoma formation	

kappa score was subsequently calculated. Disagreements were resolved by discussion between reviewers.

Primary Outcomes

Postoperative Bleeding or Hematoma Formation of Any Severity

We defined bleeding as blood loss or hematoma significant enough to require medical intervention. This included acute repadding of a dressing, cautery or diathermy outside of the theater. Mild oozing that did not lead to the patient contacting a healthcare professional or necessitate reoperation was not included. Intraoperative bleeding tendencies were not included.

Moderate Bleeding or Hematoma Formation

We defined this as bleeding necessitating in-person intervention from a healthcare professional, but short of necessitating an additional procedure. This included changing a dressing and applying pressure or a pressure dressing to the operative site.

Severe Bleeding or Hematoma Formation

We defined this as bleeding necessitating an additional procedure, which includes hematoma evacuation, chemical or electrical cauterization of a bleeding point, wound exploration, admission, or a blood transfusion.

Secondary Outcomes

We evaluated incidences of surgical site infection and wound dehiscence.

We recorded the following study characteristics: age, sex, the type of wound closure, site of surgery (classified as head and neck surgery and other sites), and how each study defined and recorded incidences of bleeding.

Data Analysis (Meta-analysis)

A random-effects model was chosen to account for sampling error inherent to the studies. Effect size calculations and study heterogeneity calculations, reported as odds ratios (ORs) and I^2, respectively, were performed on the Cochrane Review Manager (RevMan version 8.13.0).[11] A 95% confidence interval was chosen. Contrast-level and arm-level data were used for calculations, with a preference for the former when both were available.

Risk-of-bias Analysis

Each study was reviewed for risk of bias associated with the selection, comparability, and outcome reporting using the Newcastle-Ottawa tool for nonrandomized cohort studies. The results from the Newcastle-Ottawa tool were translated into the Agency for Healthcare Research and Quality (AHRQ) scores. The Risk of Bias (RoB2) tool was used to review for risk of bias in randomized cohort studies.[12]

RESULTS

The search identified 1667 records after removal of duplicates. The author K.R. filtered out reviews and studies with no relation to cutaneous surgery. Eighty-two studies were independently evaluated by K.R. and E.W. against exclusion and inclusion criteria. Sixty-two articles were excluded (Fig. 1). The interrater reliability score, Cohen kappa, was calculated as 0.83.[13] K.R. and E.W. independently reviewed study bias using the Newcastle-Ottawa tool for nonrandomized studies and RoB2 tool for randomized controlled trials (Table 2).

