NETWORK META-ANALYSIS
An illustrated guide to un-entanglement
J. C. Villasboas
The Problem

**Where:** VAMC Morning Report

**What:** House staff wants to understand if there is a difference in efficacy between BID and TID heparin for prevention of VTE in hospitalized non-ICU medical patients. After nicely laying out her PICOTT and explaining her search, she hands out to the group a copy of the paper she planned to appraise.
Dosing Frequency of Unfractionated Heparin Thromboprophylaxis

A Meta-analysis

Olivia J. Phung, PharmD; Susan R. Kahn, MD; Deborah J. Cook, MD, MSc(Epi); and Mohammad Hassan Murad, MD, MPH
Background: In medical patients, it is unclear whether thromboprophylaxis with low-dose unfractionated heparin (UFH) should be administered bid or tid.

Methods: This study was a mixed-treatment comparison meta-analysis of randomized control trials that enrolled hospitalized nonsurgical patients at risk for VTE and compared UFH bid, UFH tid, or low-molecular-weight heparin (LMWH) to one another or to an inactive control subject. DVT, pulmonary embolism (PE), major bleeding, and death were measured. A Bayesian framework using a random-effects model was applied.

Results: Sixteen trials with moderate methodologic quality enrolling 27,667 patients contributed to this analysis. The relative risk and 95% credible intervals comparing UFH tid to UFH bid for DVT, PE, death, and major bleeding were 1.56 (0.64-4.33), 1.67 (0.49-208.09), 1.17 (0.72-1.95), and 0.89 (0.08-7.05), respectively. When compared with either dose of UFH, the use of LMWH has an effect similar to UFH on all four outcomes.

Conclusions: Moderate-quality evidence suggests that subcutaneous UFH bid and UFH tid do not differ in effect on DVT, PE, major bleeding, and mortality. Either of the two dosing regimens of UFH or LMWH appears to be a reasonable strategy for thromboprophylaxis in medical patients. A future randomized trial comparing the two doses of UFH is very unlikely, considering the very large sample size that would be required to demonstrate a significant difference, which, if it exists, is undoubtedly small.

CHEST 2011; 140(2):374–381
Dosing Frequency of Unfractionated Heparin Thromboprophylaxis

A Meta-analysis

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Conceptual and Technical Challenges in Network Meta-analysis

Andrea Cipriani, MD; Julian P.T. Higgins, PhD; John R. Geddes, MD; and Georgie Salanti, PhD

goal setting

purpose

REACH ONE

life

events

better making of decision
Teaching Goals

1. To identify NMAs
2. To understand the network geometry [dots and lines]
3. To understand 5 key concepts
   - Indirect comparisons
   - Coherence
   - Loop of evidence
   - Consistency
   - Ranking
4. Highlight validity considerations when reading NMAs
Teaching NON-Goals

1. To teach everything you need to know about NMAs

2. To explain the math involved in NMAs and indirect comparisons

3. To teach the basic concepts of:
   - Systematic Reviews
   - Standard Meta-Analysis
   - Heterogeneity
<table>
<thead>
<tr>
<th>Multiple Treatments Comparison</th>
<th>Network Meta-Analysis</th>
<th>Comparative Efficacy Analysis</th>
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<tr>
<td>Multiple Treatments Meta-Analysis</td>
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<td>Adjusted Indirect Comparisons</td>
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<td>Mixed Treatment Meta-Analysis</td>
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</tbody>
</table>
Systematic Reviews

Meta-analysis
Network MA
[At Least One Indirect Comparison]

Standard (Pairwise) MA
[Only Direct Comparisons]
Network Geometry
Geometry of NMAs
Indirect Comparisons
(Coherence) // Transitivity // Similarity
(Coherence) // Transitivity // Similarity
The Loop of Evidence
Consistency
Consistency

[Graph showing various medications connected to Placebo]

The Inconsistency Plot

Loop

Aripiprazole–lithium–haloperidol
Aripiprazole–placebo–haloperidol
Aripiprazole–placebo–lithium
Haloperidol–olanzapine–risperidone
Haloperidol–quetiapine–risperidone
Lithium–divalproex–carbamazepine
Lithium–haloperidol–carbamazepine
Lithium–haloperidol–olanzapine
Lithium–haloperidol–quetiapine
Lithium–haloperidol–risperidone
Lithium–olanzapine–divalproex
Lithium–olanzapine–risperidone
Lithium–quetiapine–risperidone
Placebo–divalproex–carbamazepine
Placebo–haloperidol–carbamazepine
Placebo–haloperidol–olanzapine
Placebo–haloperidol–quetiapine
Placebo–haloperidol–risperidone

Inconsistency (95% CI)

1.03 (0.21 to 1.85)
0.21 (−0.11 to 0.53)
0.19 (−0.16 to 0.53)
0.21 (−0.13 to 0.54)
0.28 (−0.12 to 0.67)
1.68 (0.45 to 2.90)
1.47 (0.42 to 2.52)
1.14 (−0.94 to 3.23)
0.62 (−0.23 to 1.47)
0.51 (−0.58 to 1.60)
0.73 (−1.07 to 2.53)
0.90 (−1.91 to 3.72)
0.42 (−0.37 to 1.21)
1.21 (0.42 to 2.00)
0.17 (−0.46 to 0.81)
0.00 (−0.36 to 0.37)
0.24 (−0.24 to 0.72)
0.07 (−0.36 to 0.51)
Reading Results of a NMA

- LMWH to UFH BID: 0.72 (0.28 to 1.62) with N=1 study.
- UFH TID to LMWH: 0.88 (0.58 to 1.39) with N=4 studies.
- UFH TID to Placebo/Control: 0.42 (0.23 to 0.68) with N=2 studies.
- UFH BID to Placebo/Control: 0.64 (0.23 to 1.56) with N=5 studies.
- UFH BID to UFH TID: 0.28 (0.10 to 0.61) with N=1 study.
Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis

Parambir S Dula, Siddharth Singh, Evelyn Marquez, Rohan Khera, Larry J Prokop, Paul J Limburg, Samir Gupta, Mohammad Hassan Murad

Ranking
Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis

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Fig 3 | SUCRA rankings for efficacy and safety outcomes (range 1=treatment has high likelihood of being, 0=treatment has high likelihood of being worst). For efficacy outcomes, higher score=better treatment for preventing advanced metachronous neoplasia. For serious adverse event outcome, higher scores=safest treatment with lower risk of serious adverse events. Table shows median ranks on both efficacy and safety outcomes (rank 1-10 on each scale) and 95% credible intervals.
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4. Highlight validity considerations when reading NMAs
What to look out for when reading NMAs

1. Does the systematic review meet standard validity criteria?

2. Is the network of evidence well connected?

3. Was the distribution of effect modifiers (PICO) acceptably similar across comparisons? [Transitivity]

4. Were the results consistent in direct and indirect comparisons? [Consistency]

5. Do the best ranked interventions have clinically and statistically significant effect sizes?
Food for Thought

• How does indirect comparisons fit in the hierarchy of evidence?

• Is indirect comparison better than observational data?

• If there is good quality direct data, should I even be looking at indirect comparisons?
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If you want to learn more


5. Dulai PS, Singh S, Marquez E, Khera R, Prokop IJ, Limburg PJ, Gupta S, Murad MH. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. BMJ. 2016 Dec 5;355:i6188

THANK YOU