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S3-Leitlinie: Umgang mit Antikoagulantien und Thrombozytenaggregationshemmern bei Operationen an der Haut

Update 2020

Evidence to Decision Frameworks

Der systematische Review [1] wurde aktualisiert und publiziert [2] – die Ergebnisse und GRADE-Tabellen wurden übernommen. Im Folgenden werden hier die Ergebnisse dieser Aktualisierung mit Hilfe von Evidence-to-Decision-Frameworks präsentiert.

Die Schlüsselfragen der Leitlinie lauten:

Schlüsselfrage 1: Wie hoch ist das Komplikationsrisiko bei Operationen an der Haut unter Antikoagulantien- und Thrombozytenaggregationshemmergabe? (ab Seite 2)

Schlüsselfrage 2: Führt ein Pausieren von direkten oralen Antikoagulantien im Vergleich zur kontinuierlichen Gabe zu einer Reduktion der perioperativen Komplikationen bei Operationen an der Haut? (ab Seite 2)

Schlüsselfrage 3: Führt ein Pausieren von Vitamin K-Antagonisten mit Umstellung auf ein Heparin im Vergleich zur kontinuierlichen Gabe zu einer Reduktion der perioperativen Komplikationen bei Operationen an der Haut? (ab Seite 6)

Verwendete Abkürzungen:

ASA: Acetylsalicylic acid

CI: Confidence interval

PCS: Prospective cohort studies

RCT: Randomized controlled trial

RR: Risk ratio

SCHLÜSSELFRAGE 1 & 2

QUESTION

Does the perioperative discontinuation of antithrombotic agents in comparison to their continued use in patients undergoing cutaneous surgery lead to an increase in perioperative complications?

POPULATION:	Patients undergoing cutaneous surgery
INTERVENTION:	Monotherapy or combination therapy with any of the following medications: • 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, warfarin, acenocoumarol • Thrombin inhibitors: dabigatran, argatroban, desirudin, bivalirudin • Factor Xa inhibitors: rivaroxaban, apixaban, edoxaban, fondaparinux • Platelet aggregation inhibitors: acetylsalicylic acid, clopidogrel, ticlopidin, ticagrelor, prasugrel, cilostazol, dipyridamole 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.
COMPARISON:	• Placebo • No treatment • Perioperative discontinuation of one or more of the medications listed above Comparison of any of the above mentioned interventions
MAIN OUTCOMES:	Excessive intraoperative bleeding; Uncontrollable intraoperative bleeding; Minor postoperative bleeding; Significant postoperative bleeding; Any postoperative bleeding; Thromboembolic event
BIBLIOGRAPHY:	Alcalay 2001 [3], Bartlett 1999 [4], Billingsley 1997 [5], Blasdale 2008 [6], Bordeaux 2011 [7], Dixon 2007 [8], Eichhorn 2014 [9], Engheta 2016 [10], Gowrishankar 2017 [11], Harbottle 2014 [12], Kargi 2002 [13], Koenen 2017 [14], Kramer 2010 [15], Lawrence 1994 [16], O'Neill 2014 [17], Shalom 2003 [18], Shalom 2008 [19], Shipkov 2015 [20], Sun 2017 [21], Syed 2004 [22]

ASSESSMENT

Problem

Is the problem a priority?

RESEARCH EVIDENCE

The incidence rates for skin cancer in Europe are projected to increase significantly in the first half of the 21st century due to an aging population [23]. Hence, more surgeries treating these cutaneous conditions will be required. Furthermore, between 2014 and 2018 the prescriptions of vitamin k antagonists and direct oral anticoagulants have increased by more than 37% in Germany [24]. Additionally, in Germany direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, dabigatran) have overtaken vitamin k antagonists (phenprocoumon) as the most prescripted anticoagulants [24]. Moreover, a survey conducted in 2017 among German dermatologist showed that there is significant heterogeneity in the perioperative management of antithrombotic agents during cutaneous surgeries [25]. Therefore, up-to-date guidelines regarding the perioperative management of antithrombotic agents in dermatologic surgery are of crucial importance.

Desirable Effects

How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE

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Undesirable Effects

How substantial are the undesirable anticipated effects?