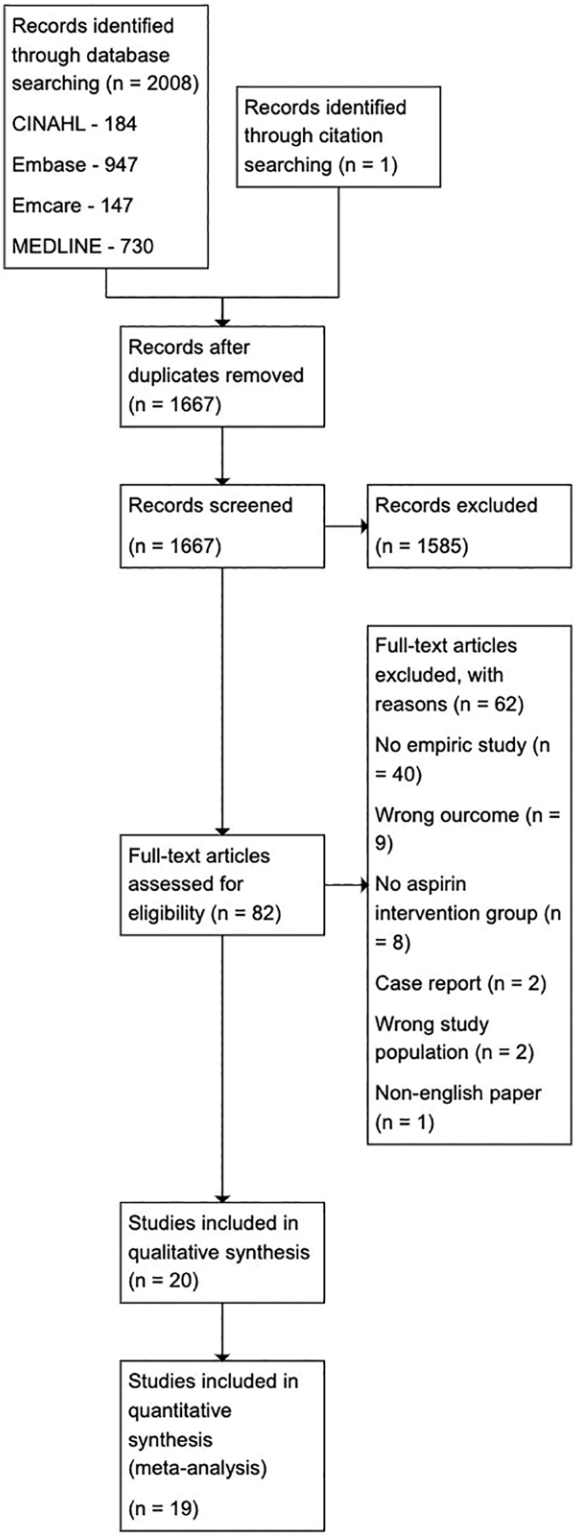

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart.

Table 2. Newcastle-Ottawa Scores and AHRQ Classification for Nonrandomized Cohort

Study	Selection Score	Comparability Score	Outcome Score	AHRQ Rating
Arguello-Guerra et al[14]	4	0	1	Poor
Bartlett[15]	4	1	2	Good
Billingsley et al[16]	4	0	2	Poor
Bordeaux et al[17]	4	1	1	Poor
Cook-Norris et al[18]	4	2	3	Good
Dhiwakar et al[19]	4	1	3	Good
Dixon et al[20]	4	1	3	Good
Eichhorn et al[21]	4	0	2	Poor
Fahmy et al[22]	4	2	3	Good
Hasselgren et al[23]	4	0	3	Poor
Jorgensen et al[24]	4	0	2	Poor
Kargi et al[25]	4	0	2	Poor
Koenen et al[26]	4	2	3	Good
Lawrence et al[27]	4	0	1	Poor
O'Neill et al[28]	4	0	1	Poor
Shalom et al[29]	4	0	2	Poor
Shalom et al[30]	4	1	3	Good
Shimizu et al[31]	4	0	3	Poor
Taylor et al[32]	4	0	2	Poor

Table 3. Risk-of-bias Tool for Randomized Trials (RoB 2.0)

Risk-of-bias Domains						
	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Engheta et al[33]	+	+	+	+	+	+

Domain 1, bias arising from the randomization process; Domain 2, bias due to deviations from intended interventions; Domain 3, bias due to missing outcome data; Domain 4, bias in the measurement of the outcome; Domain 5, bias in the selection of the reported results; +, low risk.

Twenty studies (19 cohort studies and 1 randomized controlled trial) met inclusion criteria, from which 26,860 procedures could be evaluated. (**See table, Supplemental Digital Content 2**, which displays study characteristics, **http://links.lww.com/PRSGO/E33**.) Nineteen studies, 26,790 procedures, were included in statistical analysis (mean participant age 66.9 y; 58% were men). In 8,585 of the 11,120 procedures with a reported operative site, the procedures were performed on the head and neck. In 16,803 procedures, the method of closure was reported. Nineteen percent of excisions healed by secondary intention, 46% were closed primarily, 26% used a local flap, 9% were grafted, and 1% used another method of wound closure (Table 3).

Engheta et al[33] is the only randomized controlled trial and described a sample of 70 patients; none of whom developed a complication—this precluded inclusion in all meta-analyses. Seven of the included studies were of good quality, and 12 were of poor-quality according to the AHRQ standards. Ten studies had evidence of comparability bias, and 3 studies demonstrated evidence of outcome bias.

