TARTU ÜLIKOOL

Tõendusmaterjali kvaliteedi hindamine

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Eriline tänu: Holger Schünemann ja GRADE working group

www.gradeworkinggroup.org

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GRADE metoodika 8 sammu

GRADE metoodika sammud

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1. Määratle täpselt kliiniline küsimus
2. Vali kliinilise soovituse (ingl *health decision*) tegemiseks tulemid
3. Hinda valitud tulemite suhtelist olulisust
4. Koosta tõenduse kokkuvõte (ingl *evidence profile*) − iga tulemi kohta eraldi, arvestades kõiki asjakohaseid uuringuid
5. Hinda iga tulemi (kohta kokku võetud) tõenduse kvaliteeti
   sh kaalu tõenduse taseme tõstmist/langetamist
6. Hinda kliinilise küsimuse kohta käiva kogu tõenduse kvaliteeti − kõigi väga oluliste (kriitiliste) tulemite peale kokku
7. Liigu tõendusest kliinilise soovituseni (ingl *from evidence to decision/ recommendation*)
8. Otsusta kliinilise soovituse tugevus: tugev *versus* nõrk ehk tingimuslik soovitus

Formulate question

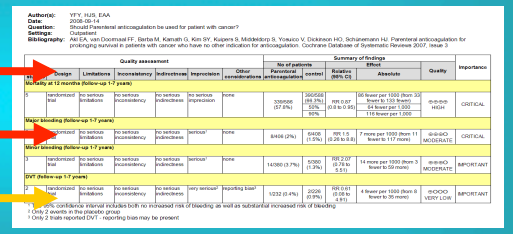
Select outcomes

Rate importance

P	Outcome	Critical
I	Outcome	Critical
C	Outcome	Important
O	Outcome	Not important

Outcomes across studies

Create evidence profile with GRADEpro



Summary of findings & estimate of effect for each outcome

Rate quality of evidence for each outcome

High
Moderate
Low
Very low

RCT start high, obs. data start low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

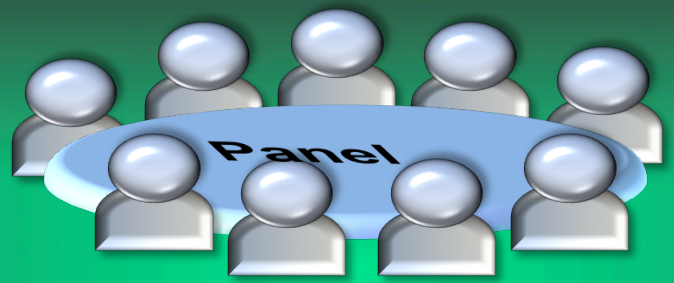
Systematic review

Guideline development

Formulate recommendations:
- For or against (direction)
- Strong or weak (strength)

By considering:
- ❑ Quality of evidence
- ❑ Balance benefits/harms
- ❑ Values and preferences

Revise if necessary by considering:
- ❑ Resource use (cost)



Rate
overall quality of evidence
across outcomes based on lowest quality
of ***critical*** outcomes

- "We recommend using…"
- "We suggest using…"
- "We recommend against using…"
- "We suggest against using…"

1. Määratle täpselt kliiniline küsimus

PATIENT	patsient
INTERVENTION	sekkumine
COMPARISON	võrdlus sekkumisele
OUTCOME	tulem

Vaata nii “enda” kliinilist küsimust kui süstemaatilise ülevaate / üksikuuringu uurimisküsimust

Tõenduse kvaliteeti [ingl *quality of evidence (QoE)*] hinnatakse ‘sekkumine’ *vs* ‘võrdlus sekkumisele’ iga tulemi kohta eraldi

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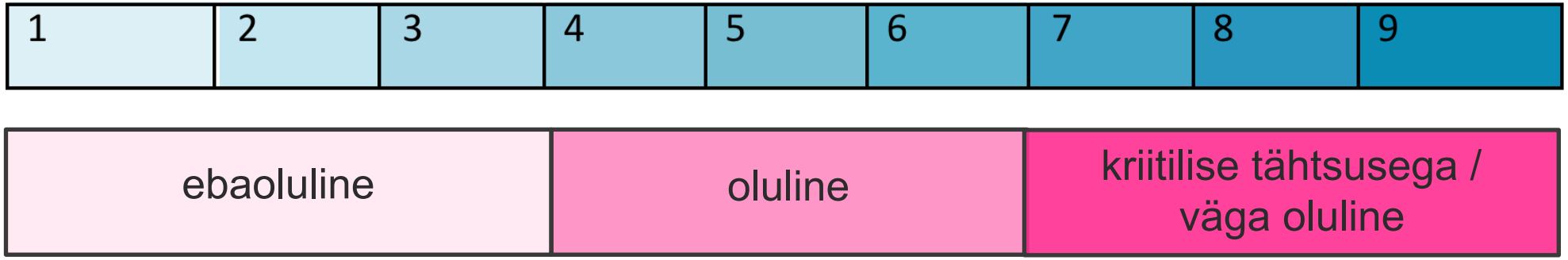
2. Vali kliinilise soovituse tegemiseks tulemid

Patsiendi seisukohast olulised tulemid!

- soovitavad tulemid (kasu)
  - suremuse vähenemine
  - haiguse kestuse lühenemine
  - (haigla)ravi kestuse lühenemine jne
- ebasoovitavad tulemid (kahju)
  - tõsised kõrvaltoimed
  - (ravim)resistentsuse teke
  - kulude teke jne