RESEARCH EVIDENCE

1. ASA versus no ASA

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	4037 (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)	4830 (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)

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 1000) 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 1000) 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 1000) twice.
g. No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 791 of 9700 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 1000) 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 1000) twice.
m. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) twice.

2. Clopidogrel versus no clopidogrel

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with no clopidogrel	Risk difference with clopidogrel (95% CI)

Significant postoperative bleeding	1593 (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	2105 (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)

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 1000) 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 1000) once. The width of the confidence interval for the risk difference exceeds twenty percentage points.

3. ASA & clopidogrel versus neither ASA nor clopidogrel

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	6048 (2 PCS)	⊕◯◯◯ VERY LOW [a, b]	not estimable	5 per 1,000	**8 more per 1,000** (from 18 fewer to 33 more)

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 1000) twice.

4. Phenprocoumon versus no phenprocoumon

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)

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.

Research evidence for ten more comparisons can be found at the end of this document (see page 9 to 11).

Outcome importance

What is the overall certainty of the evidence of effects?

RESEARCH EVIDENCE

Outcome	Definition	Importance
Excessive intraoperative bleeding	”significant [intraoperative] bleeding that was difficult to control” (p. 757) [3]	CRITICAL
Uncontrollable intraoperative bleeding	“[s]evere [intraoperative] bleeding necessitating termination of procedure” (p. 523) [6]	CRITICAL
Minor postoperative bleeding	postoperative bleeding that was managed by patients themselves [4]	IMPORTANT
Significant postoperative bleeding	postoperative bleeding that “require[d] some form of professional medical help […] or compromis[ed] the surgical outcome” (p. 215) [4]	CRITICAL
Any postoperative bleeding	any kind of postoperative bleeding	OF LIMITED IMPORTANCE

Thromboembolic event	a perioperative thromboembolic complication that leads to relevant morbidity or causes death	CRITICAL

The quality of evidence for all assessed outcomes was judged to be very low. Therefore, additional well-conducted large-scale research is needed.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Judgments about the probable balance of effects depend on clinical experience and additional considerations (see to the right).	Six guidelines from other societies give recommendations regarding the perioperative management of antithrombotic agents in cutaneous surgeries [26-31].

Resources required

How large are the resource requirements (costs)?

ADDITIONAL CONSIDERATIONS

In comparison a discontinuation protocol the perioperative continuation of antithrombotic agents requires additional doses of the medications.

Equity, Acceptability & Feasibility

What would be the impact on health equity? Is the intervention acceptable to key stakeholders? Is the intervention feasible to implement?

RESEARCH EVIDENCE
ADDITIONAL CONSIDERATIONS

The intervention, namely the perioperative continuation of any antithrombotic therapy, would have minimal impact on health equity because private and statutory health insurance in Germany would cover its costs. The intervention is feasible to implement and facilitates the perioperative management of any antithrombotic therapy significantly which might increase its acceptability to key stakeholders. Patients stay on the therapy regime they are used to. Doctors do not need to oversee the controlled restart of any antithrombotic agent. Health insurers do not face additional costs for potentially necessary additional laboratory tests and consultations due to the resumption of the antithrombotic therapy.
Especially continuing any vitamin K antagonist therapy perioperatively requires significantly fewer resources (e.g. laboratory tests and consultations) than having to restart a vitamin K antagonist therapy after its perioperative discontinuation.

SCHLÜSSELFRAGE 3

QUESTION

Does the perioperative discontinuation of a vitamin k antagonist and bridging with heparin in comparison to the continued use of the anticoagulant in patients undergoing cutaneous surgery lead to an increase in perioperative complications?

POPULATION:	Patients undergoing cutaneous surgery
INTERVENTION:	Perioperative discontinuation of a vitamin K antagonist and bridging with unfractionated heparin or with low molecular weight heparin
COMPARISON:	Perioperative continuation of a vitamin K antagonist
MAIN OUTCOMES:	Excessive intraoperative bleeding; Significant postoperative bleeding; Any postoperative bleeding; Thromboembolic event
BIBLIOGRAPHY:	Koenen 2017 [14], Lam 2001 [32]

ASSESSMENT

Problem
Is the problem a priority?