Postoperative Bleeding

OR for postoperative hemorrhage or hematoma of any severity in patients taking aspirin was 1.39 (1.02–1.90) (Z = 2.07; $P = 0.04$) and was calculated from inclusion of 16,748 procedures, across 14 studies. Effect size heterogeneity was low ($I^2 = 0\%$) (Fig. 2). Five studies were excluded: Cook-Norris et al[18] due to the fact that their severe complication category grouped bleeding with other complications, and hence, we risked counting nonbleeding complications in our analysis; Dhiwakar et al,[19] Fahmy et al,[22] and Koenen et al[26] only recorded severe bleeding, and inclusion was not felt to capture the full severity spectrum of bleeding complications; Lawrence et al[27] only recorded postoperative oozes several hours postprocedure.[18]

Dixon et al[20] is the study with the greatest weighting (20.3%). Despite a large cohort of 5630 participants, no raw data on subgroup population characteristics are available for analysis. Notably, a univariate and multivariable logistic regression reveals a discrepancy in the OR; 2.2 versus 1.4; with the latter failing to attain statistical significance. We included the univariate result in our analysis. This discrepancy is suggestive of confounding variables once adjusted for during logistic regression attributing a smaller risk to aspirin. Their binary logistic regression considered age, reconstruction with a flap or graft, and ear surgery as statistically significant characteristics that increased the odds of postoperative bleeding.

Forty-five percent of the weighting was accounted for by a further 4 studies. Only Eichhorn et al[21] explicitly stated that procedures were carried out on the head and neck. All 4 included Mohs surgery patients.[16,17,32] In studies by Bordeaux et al, Billingsley et al, and Taylor et al, no data were available for the age or sex of the patient groups. Outcomes for bleeding were defined slightly differently in each group. Eichhorn et al did not break down incidence of bleeding events by severity but specified exclusion of simple oozing, slight bleeding, and temporary hematoma formation

