

Kort klinisk retningslinje vedr.

Tromboseprofylakse ved ankelfrakturer 2023:

Titel: Kort klinisk retningslinje vedr. Tromboseprofylakse ved ankelfrakturer

Anbefaling:

↑Svag anbefaling for rutinemæssig anvendelse af tromboseprofylakse med LMWH ifm. immobilisering af ankelfrakturer (operativt og non-operativt) hos voksne.

For symptomatiske DVT'er er Number Needed to Treat = 86. Der er ikke fundet nogen effekt på LE. Hver for sig er de inkluderede delstudier (RCT'er) af moderat kvalitet, men da de er meget heterogene i inklusionskriterier, behandlingsregimer og måling af outcome, bliver metaanalyser usikre og af meget lav kvalitet (+) () ().

√ God praksis at benytte tromboseprofylakse i 1 uge, da der ikke er yderligere effekt af behandling herudover.

Evidensniveau:

(+)()() = meget lavt

Udarbejdet af: Dansk Ortopædisk Traumeselskab

Forfattere: Christian Cavallius, Louise Thuren Jørgensen, Nikoline Møller Lynnerup og Ole Brink

Afventer: Godkendelse forud for DOS kongressen 2023 efter høring på DOS hjemmesiden.

Baggrund for valg af spørgsmål:

Ankelfrakture er en hyppig forekommende skade i skadestuen med en forekomst på ca. 1/3 af alle frakturer set i skadestuer i England (Kaye et al., 2004). De kan underinddeles ud fra AO principper og kan groft sagt vurderes som: Stabile og ustabile, samt dislocerede og udislocerede frakturer, alt efter fraktur-sted og involvering af syndesmosen. Oftest behandles frakturerne med immobilisering i kortere eller længere tid (jf. regionale guidelines).

Venøse tromboembolier (VTE) er en velkendt komplikation til ortopædkirurgiske indgreb (Zee et al., 2017). Risikoen for dyb venetrombose (DVT) er en velkendt komplikation til immobilisering. DVT kan potentielt udvikle sig til en fatal lungeemboli (LE) og post-thrombotisk syndrom (PTS) (Hickey et al., 2015).

Hverken i Danmark eller udlandet er der konsensus om farmakologisk profylaktisk behandling af DVT ifm. ankelfrakture eller andre fod- og ankelskader, som kræver immobilisering, som led i behandlingen. Aktuelt er der således ingen national dansk klinisk retningslinje (Sundhedsstyrelsen), hvorfor det op til den respektive behandlingsansvarlige kirurg at tage stilling til profylakse med baggrund i eventuelle risikofaktorer, som patienten måtte besidde (jf. VIP HGH) - men oftest er det baseret en subjektiv vurdering. Nogle afdelinger har besluttet som standard at give tromboseprofylakse til alle ankelfrakture, som skal opereres (jf. VIP NOH, PRI AaUH).

Immobilisering af pågældende underekstremitet er ofte et essentielt som led i behandlingen af en ankelfraktur (Lapidus et al., 2007). I litteraturen skelnes sjældent mellem typer af bandager, og vi har derfor også valgt ikke at skelne mellem fx Walker-støvle og gips. Et Cochrane review fra 2017 viste en incidens af DVT fra 4,3% og op til 40% afhængig af skadens type, den var lavest ved frakturer og højest ved Achillesenerupturer. Fælles for patienterne i studiet var, at de alle havde immobiliseret underben som led i behandlingen (Zee et al., 2017).

Formålet med denne korte kliniske retningslinje (KKR) er at belyse tromboseprofylakse ved ankelfrakture, som behandles operativt med efterfølgende immobiliserende bandage samt de patienter, som behandles konservativt alene med immobiliserende bandage.

I litteratur søgestreng er der fokuseret på isolerede ankelfrakture som uni-, bi- eller trimalleolære frakturer. Vi har valgt ikke at inkludere frakturer i fod og herunder Lisfranc-frakturer og Charcot-fod. Herudover er er bløddelsskader som Achilleseneruptur samt frakturer proksimalt for ankelled fravalgt.

