

INCEPT-Trombose-profylakse

Lav vs. intermediær vs. vægtjusteret LMWH dosis

Version 1.2, 01-09-2025

novo nordisk foundation

REGION H Rigshospitalet

CRIC
Collaboration for Research in Intensive Care

Tromboseprofylakse

OPEN ACCESS

Check for updates

Anticoagulants for thrombosis prophylaxis in acutely ill patients admitted to hospital: systematic review and network meta-analysis

Ruben J Eck,[1] Tessa Elling,[2] Alex J Sutton,[3] Jørn Wetterslev,[4] Christian Gluud,[4,5] Iwan C C van der Horst,[6,7] Reinold O B Gans,[1] Karina Meijer,[2] Frederik Keus[8]

For numbered affiliations see end of the article

Correspondence to: R J Eck r.j.eck@umcg.nl (ORCID 0000-0001-7440-2465)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;378:e070022 http://dx.doi.org/10.1136/bmj-2022-070022

Accepted: 21 May 2022

ABSTRACT

OBJECTIVE
To assess the benefits and harms of different types and doses of anticoagulant drugs for the prevention of venous thromboembolism in patients who are acutely ill and admitted to hospital.

DESIGN
Systematic review and network meta-analysis.

DATA SOURCES
Cochrane CENTRAL, PubMed/Medline, Embase, Web of Science, clinical trial registries, and national health authority databases. The search was last updated on 16 November 2021.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Published and unpublished randomised controlled trials that evaluated low or intermediate dose low-molecular-weight heparin, low or intermediate dose unfractionated heparin, direct oral anticoagulants, pentasaccharides, placebo, or no intervention for the prevention of venous thromboembolism in acutely ill adult patients in hospital.

MAIN OUTCOME MEASURES
Random effects, bayesian network meta-analyses used four co-primary outcomes: all cause mortality, symptomatic venous thromboembolism, major bleeding, and serious adverse events at or closest timing to 90 days. Risk of bias was also assessed using the Cochrane risk-of-bias 2.0 tool. The quality of evidence was graded using the Confidence in Network Meta-Analysis framework.

RESULTS
44 randomised controlled trials that randomly assigned 90 095 participants were included in the main analysis. Evidence of low to moderate quality suggested none of the interventions reduced all cause mortality compared with placebo. Pentasaccharides (odds ratio 0.32, 95% credible interval 0.08 to 1.07), intermediate dose low-molecular-weight heparin (0.66, 0.46 to 0.93), direct oral anticoagulants (0.68, 0.33 to 1.34), and intermediate dose unfractionated heparin (0.71, 0.43 to 1.19) were most likely to reduce symptomatic venous thromboembolism (very low to low quality evidence). Intermediate dose unfractionated heparin (2.63, 1.00 to 6.21) and direct oral anticoagulants (2.31, 0.82 to 6.47) were most likely to increase major bleeding (low to moderate quality evidence). No conclusive differences were noted between interventions regarding serious adverse events (very low to low quality evidence). When compared with no intervention instead of placebo, all active interventions did more favourably with regard to risk of venous thromboembolism and mortality, and less favourably with regard to risk of major bleeding. The results were robust in prespecified sensitivity and subgroup analyses.

CONCLUSIONS
Low-molecular-weight heparin in an intermediate dose appears to confer the best balance of benefits and harms for prevention of venous thromboembolism. Unfractionated heparin, in particular the intermediate dose, and direct oral anticoagulants had the least favourable profile. A systematic discrepancy was noted in intervention effects that depended on whether placebo or no intervention was the reference treatment. Main limitations of this study include the quality of the evidence, which was generally low to moderate due to imprecision and within-study bias, and statistical inconsistency, which was addressed post hoc.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42020173088.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The optimal anticoagulant type and dose for the prevention of venous thromboembolism in acutely ill adults in hospital is unknown

Previous pairwise meta-analyses have had a limited number of direct comparisons between different anticoagulant drugs and doses

WHAT THIS STUDY ADDS

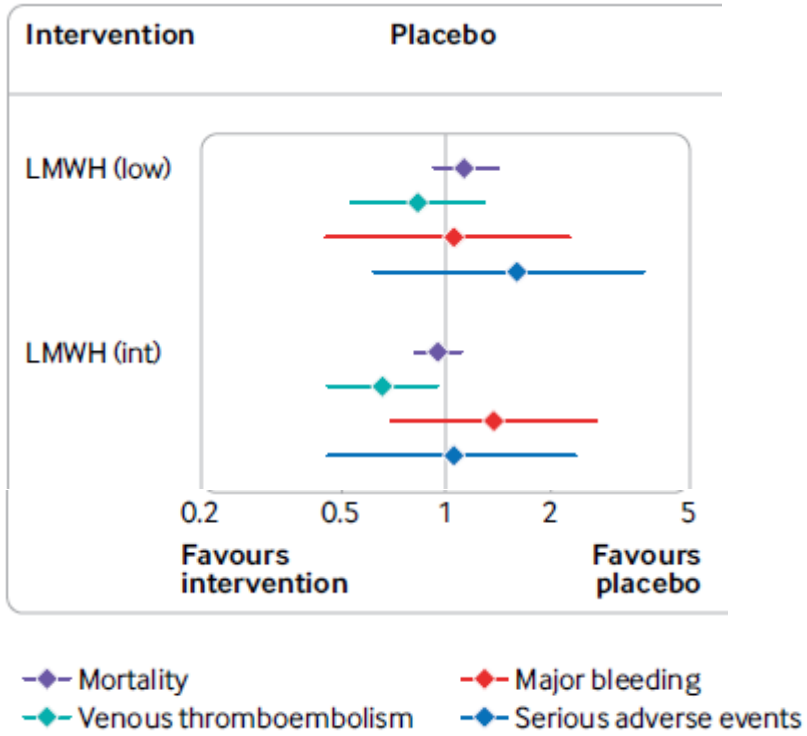
Low-molecular-weight heparin in an intermediate dose might confer the best balance between benefits and harms for prevention of venous thromboembolism; other anticoagulant types and doses had smaller thromboembolism reductions or an increased bleeding risk