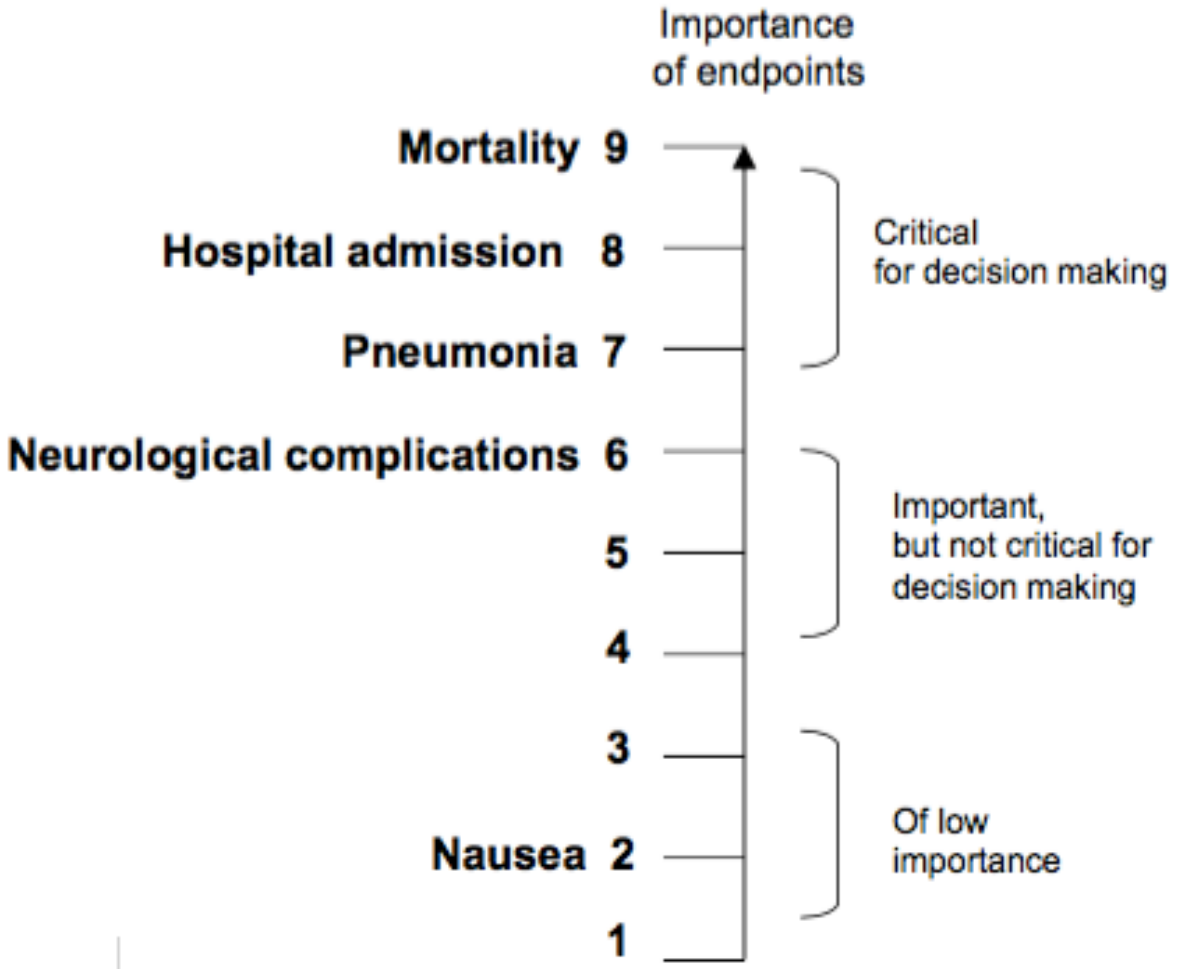
3. Hinda valitud tulemite suhtelist olulisust



Tõenduse kvaliteeti [ingl *quality of evidence (QoE)*] hinnatakse ‘sekkumine’ *vs* ‘võrdlus sekkumisele’ iga tulemi kohta eraldi

Näide

Tulemite hierarhia olulisuse alusel: oseltamiviir H5N1 gripiviiruse korral



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4. Koosta tõenduse kokkuvõte* – iga tulemi kohta eraldi, arvestades kõiki asjakohaseid uuringuid

- kasuta süstemaatilist ülevaadet või ülevaateid
  - hinda ülevaate kvaliteeti (ROBIS töövahendiga)
  - hinda ülevaatesse kaasatud huvipakkuvaid tulemeid sisaldavate üksikuuringute kvaliteeti ehk nihkevõimalusi (ingl *risk of bias*)

VÕI

- koosta süstemaatiline ülevaade
  - aluseks “Cochrane Handbook for Systematic Reviews of Interventions”

*ingl *evidence profile*

…

GRADE tõenduse kokkuvõte (ingl *evidence profile*)

Author(s): Ele Akl & Holger Schunemann **Date:** 2008-09-11
Question: Should parenteral anticoagulation be used in prolonging survival of patients with cancer? **Settings:** Outpatient
Bibliography: EA Akl, FF van Doormaal, M Barba, G Kamath, SY Kim, S Kuipers, S Middeldorp, V Yosuico, H Dickinson, HJ Schünemann. Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. CDSR Reviews. 2007 Issue 3

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation	control	Relative (95% CI)	Absolute		
Survival at 12 months (study follow up)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	335/586 (57.8%)	390/588 (66%)	RR 0.87 (0.8 to 0.95)	78 fewer per 1000 (from 30 to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Survival (overall - study follow up at 24 to 84 months)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	477/586 (81.4%)	520/588 (85%)	HR 0.77 (0.65 to 0.91)	82 fewer per 1000 (from 28 to 141 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DVT												
2	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	1/232 (0.4%)	2/226 (4%)	RR 0.61 (0.08 to 4.91)	16 fewer per 1000 (from 37 fewer to 156 more)	⊕◯◯◯ VERY LOW	CRITICAL
Major bleeding												
3	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	8/406 (2%)	6/408 (1.5%)	RR 1.50 (0.26 to 8.8)	7 more per 1000 (from 11 fewer to 117 more)	⊕⊕◯◯ LOW	CRITICAL
Minor bleeding												
3	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	14/380 (3.7%)	5/380 (1.3%)	RR 2.07 (0.78 to 5.51)	14 more per 1000 (from 3 fewer to 59 more)	⊕⊕◯◯ LOW	IMPORTANT

[1] Unclear concealment in one of the five trials did not lead to downgrading the quality of evidence.
[2] The studies used different LMWHs but indirectness is not likely given the similarity in results across studies.
[3] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm
[4] Out of 5 included studies, only 2 reported DVT. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.
[5] Out of 5 included studies, only 3 reported major bleeding. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.