Hovedspørgsmålet i denne korte kliniske retningslinje er:

Skal gives farmakologisk profylaktisk anti-trombotika til patienter med ankelfrakture, som behandles operativt med efterfølgende immobiliserende bandage eller som behandles konservativt fra start med immobiliserende bandage.

Denne retningslinje omhandler:

PICO spørgsmål:

Er tromboseprofylakse bedre behandling end ingen tromboseprofylakse, ved immobilisering i forbindelse med ankelfraktur, hvad angår risiko for VTE.

Population:

- Patienter over 18 år
- Immobiliserende bandage som led i behandling af ankelfraktur
- Ingen forudgående risikofaktorer for VTE herunder DVT og LE.
- Operativ og non-operativ behandling

Intervention:

- Lavmolekylært heparin

Comparison:

- Ingen tromboseprofylakse

Outcome:

- Primært for beslutningstagen:
 - o Primære/kritiske outcome:
 - § VTE herunder DVT og LE
 - § Død
 - o Sekundært:
 - § Komplikationer: Serious Adverse Events (blødning, infektion).

Anbefaling:

↑ Svag anbefaling for rutinemæssig anvendelse af tromboseprofylakse med LMWH ifm. immobilisering af ankelfrakturer (operativt og non-operativt) hos voksne.

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Evidensniveau:

(+) () () = meget lavt

Litteratur:

Efter gennemgang af litteratur er der fundet 7 artikler, heraf 4 systematiske reviews/metaanalyser (Folsom 2022, Weisman 2017, Hickey 2018, Zee 2017), 1 randomized controlled trial (RCT) (Lapidus 2007), 1 subgruppeanalyse af et tidligere publiceret RCT (Nemeth 2019) og 1 retrospektiv opgørelse (Elliot 2023).

Lapidus 2017 og data fra Nemeth 2019 indgår i flere af de systematiske opgørelser, hvorfor de ikke vil blive gennemgået separat. Det er dog værd at nævne, at Lapidus 2017 ikke finder forskel i incidens af asymptomatisk DVT ved behandling med LMWH i 1 uge i forhold til behandlingsvarighed på 5 uger (RR=0,8(0,6-1,1)). I Nemeth 2019 identificeres en række risikofaktorer for udvikling af DVT (se nedenstående tabeller 1 og 2, hhv. tabel 4 og 6 Nemeth et al.), men der fandtes ikke signifikant effekt af LMWH i forhold til udvikling af DVT i nogen af subgrupperne, sammenlignet med ingen behandling.

Risikofaktor	Point
Mandligt køn	1
BMI ≥ 25 og ≤ 35 kg/m ²	1
Komorbiditet (Reumatoid arthrit, nyresvigt, KOL, MS)	1
Alder ≥ 35 og ≤ 55 år	2
BMI ≥ 35 kg/m ²	2
1. gradsslægtning med VTE	2
Indlæggelse i de seneste 3 måneder	2
Sengeliggende i de seneste 3 måneder	2
Kirurgi i de seneste 3 måneder	2
Gips, cirkulær omkring knæ (fri ankel)	2
Gips, fod	2
Alder ≥ 55 år	3
Cancer i de seneste 5 år	3
Graviditet eller puerperium	3
Pneumoni	3
Overfladisk DVT	3
Oral antikonception	4
Gips, underben	4
Gips, hele benet	5

Tabel 1: sv.t. tab. 4, Nemeth et al.

Score	Sensitivitet (%)	Specificitet (%)	Absolut risiko for DVT (CI ikke nævnt)
4	100	0	0,0
5	100	3	
6	100	15	1,3
7	91	27	
8	75	45	1,6
9	59	71	
10	37	85	2,8
11	22	92	
12	17	97	
13	13	99	
14	4	99	8,1
15	4	100	
16	4	100	
17	4	100	

Tabel 2: sv.t. tab. 6, Nemeth et al.