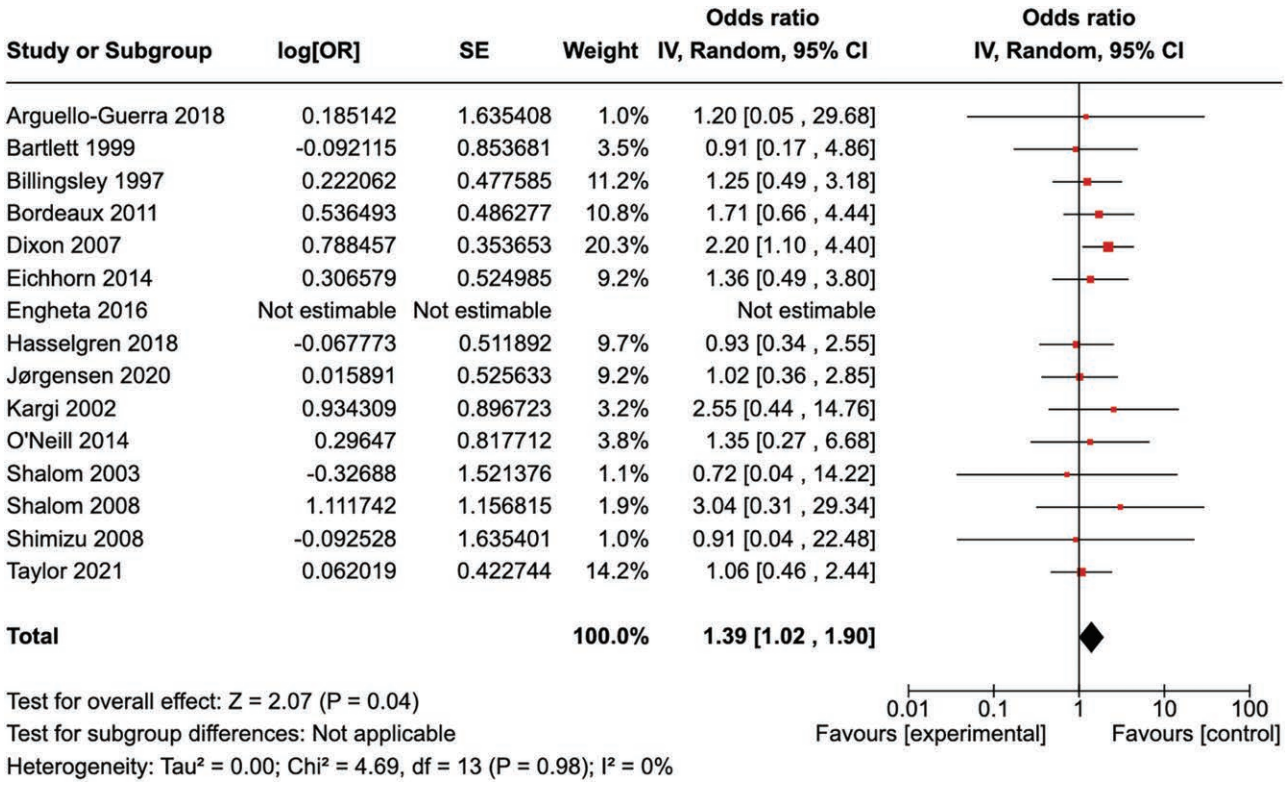

Fig. 2. Meta-analysis. Postoperative bleeding or hematoma formation of any severity (aspirin vs control). CI, confidence interval; OR, odds ratio; SE, standard error.

in their analysis. Our definition of "any severity" includes bleeds that required medical intervention, and it is possible that in the scope of their definition, some additional events that meet our criteria but not theirs could be missed. Bordeaux et al reviewed patients more than 24 hours postprocedure to assess for hemorrhage or hematoma formation, whereas Billingsley et al contacted their patients over telephone and reviewed them in clinic at a later date. Taylor et al defined bleeding as evidence of blood exiting through the wound or formation of a hematoma but did not specify if additional procedures were performed.

The methodology for collecting complications relating to postoperative bleeds varied between studies. Hasselgren et al[23] and Shimizu et al[31] both performed retrospective studies. The former reviewed patients at a 1-week follow-up, and the latter reviewed complications entered in a logbook. This made both studies susceptible to anomalies in how clinicians recorded complications.[23,31]

Shalom et al[29,30] are notable for significant differences in their study population characteristics. The mean age of their aspirin group was greater than the control (63.7 versus 44.4) and (72 versus 45); men made up a larger proportion of their aspirin cohort than in controls.[29,30]

Moderate Postoperative Bleeding

The OR for postoperative hemorrhage or hematoma of moderate severity in patients taking aspirin did not attain statistical significance and was calculated from inclusion of 7 studies as 0.92 (0.46–1.81) (Z = 0.25; $P = 0.80$) (Fig. 3). Study effect size heterogeneity was low ($I^2 = 0\%$). A total of 1,629 participants were included, fewer than the severe and all severity analyses.

Jorgensen et al[24] accounted for 43.6% of the weighting and included patients not established on aspirin and those that discontinued it before their procedure. In our results, we included both groups in the control category. This study exclusively looked at skin grafting (full and split thickness) at the excision site.

Billingsley et al had the second largest weighting and is discussed previously. Kargi et al[25] had characteristics comparable between intervention and control groups but did not give a breakdown as to the closure technique used (Fig. 3).

Severe Postoperative Bleeding

The OR for postoperative hemorrhage or hematoma in patients taking aspirin attained statistical significance and was calculated from inclusion of 12,311 procedures, across 7 studies as 2.46 (1.53–3.95) (Z = 3.73; $P = 0.0002$) (Fig. 4). Study effect size heterogeneity was low ($I^2 = 0\%$).