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5. Hinda iga tulemi (kohta kokku võetud) tõenduse kvaliteeti

Iga tulemi puhul arvesta kõiki uuringuid, milles sekkumise mõju selle tulemi alusel on hinnatud

- randomiseeritud kontrollitud uuring: põhimõtteliselt kõrge kvaliteediga tõendus
- vaatlusuuringud (juht-kohtroll-, kohortuuring jt): põhimõtteliselt madala kvaliteediga tõendus

5 tegurit, mille tõttu kvaliteedi tase langeb
3 tegurit, mille tõttu kvaliteedi tase tõuseb

Pane tõenduse kvaliteedi tõstmise/langetamise selgitus kirja (ingl *footnote*)

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5.1. Tegurid, mille tõttu tõenduse kvaliteedi tase langeb

1. uuringutes esinesid piirangud (ingl *study limitations*) = nihke tõenäosus (ingl *risk of bias*)
2. uuringute tulemused ei ole kooskõlas (ingl *inconsistency of results*)
3. tõendus on kaudne (ingl *indirectness of evidence*)
4. uuringute tulemused on ebatäpsed (ingl *imprecision*)
5. uuringute tulemused on avaldatud valikuliselt (ingl *publication bias*)

Kui esineb mistahes eelnimetatud olukord (tegur), hinda tõendus:

- 1 taseme võrra madalamaks, kui probleem tõsine *või*
- 2 taseme võrra madalamaks, kui probleem väga tõsine

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GRADE guidelines: 3. Rating the quality of evidence

Howard Balshem[a,*], Mark Helfand[a,b], Holger J. Schünemann[c], Andrew D. Oxman[d], Regina Kunz[e], Jan Brozek[c], Gunn E. Vist[d], Yngve Falck-Ytter[f], Joerg Meerpohl[g,h], Susan Norris[i], Gordon H. Guyatt[c]

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5.1.1. Tõenduse kvaliteedi taseme langetamine uuringu piirangute tõttu

vt koolituse LISAMATERJAL 1 & 2

Nihke teke on tõenäoline (ingl *risk of bias*) **järgmiste**

- randomiseerimine oli ebakorrektne
- uuringurühmadesse jagamine ei toimunud korrektselt (ingl *lack of allocation concealment*)
- uuringus osalenuid* ei pimendatud (ingl *blinding*)
- palju uuritavaid langes uuringust välja / uuritavaid jälgiti valikuliselt (ingl *loss to follow-up / selective follow-up*)
- ravikavatsuse (ingl *intention-to-treat*) põhimõttest ei peetud kinni
- uuringutulemused ei ole korrektselt avaldatud

** uuritavaid, otseselt uuritavatega suhtlevaid ja/või uuringutulemusi hindavaid uurijaid*

Näide: Nihke tõenäosuse hindamise kokkuvõte (ingl *risk of bias summary*)

Nihke tõenäosust hinnatakse iga tulemi kohta ehk seda tulemit sisaldavates uuringutes eraldi!

Akl E et al, 2007: uuringud, milles olid 12. uuringukuu suremuse andmed

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GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

Gordon H. Guyatt[a,*], Andrew D. Oxman[b], Gunn Vist[b], Regina Kunz[c], Jan Brozek[a], Pablo Alonso-Coello[d], Victor Montori[e], Elie A. Akl[f], Ben Djulbegovic[g,h,i], Yngve Falck-Ytter[j], Susan L. Norris[k], John W. Williams Jr.[l], David Atkins[m], Joerg Meerpohl[n,o], Holger J. Schünemann[a]

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5.1.2. Tõenduse kvaliteedi taseme langetamine uuringutulemuste mittekooskõlalisuse tõttu (ingl *inconsistency of results*)

- **kliiniline heterogeensus**

  Kas uuringud (neid iseloomustavad tunnused) on sarnased? PICO(T) alusel

  Näited sekkumise mõju erinevuste “allikate” kohta:

P (patient)	haiguse erineva raskusastmega patsientidel
I (intervention)	ravimi erinevate annuste korral
O (outcome)	aja jooksul muutumine (nt mõju vähenemine)
T (type of study)	uuringukavand(id) erinev(ad)

- **statistiline heterogeensus**

  Kas uuringute tulemused on sarnased? Sekkumise mõju suuna ja suuruse alusel

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Meeldetuletuseks eelmisest koolitusest: uuringute erinevused ehk heterogeensus (1)

Üldjuhul *(ceteris paribus)*:

- **kliiniline heterogeensus**

  Mida suurem kliiniline heterogeensus, seda paremini on metaanalüüsi tulemus üldistatav, tavaellu ülekantav

- **statistiline heterogeensus**

  Mida suurem statistiline heterogeensus, seda nõrgemad on järeldused sekkumise mõju suuruse kohta

Meeldetuletuseks eelmisest koolitusest: uuringute erinevused ehk heterogeensus (2)

Kas sekkumise mõju uuringutes (tulemused) erinevad üksteisest rohkem kui juhuse tõttu?

Vaata uuringute tulemusi koondavaid jooniseid:

- **forest plot**
  - tulemuste (sh usaldusvahemike) “pilt”
  - hii-ruut test ja selle p-väärtus
  - ii-ruut (I^2) statistik (oluline > 60%)
- **funnel plot** e lehterdiagramm
  - sekkumise mõju suurus vs uuringu suurus/täpsus
    ingl *intervention effect vs study size/precision*

  vt uuringute jaotust joonisel

Näide eelmisest koolitusest:
statistilise heterogeensuse hindamine

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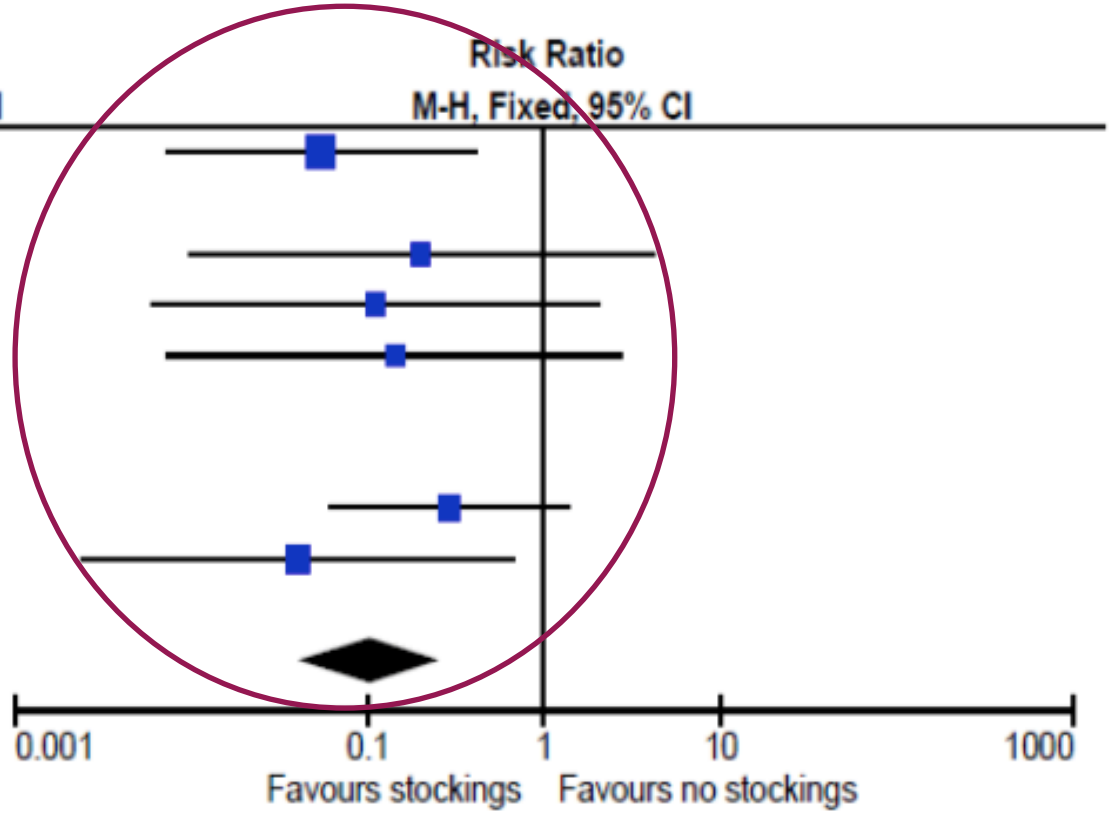
Figure 11.3.a: Example of a RevMan forest plot