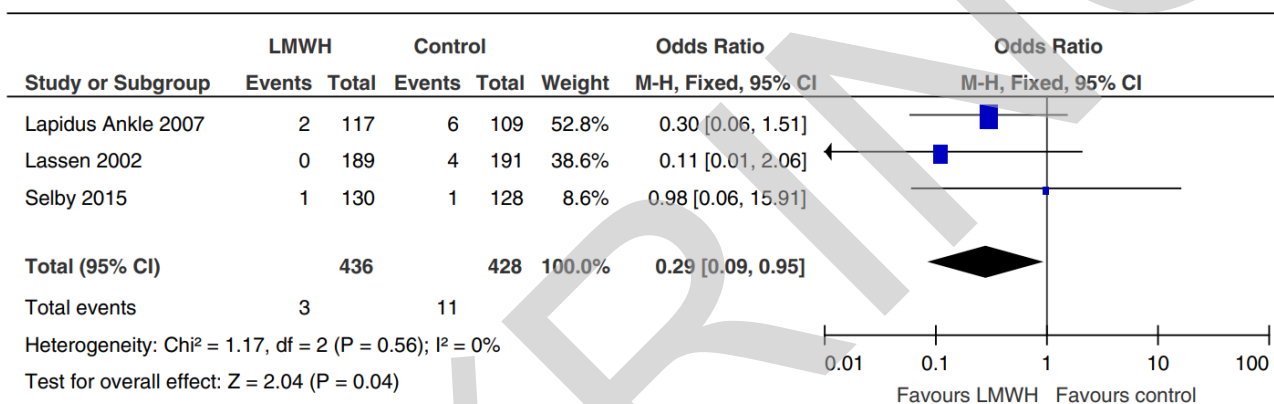
Den retrospektive opgørelse (Elliot 2023) ekskluderes, da der ikke redegøres for allokering til behandlingsgrupperne og derfor stor risiko for selektionsbias til følge.

De systematiske opgørelser er vurderet vha. AMSTAR2 til at være af lav eller kritisk lav kvalitet. Folsom 2022 scorer 11 ud af 16 point, Weisman 2017 scorer 0 point, Hickey 2018 10,5 point og Zee 2017 11 point. Weisman 2017 ekskluderes derfor af KKR. Folsom 2022 er en systematisk gennemgang af kvaliteten af 9 RCT'er. Der er ikke lavet metaanalyse, og studiet ekskluderes herfor. Efter yderligere gennemgang af litteraturen inkluderes derfor kun Hickey 2018 og Zee 2017.

Hickey 2018 (AMSTAR2: 10,5 af 16 point)

Systematisk review og metaanalyse baseret på 7 RCT'er af lav til moderat kvalitet. 3 af de inkluderede studier omhandler frakturer på underben, ankel og fod (n= 864). Alle randomiserede interventionsgruppe til LMWH og kontrolgruppe til placebo (4 studier) eller ingen behandling (3 studier). Primære outcome var DVT, der blev vurderet ved UL og/eller flebografi ved afbandagering (3 studier) eller ved symptomer på DVT (4 studier). De inkluderede studier er meget heterogene i forhold til inklusionskriterier (ankel- eller fodtraume: frakturer, forstuvninger, Achillessenelæsioner, opererede, ikke-opererede). Samlet fandtes Number Needed to Treat (NNT)=86 for at undgå én symptomatisk DVT. Der var komplikationer i form af "major bleeding" hos 1pt. (ikke-dødelig retroperitoneal blødning) af 886 ptt. behandlet med LMWH . I forhold til LE var der ingen signifikant forskel på grupperne.