Koenen et al evaluated the greatest number of procedures in our review: 1,267 interventions and 5,009 controls. Of the controls, 4,769 were not established on aspirin, whereas 240 discontinued it before the procedure was performed (in none of the patients, aspirin was replaced with another anticoagulant or antiplatelet agent, during the omission period). This study accounted for 60.9% of the meta-analysis weighting and records an OR of 2.66 for severe bleeds. Although both severe and mild bleeds were recorded, bleeding risk for intervention

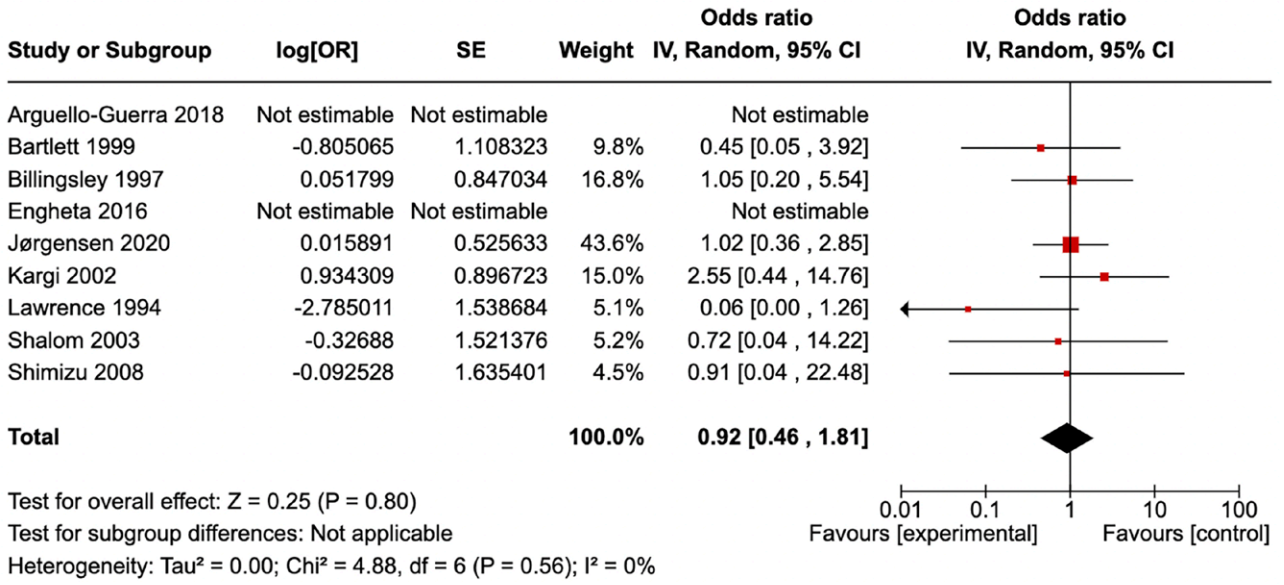

Fig. 3. Meta-analysis. Moderate bleeding or hematoma formation (aspirin vs control). CI, confidence interval; OR, odds ratio; SE, standard error.