RESEARCH EVIDENCE

Several systematic reviews [33-36] have compared the perioperative bridging of vitamin k antagonists with heparin to the continued use of the anticoagulant for surgical interventions. They suggest that bridging increases the risk of bleeding complications while not decreasing the occurrence of thromboembolic events.
In the first version of these S3 guidelines from 2014 [37] the expert consensus was to advise against bridging but no study had been identified which directly analyzed the bridging of phenprocoumon with heparin in the case of cutaneous surgery.
In contrast to the above mentioned findings and recommendations, a survey from 2017 found that 19.7% of office-based and 27.9% of hospital-based dermatologists in Germany bridge phenprocoumon with heparin in case of large excisional surgeries [25].

Desirable Effects
How substantial are the desirable anticipated effects?

RESEARCH EVIDENCE

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Undesirable Effects
How substantial are the undesirable anticipated effects?

RESEARCH EVIDENCE

1. Bridging phenprocoumon with heparin versus phenprocoumon

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with phenprocoumon	Risk difference with bridging phen-procoumon 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)

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.

2. Bridging warfarin with heparin versus 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
Excessive intraoperative bleeding	26 (1 RCT)	⊕◯◯◯ VERY LOW [a, b]	-	-	-	"no excessive intraoperative-bleeding […] in either of [the] study groups" [32]
Any postoperative bleeding	26 (1 RCT)	⊕◯◯◯ VERY LOW [a, b]	-	-	-	"[t]here were no statistically signifcant differences in the rate of postoperative bleeding complications (P = 0.48 at the operative site and P = 0.59 at the donor site)" [32]
Thromboembolic event	26 (1 RCT)	⊕◯◯◯ VERY LOW [a, b]	-	-	-	"no […] thromboembolic complications in either of [the] study groups" [32]

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.

Outcome importance

How important is each assessed outcome?

RESEARCH EVIDENCE

Outcome	Definition	Importance
Excessive intraoperative bleeding	”significant [intraoperative] bleeding that was difficult to control” (p. 757) [3]	CRITICAL
Significant postoperative bleeding	postoperative bleeding that “require[ed] some form of professional medical help […] or compromis[ed] the surgical outcome” (p. 215) [4]	CRITICAL
Any postoperative bleeding	any kind of postoperative bleeding	OF LIMITED IMPORTANCE
Thromboembolic event	a perioperative thromboembolic complication that leads to relevant morbidity or causes death	CRITICAL

The quality of evidence for all assessed outcomes was judged to be very low. Therefore, additional well-conducted large-scale research is needed.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

Judgments about the probable balance of effects depend on clinical experience and additional considerations (see to the right).	Five guidelines from other societies give recommendations regarding the perioperative management of vitamin k antagonists in cutaneous surgeries [26, 28-31]. Five systematic reviews assess the available evidence regarding periprocedural heparin bridging of vitamin k antagonists [33-36, 38]. One study that was included in the first version of the German S3 guidelines for the management of anticoagulation in cutaneous surgery but not in this update looked at bridging versus no bridging vitamin k antagonists with heparin during extraction of teeth [39].

Resources required

How large are the resource requirements (costs)?

ADDITIONAL CONSIDERATIONS

Resuming the vitamin K antagonist therapy after its perioperative discontinuation requires significant additional resources (e.g. laboratory tests and consultations).

Equity, Acceptability & Feasibility

What would be the impact on health equity? Is the intervention acceptable to key stakeholders? Is the intervention feasible to implement?

ADDITIONAL CONSIDERATIONS

The intervention, namely the perioperative discontinuation of a vitamin K antagonist and bridging with unfractionated heparin or with low molecular weight heparin, would have minimal impact on health equity because private and statutory health insurance in Germany would cover its costs. The intervention is feasible to implement but complicates the perioperative management of the anticoagulation significantly which might decrease its acceptability to key stakeholders. Patients need to attend additional medical appointments. Doctors need to oversee the controlled restart of the anticoagulation. Health insurers face additional costs for the necessary laboratory tests and consultations.