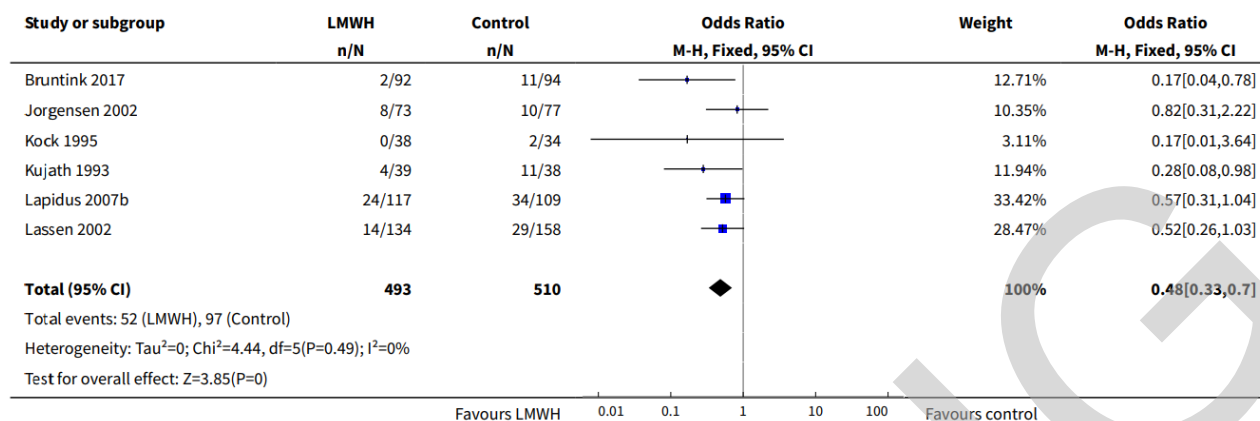
Symptomatic DVT meta-analysis.



Zee 2017 (AMSTAR2: 11 af 16 point)

Cochrane review baseret på 8 RCT'er af lav til moderat kvalitet. Der blev sammenlignet risiko for udvikling af DVT og LE efter immobilisering af underben med gips eller skinne. Effekten af LMWH i forhold til placebo eller ingen behandling blev undersøgt. 6 af de 8 inkluderede studier involverede patienter med immobilisering grundet fraktur (n=1003). Primære outcome var DVT fundet ved UL (3 studier) eller flebografi (3 studier) ved eller efter afbandagering, og asymptomatiske DVT'er er således inkluderet. En stor svaghed ved reviewet er, at der i de inkluderede RCT'er om frakturer, både er medtaget opererede og konservativt behandlede patienter. Desuden inkluderer de også patienter med fraktur i både ankel og fod. I reviewet findes signifikant færre DVT'er ved anvendelse af LMWH i forhold til placebo eller ingen behandling.

Analysis 1.5. Comparison 1 Low molecular weight heparin versus no prophylaxis or placebo, Outcome 5 Deep venous thrombosis: fractures.



I forhold til lungeemboli, var der få tilfælde inkluderet i studierne, og der var ikke signifikant forskel på gruppen i behandling med LMWH og gruppen der fik placebo/ingen behandling.

Arbejdsgruppens overvejelser:

Litteraturen på området er af lav kvalitet og meget heterogen i forhold til inklusionskriterier og outcome (symptomatiske DVT'er vs. alle ptt. skannes med UL eller flebografi). Ved anvendelse af LMWH finder både Zee 2017 (OR 0,48 (0,33;0,7) for asymptomatisk DVT) og Hickey 2018 (OR 0,29 (0,09;0,95) for symptomatisk DVT) signifikant færre DVT'er i gruppen, der får LMWH i forhold til kontrolgruppen.

I forhold til LE er der ingen forskel på grupperne, men her er studierne formentligt underpowered, da incidensen var 0,3%.

I forhold til balancen mellem effekt og skadevirkninger, skal det bemærkes, at hvis man vælger at give tromboseprofylakse, kan der opstå svære komplikationer (*major bleeding*). Forholdet er ca. 1 *major bleeding* for hver 10 symptomatisk DVT, der bliver undgået, men dette er baseret på 1 event blandt 886 patienter i behandling med LMWH.

Kvaliteten af evidensen:

Hver for sig er de inkluderede RCT'er af moderat kvalitet, men da de er meget heterogene i inklusionskriterier, behandlingsregimer og måling af outcome, bliver metaanalyser usikre og af meget lav kvalitet (+)()().