Study or Subgroup	Stockings Events	Total	No stockings Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
LONFLIT 2	1	411	19	422	38.5%	0.05 [0.01, 0.40]
LONFLIT 4 - Kendall1	0	72	0	72		Not estimable
LONFLIT 4 - Kendall2	0	66	2	66	5.1%	0.20 [0.01, 4.09]
LONFLIT 4 - Scholl1	0	179	4	179	9.2%	0.11 [0.01, 2.05]
LONFLIT 4 - Scholl2	0	136	3	135	7.2%	0.14 [0.01, 2.72]
LONFLIT 4 - Traveno1	0	97	0	98		Not estimable
LONFLIT 4 - Traveno2	0	75	0	71		Not estimable
LONFLIT 5	2	178	7	180	14.3%	0.29 [0.06, 1.37]
Scurr 2001	0	100	12	100	25.7%	0.04 [0.00, 0.67]
Total (95% CI)	**3**	**1314**	**47**	**1323**	**100.0%**	**0.10 [0.04, 0.26]**

Heterogeneity: Chi² = 2.75, df = 5 (P = 0.74); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)



http://handbook.cochrane.org/index.htm#chapter_11/figure_11_3_a_example_of_a_revman_forest_plot.htm

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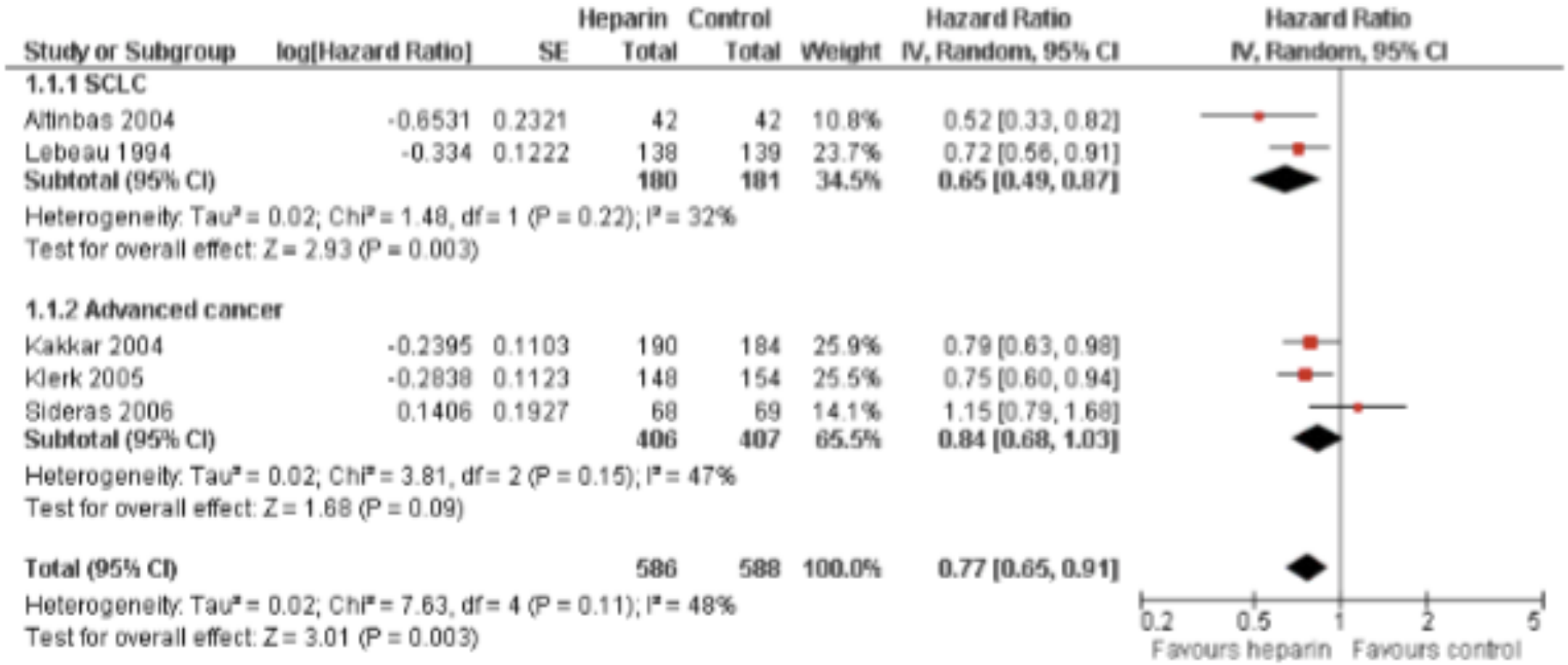
5.1.2. Tõenduse kvaliteedi taseme langetamine uuringutulemuste mittekooskõlalisuse tõttu (ingl *inconsistency of results*)

Langeta tõenduse taset, kui esineb seletamatu heterogeensus

Kui sekkumise mõju erineb alarühmiti (ingl *by subgroup*), esita uuringute tulemused alarühmade kaupa

Näide 1: uuringutulemuste kooskõla hindamine

Figure 1. Forest plot of comparison: 1 Heparin vs placebo, outcome: 1.1 Mortality over duration of study.