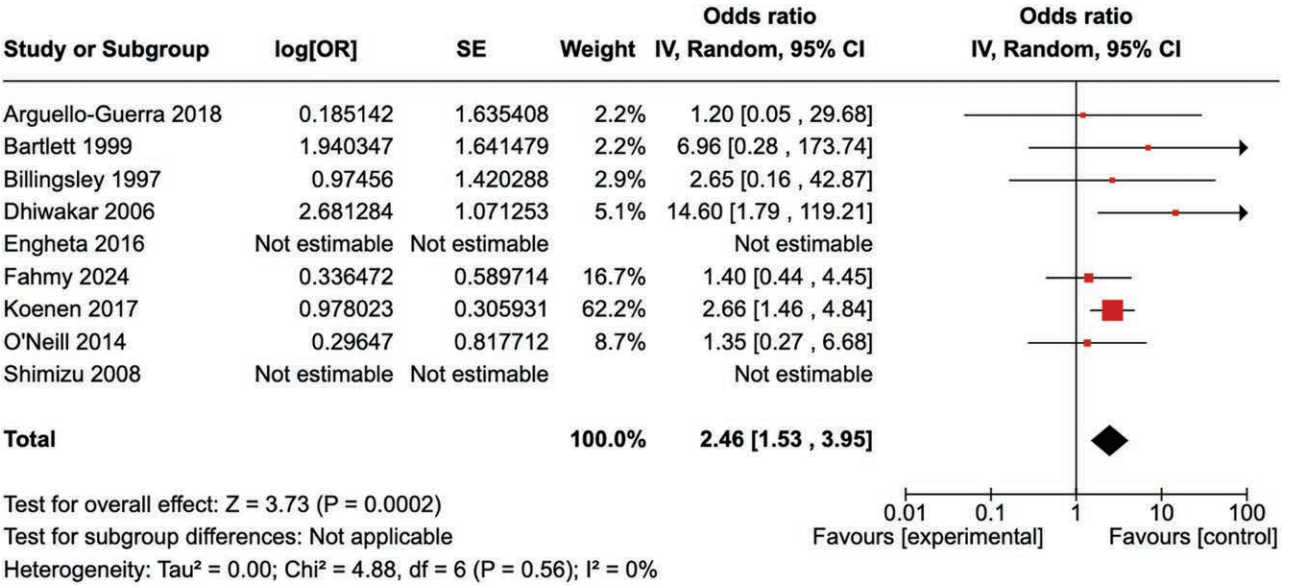

Fig. 4. Meta-analysis. Severe bleeding or hematoma formation (aspirin vs control). CI, confidence interval; OR, odds ratio; SE, standard error.

and control groups was only given in the severe category. The incidence of severe bleeds in those not established on anticoagulants and in those who discontinued aspirin was 0.53% and 0.43%, respectively. In those continuing aspirin, the incidence was 1.42%.[26]

The study by Dhiwakar et al[19] had the greatest OR of 14.60. It evaluated excision of lesions on the head and neck. Twenty-nine percent of their patients had a local flap reconstruction performed. A multivariate analysis identified aspirin use and local flap or graft reconstruction as statistically significant variables for postoperative hemorrhage.

Fahmy et al[22] computed a multivariable and univariable risk for patients on aspirin monotherapy. We included the univariable OR in our calculation of 1.40, but once adjusted for age and sex the OR reduces to 1.27 ($P = 0.71$).[22]

O'Neill et al[28] mainly evaluated patient undergoing lesion excision of the head and neck (74%). Three of 881 patients on aspirin developed a bleed, compared with 3 of 1,184 controls. No subgroup or regression analysis is available.

In study, death was reported as a complication.[14–16]

Infection and Wound Dehiscence

Only 2 studies were included in the evaluation for infection; 3 were included for wound dehiscence. Neither