Plan for implementering af aktuelle KKR:

Fremlægelse af KKR til DOS Kongres 2023

Litteraturliste:

Kaye 2004	Kaye JA, Jick H. Epidemiology of lower limb fractures in general practice in the United Kingdom. <i>Inj Prev.</i> 2004 Dec;10(6):368-74. doi: 10.1136/ip.2004.005843. PMID: 15583259; PMCID: PMC1730161.
Regionale vejledninger med adgang til	Vejledninger vedrørende ankelfrakturet fra Aalborg Universitetshospital, Region Nord; Herlev-Gentofte Hospital, Region H; NOH, Region H; Frederiksberg-Bispebjerg Hospital, Region H; Amager-Hvidovre Hospital, Region H; Rigshospitalet-Glostrup Hospital, Region H, Skadestueinstruks for ankelfrakturet AUH, Region Midt.
Elliot 2023	Elliott IS, Rane AA, DeKeyser GJ, Kellam PJ, Dowdle PT, Safaee TM, Marchand LS, Haller JM. Venous thromboembolism in patients with surgically treated ankle fractures. <i>Arch Orthop Trauma Surg.</i> 2023 Mar;143(3):1237-1242. doi: 10.1007/s00402-021-04192-5. Epub 2021 Nov 10. PMID: 34757461.
Folsom 2022	Folsom AJ, Polmear MM, Scaliato JP, Dunn JC, Adler AH, Orr JD. Qualitative analysis of randomized controlled trials informing recommendations for venous thromboembolism prophylaxis after distal lower extremity injuries. <i>OTA Int.</i> 2022 Mar 18;5(2):e201. doi: 10.1097/OI9.000000000000201. PMID: 35919108; PMCID: PMC9278901.
Hickey 2018	Hickey BA, Watson U, Cleves A, Alikhan R, Pugh N, Nokes L, Perera A. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. <i>Foot Ankle Surg.</i> 2018 Feb;24(1):19-27. doi: 10.1016/j.fas.2016.06.005. Epub 2016 Jul 18. PMID: 29413769.
Lapidus 2007	Lapidus LJ, Ponzer S, Elvin A, Levander C, Lärffars G, Rosfors S, de Bri E. Prolonged thromboprophylaxis with Dalteparin during immobilization after ankle fracture surgery: a randomized placebo-controlled, double-blind study. <i>Acta Orthop.</i> 2007 Aug;78(4):528-35. doi: 10.1080/17453670710014185. PMID: 17966008.
Nemeth 2019	Nemeth B, van Adrichem R, Nelissen R, le Cessie S, Cannegieter SC. Individualized Thromboprophylaxis in Patients with Lower-Leg Cast Immobilization-A Validation and Subgroup Analysis in the POT-CAST Trial. <i>Thromb Haemost.</i> 2019 Sep;119(9):1508-1516. doi: 10.1055/s-0039-1693410. Epub 2019 Jul 28. PMID: 31352679.
Weisman 2017	Weisman MHS, Holmes JR, Irwin TA, Talusan PG. Venous Thromboembolic Prophylaxis in Foot and Ankle Surgery: A Review of Current Literature and Practice. <i>Foot Ankle Spec.</i> 2017 Aug;10(4):343-351. doi: 10.1177/1938640017692417. Epub 2017 Feb 1. PMID: 28719780.
Zee 2017	Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. <i>Cochrane Database Syst Rev.</i> 2017 Aug 6;8(8):CD006681. doi: 10.1002/14651858.CD006681.pub4. PMID: 28780771; PMCID: PMC6483324.

Summary:

Background:

Immobilization due to ankle fracture increases the risk of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE).. There's no national Danish guideline about the use of thromboprophylaxis with low molecular weight Heparin (LMWH) when immobilizing patients due to ankle fracture, and current international guidelines disagree whether or not to use thromboprophylaxis .

Aim:

The purpose of this short clinical guideline is to review current literature on the subject and to offer support when deciding for or against thromboprophylaxis when immobilizing patients with a brace or cast due to ankle fracture.

Methods:

A systematic search of relevant literature was conducted on Pubmed, Embase and Cochrane on March 9th, 2023. The evidence was rated by standardized forms (AMSTAR2, Cochrane Risk of Bias-tool and GRADE).

Results:

From a total of 545 studies, 441 were excluded on titles and abstracts, and 97 studies were excluded after reading full text by at least two of the authors. Further two studies were excluded due to wrong study design, and one was excluded due to a low score on AMSTAR2. Of the remaining four studies, two were meta analyses, and two RCTs that already were included in the two meta analyses.