A systematic discrepancy was noted in intervention effects that depended on whether placebo or no intervention was the reference treatment; future network meta-analyses should consider separating placebo and no intervention arms

The main limitations of this study were the quality of the evidence, which was generally low to moderate, and statistical inconsistency, which was dealt with post hoc

Introduction

Venous thromboembolism is a multifactorial disease frequently complicating the course of acute illness.[1] Up to half of all thrombotic events have been estimated to be attributable to a current or recent hospitalisation, making prevention of in-hospital venous thromboembolism a worthwhile aim.[2] Any anticoagulant intervention such as coumarin, unfractionated heparin, low-molecular-weight heparin, pentasaccharides, or direct oral anticoagulants can be



BMJ 2022;378:e070022

Overlevelse uden for hospitalet?

Lav vs. intermediær vs. vægtjusteret dosis

Bedret tromboseprofylakse



Blødning

Tromboseprofylakse

Inklusionskriterier

- Beslutning af den behandlende kliniker om at starte/fortsætte tromboseprofylakse med LMWH
- Alle 3 interventioner er klinisk passende (lav vs. intermediær vs. vægtjusteret dosis)

- Afdelinger, der systematisk screener alle patienter for DVT kan ikke være med i domænet

Eksklusionskriterier

- Mere end én profylaktisk dosis antikoagulans givet under nuværende ITA-ophold (inklusive dage på anden ITA)
- Kendt/mistænkt tidligere bivirkning til enhver type heparin, herunder allergi og heparin-induceret trombocytopeni
- Kendt graviditet
- Mekanisk kredsløbsstøtte
- Organtransplantation under nuværende hospitalsindlæggelse
- Vægt < 40 kg
- Inklusion i andet domæne/forsøg som ikke kan ko-inkludere med INCEPT-Thrombo

Intervention

Hver afdelingen vælger ét LMWH, som de bruger til alle

I DK dalteparin, enoxaparin eller tinzaparin

Hyldemedicin

Lav vs. intermediær vs. vægtjusteret LMWH-profylakse på ITA i maks. 90 dage

INCEPT
The Intensive Care Platform Trial

Tromboseprofylakse

Intervention

Site preferred LMWH Intervention	Weight (kg)*	Enoxaparin dose (mg)	Tinzaparin dose (IE)	Dalteparin dose (IE)	Nadroparin dose (IE)
Fixed low dose	All	40	2500	2500	2850
Fixed intermediate dose	All	60	4500	5000	5700
Weight-adjusted dose	≥40 - 50	40	2500	2500	2850
	≥50 - 60	40	2500	2500	3800
	≥60 - 70	40	4500	5000	3800
	≥70 - 80	60	4500	5000	3800
	≥80 - 90	60	4500	5000	5700
	≥90 - 100	80	7000	7500	5700
	≥100 - 110	80	7000	7500	7600
	≥110 - 120	80	8000	7500	7600
	≥120	100	8000	10000	7600

*Actual body weight as estimated or measured at screening

Intervention

Dosisjustering eller pausering af interventionen er tilladt efter klinikerens skøn ved …

- Akut eller kronisk nyresvigt eller dialyse
- Trombocytopeni
- Invasive procedurer
- Brug af trombolyse
- Aktiv (større) blødning

Forslag til trigger og evt. dosisjustering i protokollen og patientmappen

Intervention

Dosisjustering eller pausering af interventionen er tilladt efter klinikerens skøn ved …

- Akut eller kronisk nyresvigt eller dialyse
- Trombocytopeni
- Invasive procedurer
- Brug af trombolyse
- Aktiv (større) blødning

Forslag til trigger og evt. dosisjustering i protokollen og patientmappen

Forsøgsinterventionen bør stoppes permanent ved…

- Terapeutisk antikoagulation (f.eks. behandling af VTE eller atrieflimren)
- Svær bivirkning (svær allergi eller heparin-induceret trombocytopeni

Afvigelse fra den allokerede intervention ved indikationer, der ikke er anført i protokollen, vil være et protokolbrud

Outcomes

Primært: Dage i live udenfor hospital ved 30 dage

Sekundære: INCEPT kerneeffektmål

- Mortalitet ved 30, 90 og 180 dage
- Dage i live uden livsunderstøttende behandling ved 30 og 90 dage
- Dage i live uden delir ved 30 dage
- Dage i live udenfor hospital ved 90 dage
- HRQoL (EQ-5D-5L indeksværdier og EQ-VAS) og kognitiv funktion (MiniMoCA) ved 180 dage

Domænespecifikke effektmål

- Venøs tromboemboli (DVT eller lunge emboli)
- Alvorlige bivirkninger: Større blødning, anafylaksi, heparin-induceret trombocytopeni

Tromboseprofylakse

?