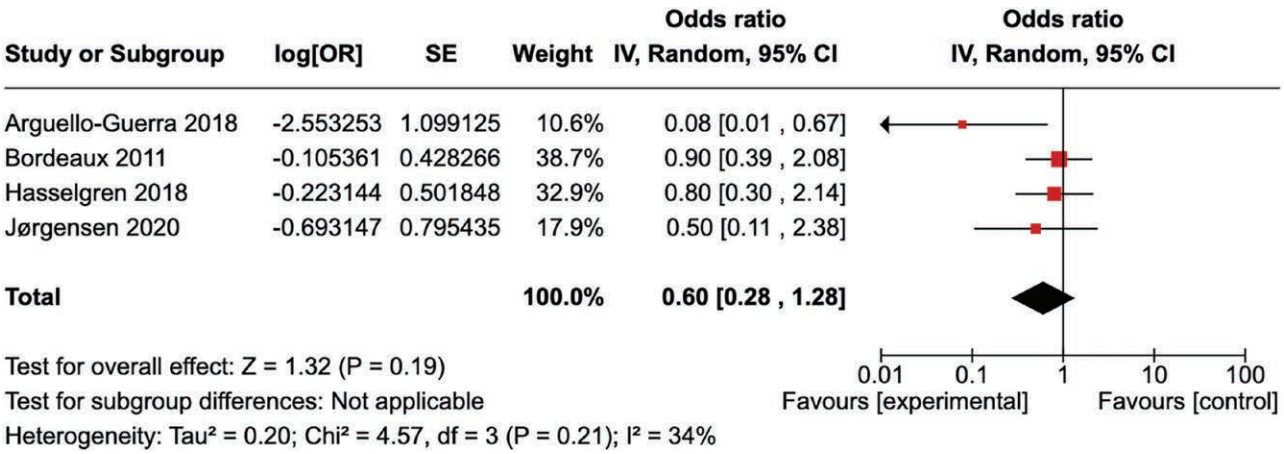

Fig. 5. Meta-analysis. Infection (aspirin vs control). CI, confidence interval; OR, odds ratio; SE, standard error.

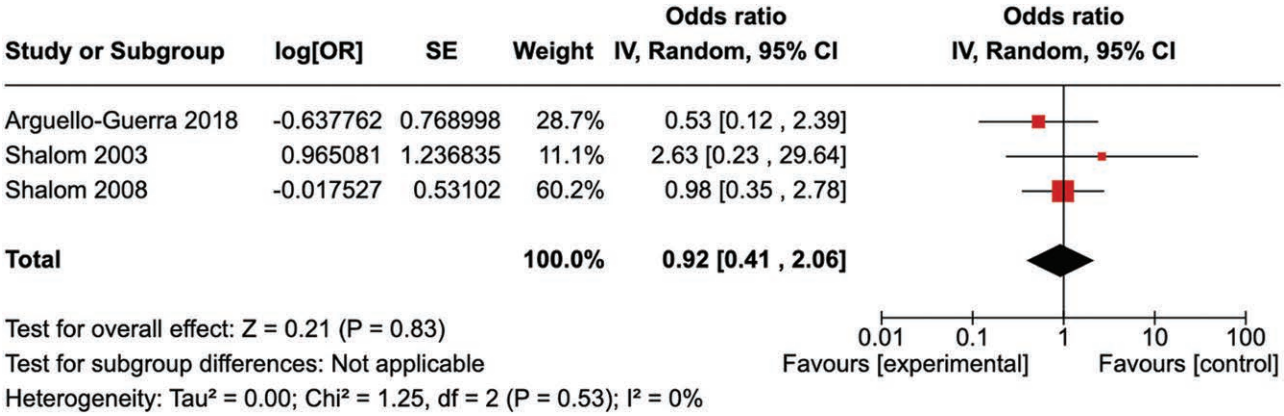

Fig. 6. Meta-analysis. Wound dehiscence (aspirin vs control). CI, confidence interval; OR, odds ratio; SE, standard error.

OR (0.60 for infection and 0.92 for wound dehiscence) attained statistical significance. A more detailed breakdown is described in Figures 5 and 6.

DISCUSSION

This meta-analysis included 26,790 procedures. The OR for bleeding of any severity and severe bleeding attained statistical significance. To our knowledge, our meta-analysis evaluated the greatest number of studies and participants to date. Previous meta-analysis by Lewis et al[34] and Nast et al[35] included 472 and 3,160 participants in their analysis, respectively. Lewis et al calculated an OR of 2.0 (P = 0.061) for moderate-to-severe complications, which included bleeding that required intervention by a medical professional, hematoma, wound dehiscence, and superficial slough or failure of a graft or flap.[34] Nast et al calculated a risk ratio 1.1 (0.52–2.31) for mild-to-moderate postoperative bleeding and 0.92 (0.18–4.57) for severe bleeding in their meta-analysis.[35] Our risk estimate is of a similar order of magnitude, but the greater number of trials included enables us to calculate a more accurate value. A meta-analysis by Bonadurer et al had a large overlap with the studies we included but included studies that evaluated bleeding in more complex procedures such as facial plastic surgery or grafting onto chronic wounds. Although they identified an increased OR of bleeding of any severity (OR 1.87 [95% confidence interval: 1.37–2.55]; P< 0.001), their inclusion of procedures beyond the scope of skin lesion surgery makes It hard to appreciate the effect surgical complexity can have on bleeding risk.[36]