One meta-analysis showed significant lower incidence of asymptomatic DVTs, when using LMWH compared to placebo or no treatment (OR=0,48 (0,33;0,7)). The other meta-analysis showed significant lower incidence of symptomatic DVTs, when using LMWH compared to placebo or no treatment (OR 0,29 (0,09;0,95)).

No clear differences were found between the LMWH and control groups for PE. Major adverse events were rare.

Discussion:

Low-quality evidence showed that the use of LMWH reduced the incidence of DVT when immobilizing the lower limb due to ankle fracture, when compared with no prophylaxis or placebo. Low-quality evidence showed no clear differences in PE rates. The quality of evidence was reduced to very low because of heterogenicity in inclusion criteria, treatment protocols and measurement of outcome in the studies included in the two meta analyses, resulting in a high risk of bias.

Bilag 1: Søgestrategi og søgestreng (id. 9/3 2023)

PudMed:

Search: #9 AND #10

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Søgestreng med overblik:

("Ankle Fractures" [MeSH Terms]

OR

("ankle*" [Text Word] OR "malleolar*" [Text Word])

AND

("fracture*" [Text Word]

OR

"broken" [Text Word]))

AND

("anticoagula*" [Text Word]

OR

("thrombo*" [Text Word]

OR

"emboli*" [Text Word]

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"thromboemboli*" [Text Word])

OR

"Anticoagulants" [MeSH Terms]

OR

"Embolism and Thrombosis" [MeSH Terms])

Search	Actions	Details	Query	Results	Time
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#10	...	>	Search: (((anticoagula*[Text Word]) OR (((thrombo*[Text Word]) OR (emboli*[Text Word])) OR (thromboemboli*[Text Word]))) OR ("Anticoagulants"[Mesh])) OR ("Embolism and Thrombosis"[Mesh]))	718,759	12:13:01
#9	...	>	Search: ("Ankle Fractures"[Mesh] OR ((ankle*[Text Word]) OR (malleolar*[Text Word])) AND ((fracture*[Text Word]) OR (broken[Text Word])))	13,183	12:12:22
#8	...	>	Search: ((ankle*[Text Word]) OR (malleolar*[Text Word])) AND ((fracture*[Text Word]) OR (broken[Text Word]))	13,183	12:12:04
#7	...	>	Search: anticoagula*[Text Word]	152,117	12:08:48
#6	...	>	Search: (((thrombo*[Text Word]) OR (emboli*[Text Word])) OR (thromboemboli*[Text Word]))	634,099	12:08:35
#5	...	>	Search: (fracture*[Text Word]) OR (broken[Text Word])	380,827	12:06:34
#4	...	>	Search: "Anticoagulants"[Mesh] Sort by: Most Recent	95,163	12:05:51
#3	...	>	Search: "Embolism and Thrombosis"[Mesh] Sort by: Most Recent	248,383	12:04:48
#2	...	>	Search: (ankle*[Text Word]) OR (malleolar*[Text Word])	81,219	12:04:03
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Cochrane:

cochranelibrary.com

Search manager | Medical terms (MeSH) | Full search

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-	+	#1	MeSH descriptor: [Ankle Fractures] explode all trees	MeSH	238	
-	+	#2	ankle* OR malleolar*	Limits	13112	
-	+	#3	MeSH descriptor: [Embolism and Thrombosis] explode all trees	MeSH	9446	
-	+	#4	MeSH descriptor: [Anticoagulants] in all MeSH products	MeSH	6111	
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-	+	#7	anticoagula*	Limits	16789	
-	+	#8	#2 AND #5	Limits	1616	
-	+	#9	#1 OR #8	Limits	1616	
-	+	#10	#3 OR #4 OR #6 OR #7	Limits	76751	
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-	+	#12	Type a search term or use the S or MeSH buttons to compose	S	MeSH	Limits N/A