Akl et al, 2007

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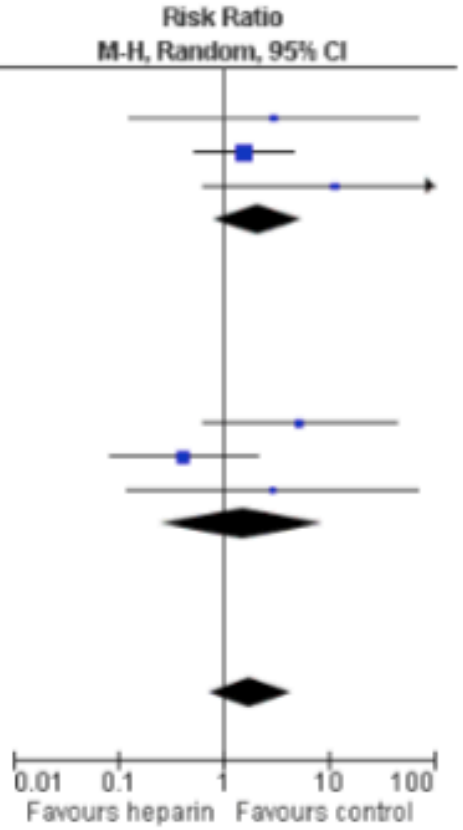
Näide 2: uuringutulemuste kooskõla hindamine

Figure 4. Forest plot of comparison: 1 Heparin vs placebo, outcome: 1.8 Any bleeding.

Study or Subgroup	Heparin Events	Heparin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Minor Bleeding						
Altinbas 2004	1	42	0	42	7.4%	3.00 [0.13, 71.61]
Kakkar 2004	8	190	5	184	38.5%	1.55 [0.52, 4.65]
Klerk 2005	5	148	0	154	8.8%	11.44 [0.64, 205.14]
Subtotal (95% CI)		**380**		**380**	**54.6%**	**2.07 [0.78, 5.51]**
Total events	14		5			
Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.8.2 Major bleeding						
Klerk 2005	5	148	1	154	14.8%	5.20 [0.62, 44.01]
Sideras 2006	2	68	5	70	23.3%	0.41 [0.08, 2.05]
Kakkar 2004	1	190	0	184	7.3%	2.91 [0.12, 70.87]
Subtotal (95% CI)		**406**		**408**	**45.4%**	**1.50 [0.26, 8.80]**
Total events	8		6			
Heterogeneity: Tau² = 1.18; Chi² = 3.85, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**786**		**788**	**100.0%**	**1.78 [0.73, 4.38]**
Total events	22		11			
Heterogeneity: Tau² = 0.23; Chi² = 6.10, df = 5 (P = 0.30); I² = 18%						
Test for overall effect: Z = 1.26 (P = 0.21)						



Akl et al, 2007

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TARTU ÜLIKOOL

GRADE guidelines: 7. Rating the quality of evidence—inconsistency

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5.1.3. Tõenduse kvaliteedi taseme langetamine tõenduse kaudsuse tõttu (ingl *indirectness of evidence*)

Tõendus pärineb erinevatest uuringuküsimustest:

P: oseltamivir-profülaktika linnugripi *vs* hoojaalise gripi korral

I: haloperidooli fikseeritud *vs* kohandatud annused

C: huvi pakub ravim A *vs* ravim B, kuid uuringutes ravim A *vs* platseebo, ravim B *vs* platseebo

O: huvi pakuvad luumurrud, kuid uuringutes surrogaat-tulem -- luutihedus

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TARTU ÜLIKOOL

GRADE guidelines: 8. Rating the quality of evidence—indirectness

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5.1.4.1. Tõenduse kvaliteedi taseme langetamine uuringute tulemuste ebatäpsuse tõttu (ingl *imprecision*)

- valim väike

  väike juhtude (ingl *events*) arv

- sekkumise mõju hinnangu usaldusvahemik lai

  ebakindlus mõju suuruse osas

...

Optimaalne infomaht (ingl *optimal information size*)

Kui süstemaatilisse ülevaatesse kaasatud uuringutes kokku jääb uuritavate arv väiksmeaks kui tavapärane uuringuvalimi suuruse arvutus piisava võimsusega uuringu jaoks ette näeks, kaalu tõenduse kvaliteedi taseme langetamist ebatäpsuse tõttu

Seda lävendit nimetatakse **optimaalseks infomahuks**

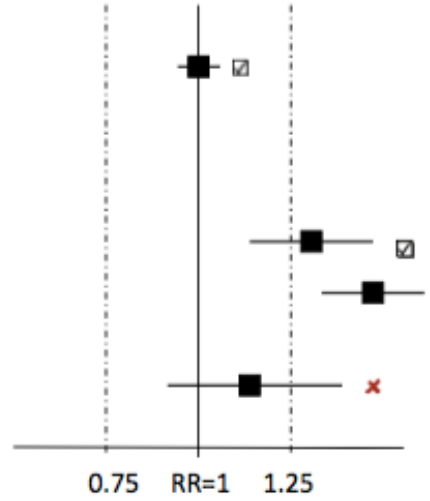
- kaheväärtuselise (binaarse, dihhotoomse) tulemi korral: juhte (ingl *events*) vähemalt 300
- pideva tulemi korral: uuritavaid vähemalt 400

Juhend optimaalse infomahu arvutamiseks:
https://cebgrade.mcmaster.ca/Imprecision/index.html (alates slaidist 7)

5.1.4.2. Tõenduse kvaliteedi taseme langetamine uuringute tulemuste ebatäpsuse tõttu (ingl *imprecision*)

Kui **infomaht**

- **ei ole optimaalne**, hinda tõenduse kvaliteedi tase madalamaks (v.a juhul kui ülevaate valim on väga suur – vähemalt 2 000 uuritavat)
- **on optimaalne** ja sekkumise mõju hinnangu 95% usaldus-vahemik ei sisalda ‘mõju ei ole’ väärtust (RR = 1), ei ole ebatäpsus probleemiks
- **on optimaalne** ja 95% usaldusvahemik sisaldab nii ‘mõju ei ole’ kui märkimisväärset kasulikku või kahjulikku mõju (RR < 0,75 või > 1,25) väärtust, siis hinda tõenduse kvaliteedi tase madalamaks



Optimaalse infomahu "rusikareeglid"

Total Number of Events	Relative Risk Reduction	Implications for meeting OIS threshold
100 or less	≤ 30%	Will almost never meet threshold whatever control event rate
200	30%	Will meet threshold for control event rates for ~ 25% or greater
200	25%	Will meet threshold for control event rates for ~ 50% or greater
200	20%	Will meet threshold only for control event rates for ~ 80% or greater
300	≥ 30%	Will meet threshold
300	25%	Will meet threshold for control event rates ~ 25% or greater
300	20%	Will meet threshold for control event rates ~ 60% or greater
400 or more	≥ 25%	Will meet threshold for any control event rate
400 or more	20%	Will meet threshold for control event rates of ~ 40% or greater