RESEARCH EVIDENCE FOR ADDITIONAL COMPARISONS

1. Warfarin versus no warfarin

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with no warfarin	Risk difference with warfarin (95% CI)
Excessive intraoperative bleeding	225 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 9.86** (3.91 to 24.89)	42 per 1,000	**375 more per 1,000** (from 123 more to 1,000 more)
Uncontrollable intraoperative bleeding	157 (1 PCS)	⊕◯◯◯ VERY LOW [c, d]	not estimable	0 per 1,000	**0 fewer per 1,000** (from 26 fewer to 26 more)
Minor postoperative bleeding	400 (3 PCS)	⊕◯◯◯ VERY LOW [e, b]	**RR 3.09** (1.41 to 6.79)	67 per 1,000	**141 more per 1,000** (from 28 more to 390 more)
Significant postoperative bleeding	1680 (3 PCS)	⊕◯◯◯ VERY LOW [f, g]	not estimable	6 per 1,000	**24 more per 1,000** (from 1 more to 47 more)
Any postoperative bleeding	4243 (3 PCS)	⊕◯◯◯ VERY LOW [h, i]	not estimable	4 per 1,000	**23 more per 1,000** (from 12 fewer to 58 more)

a. No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 10 of 332 participants.
b. The optimal information size was not reached. The width of the confidence interval for the risk difference exceeds twenty percentage points.
c. No control for likely confounders. No blinding of outcome assessors reported. Significant deviations from intended intervention in 25% of participants in the intervention group.
d. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) twice.
e. No control for likely confounders. No blinding of outcome assessors reported in Billingsley 1997 and Syed 2004. Missing outcome data for 10 of 332 participants in Billingsley 1997. 8 of 55 participants in the intervention group and 6 of 55 participants in the comparator group were lost to follow-up in Syed 2004.
f. No control for likely confounders. No blinding of outcome assessors reported. Missing outcome data for 10 of 332 participants in Billingsley 1997. 8 of 55 participants in the intervention group and 6 of 55 participants in the comparator group were lost to follow-up in Syed 2004.
g. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) once.
h. 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.
i. The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1000) once.

2. Rivaroxaban versus warfarin

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with warfarin	Risk difference with rivaroxaban (95% CI)
Minor postoperative bleeding	59 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 1.10** (0.33 to 3.62)	182 per 1,000	**18 more per 1,000** (from 122 fewer to 476 more)
Significant postoperative bleeding	59 (1 PCS)	⊕◯◯◯ VERY LOW [a, c]	**RR 0.59** (0.07 to 4.63)	114 per 1,000	**47 fewer per 1,000** (from 106 fewer to 412 more)
Any postoperative bleeding	59 (1 PCS)	⊕◯◯◯ VERY LOW [a, d]	**RR 0.90** (0.35 to 2.35)	295 per 1,000	**30 fewer per 1,000** (from 192 fewer to 399 more)

a. No control for likely confounders. No blinding of outcome assessors reported.
b. The confidence interval for the risk difference crosses the clinical decision threshold (20 per 1000) twice. The width of the confidence interval for the risk difference exceeds twenty percentage points.
c. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) twice. The width of the confidence interval for the risk difference exceeds twenty percentage points.
d. The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1000) twice. The width of the confidence interval for the risk difference exceeds twenty percentage points.

3. ASA & phenprocoumon versus neither ASA nor phenprocoumon

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with neither ASA nor phenprocoumon	Risk difference ASA & phenprocoumon (95% CI)
Significant postoperative bleeding	4816 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 3.90** (0.54 to 28.17)	5 per 1,000	**16 more per 1,000** (from 3 fewer to 149 more)

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.

4. ASA & phenprocoumon versus phenprocoumon

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with phenprocoumon	Risk difference with ASA % phenprocoumon (95% CI)
Significant postoperative bleeding	704 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 0.93** (0.13 to 6.90)	23 per 1,000	**2 fewer per 1,000** (from 20 fewer to 135 more)

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) twice.