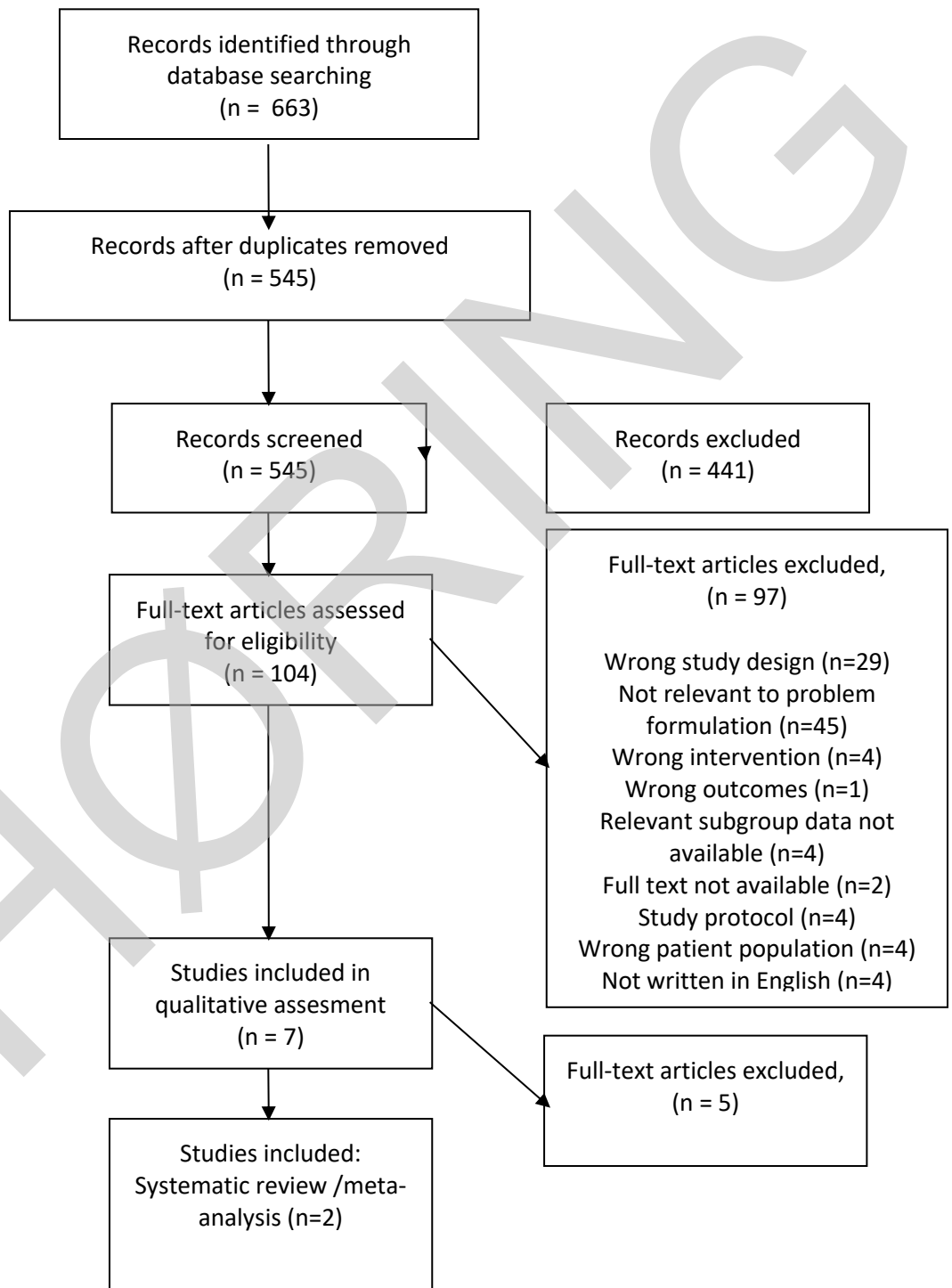
Clear all

Highlight orphan lines

Save this search | View/Share saved searches | Search help

View fewer lines | Print search history

Bilag 2: Flowskema over litteraturudvælgelse



Bilag 3: Vurdering af evidens

Folsom 2022

Folsom AJ, Polmear MM, Scanaliato JP, Dunn JC, Adler AH, Orr JD. Qualitative analysis of randomized controlled trials informing recommendations for venous thromboembolism prophylaxis after distal lower extremity injuries. *OTA Int.* 2022 Mar 18;5(2):e201. doi: 10.1097/OI9.000000000000201. PMID: 35919108; PMCID: PMC9278901.