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TARTU ÜLIKOOL

GRADE guidelines 6. Rating the quality of evidence—imprecision

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5.1.5. Tõenduse kvaliteedi taseme langetamine uuringute tulemuste valikulise avaldamise tõttu (ingl *publication bias*)

- Valikulist avaldamist tuleks alati “kahtlustada”, kui tõendus pärineb üksnes
  - väikestest “positiivsetest” uuringutest
  - kasumile orienteeritud ettevõtte, organisatsiooni poolt (või toel) läbi viidud uuringutest
- Valikulise avaldamise kindlakstegemiseks on erinevaid meetoideid – ükski pole ideaalne
  - lehterdiagramm (ingl *funnel plot*): vaja vähemalt 10 uuringut

Meeldetuletuseks eelmisest koolitusest: uuringute erinevused ehk heterogeensus (2)

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kordusslaid

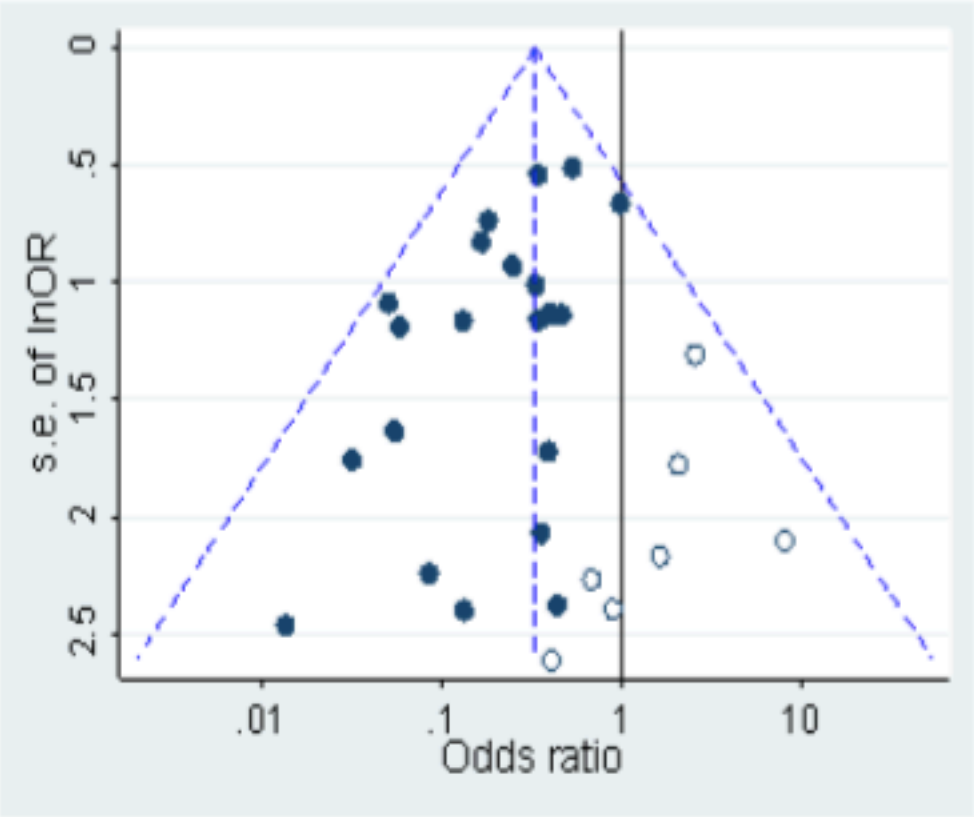
Kas sekkumise mõju uuringutes (tulemused) erinevad üksteisest rohkem kui juhuse tõttu?

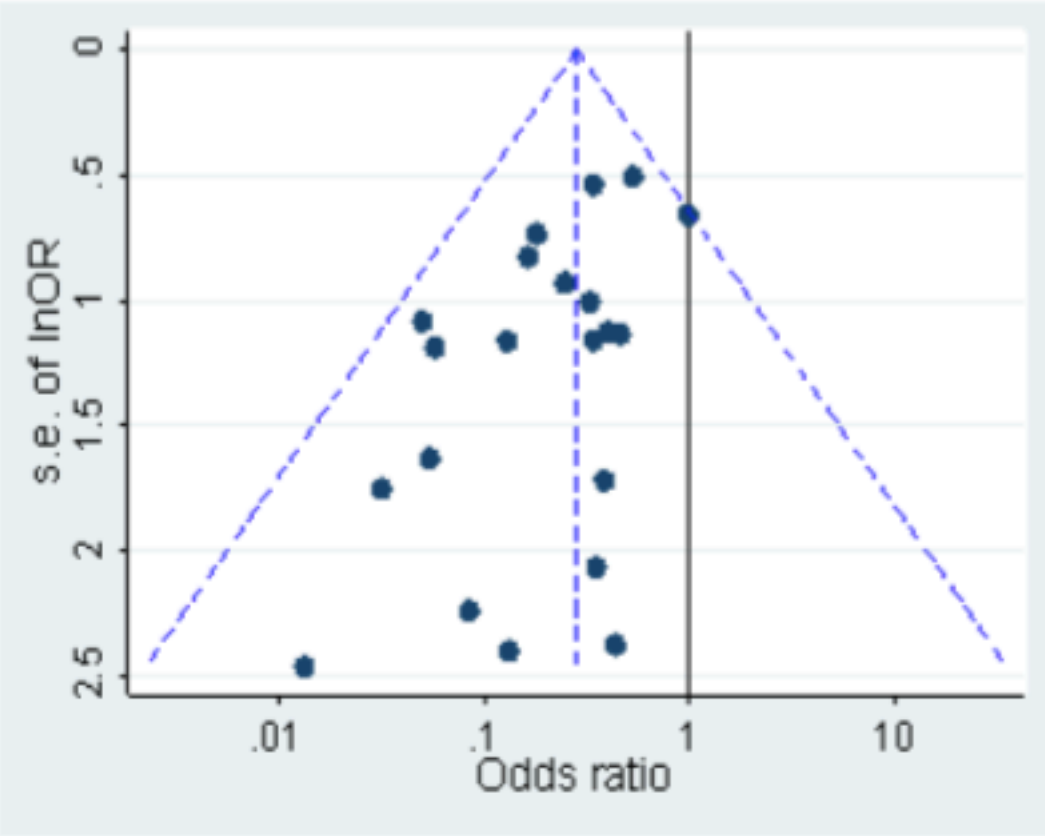
Vaata uuringute tulemusi koondavaid jooniseid:

- **forest plot**
  - tulemuste (sh usaldusvahemike) “pilt”
  - hii-ruut test ja selle p-väärtus
  - ii-ruut (I^2) statistik (oluline >60%)
- **funnel plot** e lehterdiagramm
  - sekkumise mõju suurus vs uuringu suurus/täpsus
    ingl *intervention effect vs study size/precision*

  vt uuringute jaotust joonisel

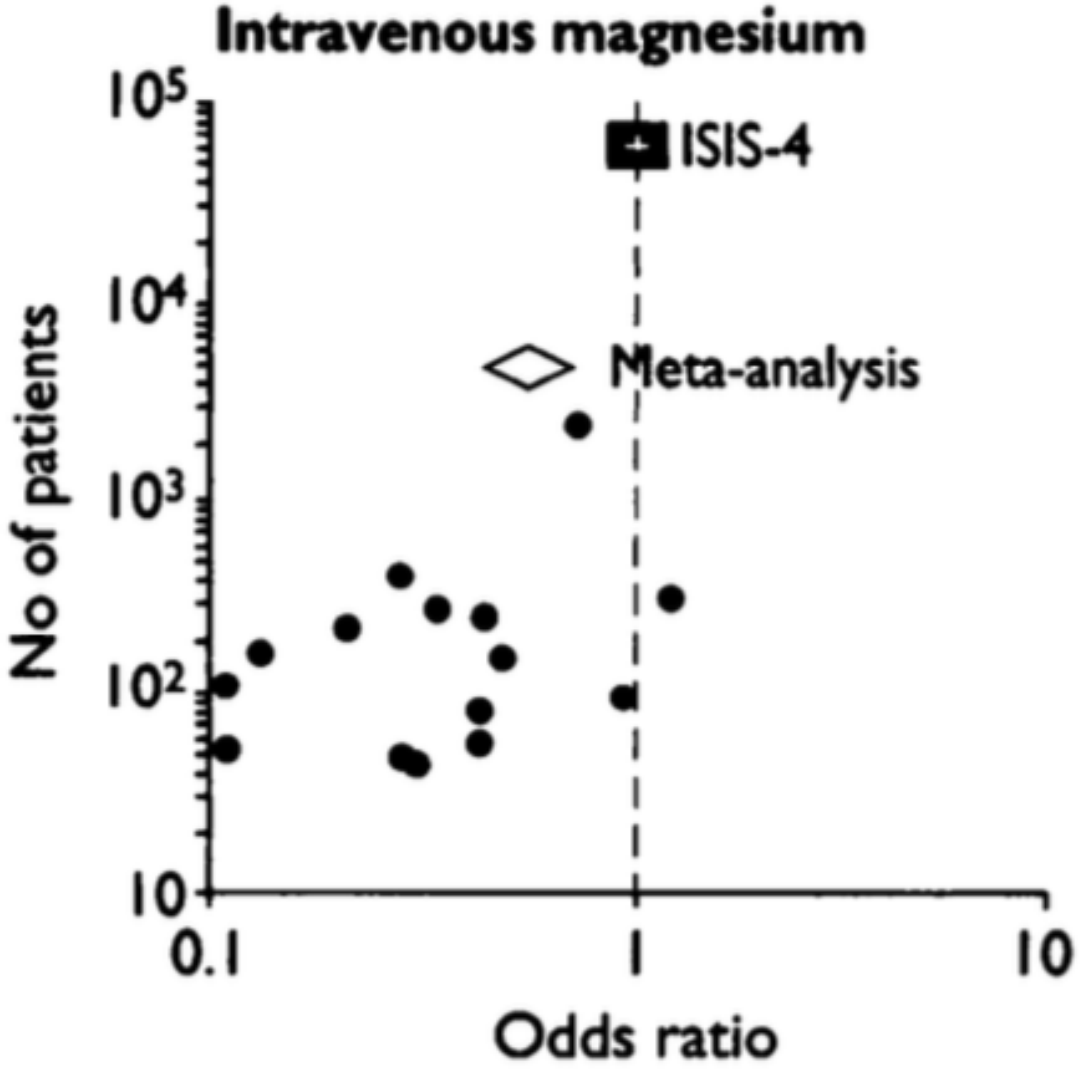
Näide eelmisest koolitusest:
statistilise heterogeensuse hindamine





http://handbook.cochrane.org/chapter_10/figure_10_4_a_hypothetical_funnel_plots.htm

Näide: eksitav metaanalüüs magneesiumi (i/v) tähtusest ägeda müokardiinfarkti ravis



*effect of Mg on mortality/survival

Egger M, Smith DS. Misleading meta-analysis. Lessons from "an effective, safe, simple" intervention that wasn't. BMJ 1995.

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TARTU ÜLIKOOL

GRADE SERIES - SHARON STRAUS, RACHEL CHURCHILL AND SASHA SHEPPERD, GUEST EDITORS

GRADE guidelines: 5. Rating the quality of evidence—publication bias

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5.2. Tõenduse kvaliteedi taseme tõstmine

Vaatlus- ja mitterandomiseeritud uuringuist pärineva tõenduse kvaliteedi tase loetakse algselt tavaliselt madalaks

Siiski on olukordi, mil meil on sekkumise mõju hinnangusse väga suur “usk”:

- anafülaktilise šoki korral epinefriin
- ketoatsidoosi korral insuliin
- raskekujulise koksartroosi korral puusaprotees

Selliseid olukordi esineb harva…

Kvaliteedi taset saab tõsta üksnes metoodiliselt ja korralduslikult “õigetest” vaatlusuuringutest pärineval tõendusel

5.2.1. Tõenduse kvaliteedi taseme tõstmine tugeva seose / suure mõju korral (ingl *large magnitude of effect*)

Tugev seos / suur mõju: RR = 2–5 or 0.2–0.5

- pea meeles, et OR >> RR, kui algne risk (ingl *baseline risk*) on suur (>40%)
- otsene tõendus (ingl *direct evidence*); väike nihke tõenäosus; puuduvad probleemid segavate teguritega
- tõenäolisem, kui mõju avaldub kiiresti ning kui seda toetavad kaudsed tõendid

Üldiselt ole konservatiivne!

...

5.2.2. Tõenduse kvaliteedi taseme tõstmine annus-vastus seose esinemisel

Annus-vastus seos võib olla põhjusliku seose tunnuseks

...