5. ASA & phenprocoumon versus ASA

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with ASA	Risk difference with ASA & phenprocoumon (95% CI)
Significant postoperative bleeding	1314 (1 PCS)	⊕◯◯◯ VERY LOW a, b	**RR 1.50** (0.20 to 10.98)	14 per 1,000	**7 more per 1,000** (from 11 fewer to 142 more)

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) twice.

6. ASA & warfarin versus neither ASA nor warfarin

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with neither ASA nor warfarin	Risk difference with ASA & warfarin (95% CI)
Significant postoperative bleeding	1242 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 6.80** (0.72 to 64.42)	3 per 1,000	**15 more per 1,000** (from 1 fewer to 159 more)
Any postoperative bleeding	1993 (1 PCS)	⊕◯◯◯ VERY LOW [c, d, e]	**RR 12.87** (1.85 to 89.59)	7 per 1,000	**84 more per 1,000** (from 6 more to 629 more)

a. No control for likely confounders. No blinding of outcome assessors reported. Exclusion of approximately one percent of participants after beginning of study period.
b. The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1000) once. The width of the confidence interval for the risk difference exceeds twenty percentage points.
c. No control for likely confounders. No blinding of outcome assessors reported.
d. In the intervention group 2 out of 58 participants took warfarin, ASA & clopidogrel and 6 out of 58 took warfarin & clopidogrel.
e. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) once.

7. ASA & warfarin versus warfarin

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with warfarin	Risk difference with ASA & warfarin (95% CI)
Significant postoperative bleeding	219 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 0.69** (0.08 to 6.08)	25 per 1,000	**8 fewer per 1,000** (from 23 fewer to 126 more)
Any postoperative bleeding	78 (1 PCS)	⊕◯◯◯ VERY LOW [c, d, e]	**RR 2.03** (0.23 to 17.81)	45 per 1,000	**46 more per 1,000** (from 34 fewer to 753 more)

a. No control for likely confounders. No blinding of outcome assessors reported. Exclusion of approximately one percent of participants after beginning of study period.
b. The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1000) twice. The width of the confidence interval for the risk difference exceeds twenty percentage points.
c. No control for likely confounders. No blinding of outcome assessors reported.
d. In the intervention group 2 out of 58 participants took warfarin, ASA & clopidogrel and 6 out of 58 took warfarin & clopidogrel.
e. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) twice.

8. ASA & warfarin versus ASA

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with ASA	Risk difference with ASA & warfarin (95% CI)
Significant postoperative bleeding	939 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 5.06** (0.53 to 47.92)	3 per 1,000	**14 more per 1,000** (from 2 fewer to 160 more)
Any postoperative bleeding	345 (1 PCS)	⊕◯◯◯ VERY LOW [c, d, e]	**RR 15.18** (1.49 to 155.12)	6 per 1,000	**85 more per 1,000** (from 3 more to 925 more)

a. No control for likely confounders. No blinding of outcome assessors reported. Exclusion of approximately one percent of participants after beginning of study period.
b. The confidence interval for the risk difference crosses the clinical decision threshold (15 per 1000) once. The width of the confidence interval for the risk difference exceeds twenty percentage points.
c. No control for likely confounders. No blinding of outcome assessors reported.
d. In the intervention group 2 out of 58 participants took warfarin, ASA & clopidogrel and 6 out of 58 took warfarin & clopidogrel.
e. The confidence interval for the risk difference crosses the clinical decision threshold (10 per 1000) once.

9. ASA & clopidogrel versus ASA

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with ASA	Risk difference with ASA & clopidogrel (95% CI)
Significant postoperative bleeding	2243 (2 PCS)	⊕◯◯◯ VERY LOW [a, b]	not estimable	10 per 1,000	**4 more per 1,000** (from 21 fewer to 30 more)

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 1000) twice.

10. ASA & clopidogrel versus clopidogrel

Outcome	Participants (studies)	Overall certainty of evidence	Relative effect (95% CI)	Risk with clopidogrel	Risk difference with ASA & clopidogrel (95% CI)
Significant postoperative bleeding	133 (1 PCS)	⊕◯◯◯ VERY LOW [a, b]	**RR 1.25** (0.14 to 11.56	29 per 1,000	**7 more per 1,000** (from 25 fewer to 302 more)

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) twice.

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