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Partial yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Amstar2: 11 af 16 point → studiet inkludres til videre analyse

Weisman 2017

Weisman MHS, Holmes JR, Irwin TA, Talusan PG. Venous Thromboembolic Prophylaxis in Foot and Ankle Surgery: A Review of Current Literature and Practice. *Foot Ankle Spec.* 2017 Aug;10(4):343-351. doi: 10.1177/1938640017692417. Epub 2017 Feb 1. PMID: 28719780.

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3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

Amstar2: 0 af 16 point → studiet ekskluderes fra videre analyse

Hickey 2018

Hickey BA, Watson U, Cleves A, Alikhan R, Pugh N, Nokes L, Perera A. Does thromboprophylaxis reduce symptomatic venous thromboembolism in patients with below knee cast treatment for foot and ankle trauma? A systematic review and meta-analysis. *Foot Ankle Surg.* 2018 Feb;24(1):19-27. doi: 10.1016/j.fas.2016.06.005. Epub 2016 Jul 18. PMID: 29413769.

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Amstar2: 10,5 af 16 point → studiet inkludres til videre analyse

Zee 207

Zee AA, van Lieshout K, van der Heide M, Janssen L, Janzing HM. Low molecular weight heparin for prevention of venous thromboembolism in patients with lower-limb immobilization. *Cochrane Database Syst Rev.* 2017 Aug 6;8(8):CD006681. doi: 10.1002/14651858.CD006681.pub4. PMID: 28780771; PMCID: PMC6483324.

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No

Amstar2: 11 af 16 point → studiet inkludres til videre analyse

Bilag 4: Summary of Findings tabel,

Quality assessment (GRADE)							Summary of findings				Quality
							No of patients		Effect		
							Intervention	comparator	Relative (95 % CI)	Absolute	
Navn på studie Zee 2017	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication					
Outcome: Kritisk outcome: DVT											
	Systematisk (Cochrane) review. Baseret på 8 RCT'er, hvoraf 6 inkluderer ptt. med fraktur i ankel/fod	Nedjusteres 2 trin pga systematiske forskelle i de inkluderedes RCT'ers studiepopulationer	Nej	Nedjusteres 1 trin, da inkluderede RCT'er både har opererede og ikke-opererede ptt med	Nej	Nej	493	510	0,48 (0,33; 0,7)		(+) (X) (X)
Outcome: Sekundære outcome:											
Outcome:											
Quality assessment (GRADE)							Summary of findings				
							No of patients		Effect		Quality
							Intervention	comparator	Relative (95 % CI)	Absolute	
							Navn på studie Hickey 2018	Design	Risk of bias	Inconsistency	
Outcome: Kritisk outcome: Symptomatisk DVT											
	Systematisk review. Baseret på 3 RCT'er	Nedjusteres 2 trin pga systematiske forskelle i de inkluderedes RCT'ers studiepopulationer	Nej	Nedjusteres 1 trin, da inkluderede RCT'er både har opererede og ikke-opererede ptt med	Nej	Nej	436	428	0,29 (0,09; 0,95)		(+) (X) (X)
Outcome: Sekundære outcome: Symptomatisk LE											
	Systematisk review. Baseret på 7 RCT'er	Nedjusteres 2 trin pga systematiske forskelle i de inkluderedes RCT'ers studiepopulationer	Nej	Nedjusteres 1 trin, da inkluderede RCT'er både har opererede og ikke-opererede ptt med	Nej	Nej	914	901	0,25 (0,03; 2,24)		(+) (X) (X)
Outcome: Sekundære outcome: Klinisk relevant blødning											
	Systematisk review. Baseret på 3 RCT'er	Nedjusteres 2 trin pga systematiske forskelle i de inkluderedes RCT'ers studiepopulationer	Nej	Nedjusteres 1 trin, da inkluderede RCT'er både har opererede og ikke-opererede ptt med	Nej	Nej	544	529	1,71 (0,86; 3,36)		(+) (X) (X)

HØRNING