Although in our results moderate severity bleeding risk was not increased, severe bleeding was significantly more likely in patients continuing aspirin. The Dhiwakar study identified that the risk is greater with flaps than direct closure, in keeping with the literature.[12] Both studies by Dhiwakar et al and Koenen et al published an absolute risk of severe bleeding of ~1.5%. In an article by Koenen et al, the absolute risk for nonaspirin users was 0.53%.

Our analysis showed low study heterogeneity. Limitations include that the studies recorded the clinical manifestation of bleeding and the definition of this was variable. The studies did not quantify bleeding on a microscopic level. Most studies compare aspirin users and nonusers, but nonusers are an imperfect control group. Studies should ideally compare users who have omitted aspirin perioperatively to those who have continued it, because users may have other characteristics that predispose them to bleeding. For example, aspirin users tend to be older, male sex, and have established cardiovascular disease.

Aging and its associated skin changes have also been shown to make patients more prone to bleeding.[37,38] This area of research would benefit from a randomized controlled trial, similar to the study by Engheta et al, but at a greater scale, which compares cohorts omitting and continuing their aspirin medication. Recent research suggests a role for aspirin in reducing the odds of nonmelanoma skin cancer, but not invasive melanoma, and hence, an accurate quantification of bleeding risk in skin cancer surgery is an important consideration as this research unfolds[39,40]

Arachidonic acid-induced platelet aggregometry studies have found that platelet function recovers within 4 days of aspirin cessation; this is despite the fact that complete restoration of thromboxane levels takes 10 days (ie, time to replace the platelet pool). This finding is corroborated by mixing studies in which a 30% proportion of non-aspirinated platelets can produce sufficient thromboxane to overcome aspirin's inhibitory effect on the remaining pool.[41,42] Naturally, the exact time from cessation to restoration of platelet function can vary between individuals and will be influenced particularly by the rate of platelet turnover and polymorphisms in the cyclooxygenase enzyme.[43,44] The recommendation of aspirin cessation 5 days before surgical intervention is based on these findings, but in no study we analyzed was platelet aggregometry undertaken. Lawrence et al measured bleeding time, which is a crude marker of platelet function. It is worth bearing in mind that the heterogenous effect of aspirin on platelet function can make some procedures more challenging on some patients than others.

The bleeding risk is greatest within the first 48 hours postprocedure, and it is important to consider ways of minimizing this. At conclusion of any procedure, the surgeon will ensure no frank arteriolar or venular bleeding persists, but resolution of capillary bleeds relies on platelet aggregation and an intact coagulation cascade.[45] To facilitate hemostasis at the capillary scale, alginate dressings, which target capillary bleeds, and pressure dressings, which reduce the potential space for hematoma formation, can be applied.[46]

To reach a conclusion on the merits of continuing or omitting aspirin prior to surgery, we must consider the risks associated with its discontinuation. Only a few studies have tried to quantify the risk of thrombotic complications. Kovich et al disseminated a questionnaire to physicians to submit their complications in retrospect. Only 33% of those contacted responded. The study results indicated that short-term omission of aspirin, which was withheld for a median of 7 days preoperatively and resumed 2 days postoperatively, had a low absolute incidence of thrombotic complications: 1 in 21,448 patients undergoing cutaneous surgery; but the study did not calculate the baseline risk of thrombotic complications in patients continuing aspirin. It is sensible to incorporate thrombotic complications as an outcome measure alongside bleeding risk when designing future studies on perioperative aspirin cessation.[47]

Future studies should aim to control for confounding variables and implement a control arm in which patients discontinue aspirin. Accurately quantifying the risk of aspirin continuation versus cessation is paramount to perioperative safety and safe prescribing of this widely used medication.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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