5.2.3. Tõenduse kvaliteedi taseme tõstmine segavate tegurite ja võimalike nihete “arvelt” (1)

Segav tegur: tulemi (nt haiguse) riski- või kaitsetegur, mis on seotud uuritava ekspositsiooniga, kuid ei ole vaheastmeks põhjuslikus jadas ekspositsiooni ja tulemi vahel

Segamine: ekspositsiooni ja tulemi seose moonutamine kolmandate tegurite mõju tulemusel

Jääksegamine (ingl *residual confounding*): mõni segav tegur või mõned segavad tegurid on jäänud uuringus mõõtmata või ei ole neid mõju kohandatud analüüsis arvestatud

5.2.3. Tõenduse kvaliteedi taseme tõstmine segavate tegurite ja võimalike nihete “arvelt” (2)

Uuringus mõeldakse võimalikele segavatele teguritele ja nihetele

Olukorras, kus segava teguri olemasolul või nihke korral “positiivset” tulemust (nt sekkumisel mõju) ei oleks, aga käesolevas uuringus on tugev positiivne tulemus (nt sekkumisel suur mõju), võib järeldada, et selles uuringus võeti see segav tegur arvesse või seda nihet ei esinenud

Kui segava teguri olemasolul või nihke korral oleks uuringul tugev “positiivne” tulemus (nt sekkumisel suur mõju), aga selles uuringus seda ei olnud, saab järeldada, et selles uuringus võeti see segav tegur arvesse või seda nihet ei esinenud

...

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TARTU ÜLIKOOL

GRADE guidelines: 9. Rating up the quality of evidence

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GRADE: tõenduse kvaliteedi kriteeriumid

TARTU ÜLIKOOL

Uuringukavand	Tõenduse kvaliteedi algne tase	Langeta tõenduse kvaliteedi taset, kui uuringutes	Tõsta tõenduse kvaliteedi taset, kui uuringutes	Tõenduse kvaliteedi lõplik tase
randomiseeritud kontrollitud uuring	kõrge →	esinevad piirangud – nihke võimalus(ed) tulemused on • mittekooskõlalised • kaudsed • ebatäpsed • avaldatud valikuliselt	mõju/seos on suur esineb annus-vastus seos	kõrge
			kõik tõenäolised segavad tegurid ja nihked • oleks vähendanud sekkumise mõju • kirjeldavad võimalikke põhjuseid, kui sekkumise mõju ei täheldatud	mõõdukas
vaatlusuuring	madal →			madal
				väga madal

TARTU ÜLIKOOL

GRADE: tõenduse profiil (ingl *evidence profile*)

Author(s): Elie Akl & Holger Schunemann **Date:** 2008-09-11
Question: Should parenteral anticoagulation be used in prolonging survival of patients with cancer? **Settings:** Outpatient
Bibliography: EA Akl, FF van Doormaal, M Barba, G Kamath, SY Kim, S Kuipers, S Middeldorp, V Yosuico, H Dickinson, HJ Schünemann. Parenteral anticoagulation for prolonging survival in patients with cancer who have no other indication for anticoagulation. CDSR Reviews. 2007 Issue 3

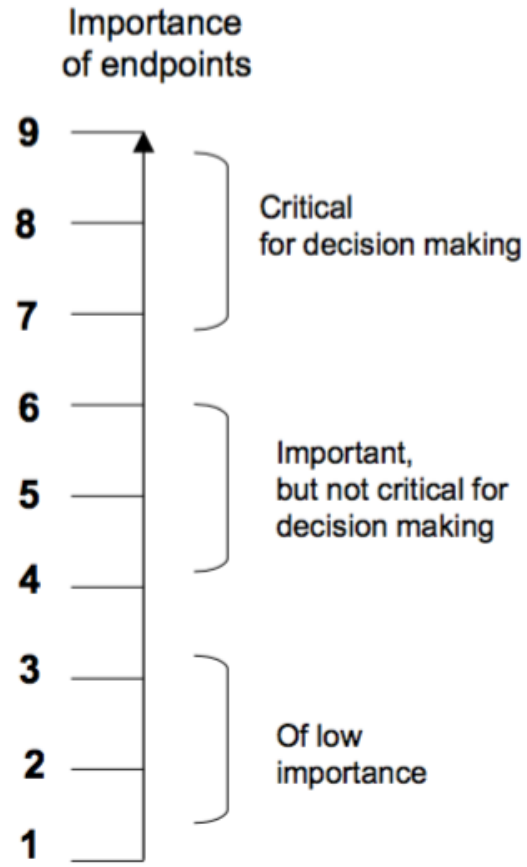
Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	anticoagulation	control	Relative (95% CI)	Absolute		
Survival at 12 months (study follow up)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	339/586 (57.8%)	390/588 (60%)	RR 0.87 (0.8 to 0.95)	78 fewer per 1000 (from 30 to 120 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Survival (overall - study follow up at 24 to 84 months)												
5	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	477/586 (81.4%)	520/588 (85%)	HR 0.77 (0.65 to 0.91)	82 fewer per 1000 (from 28 to 141 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DVT												
2	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	very serious[3]	reporting bias[4]	1/232 (0.4%)	2/226 (4%)	RR 0.61 (0.08 to 4.91)	16 fewer per 1000 (from 37 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding												
3	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	8/406 (2%)	6/408 (1.5%)	RR 1.50 (0.26 to 8.8)	7 more per 1000 (from 11 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding												
3	randomised trials	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[5]	14/380 (3.7%)	5/380 (1.3%)	RR 2.07 (0.78 to 5.51)	14 more per 1000 (from 3 fewer to 59 more)	⊕⊕OO LOW	IMPORTANT

[1] Unclear concealment in one of the five trials did not lead to downgrading the quality of evidence.
[2] The studies used different LMWHs but indirectness is not likely given the similiarity in results across studies.
[3] The 95% CI includes both negligible effect and appreciable benefit or appreciable harm
[4] Out of 5 included studies, only 2 reported DVT. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.
[5] Out of 5 included studies, only 3 reported major bleeding. We assumed that this was based on selective reporting of outcomes. The authors of the study did not provide further information.

6. Hinda kliinilise küsimuse kohta käiva kogu tõenduse kvaliteeti – kõigi väga oluliste (kriitiliste) tulemite peale kokku

- Tõenduse tase kokkuvõtlikult = madalaim kriitiliste tulemite tõenduse tase

- See, mida algselt loeti kriitiliseks (tulemiks), võib tõendusega tutvumise järgselt muutuda …



GRADE metoodika järgmised sammud

7. **Liigu tõendusest kliinilise soovituseni** (ingl *from evidence to decision/ recommendation*)
8. **Otsusta kliinilise soovituse tugevus: tugev *versus* nõrk ehk tingimuslik soovitus**

Sellest juba järgmises loengus…