Is the network meta-analysis (NETMA) bringing us closer to the truth? Insights from recent antithrombotic drug data

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In the era of rapid development of new anticoagulant alternatives to heparin and warfarin the door opens to a variety of possible analyses of the data. A new anticoagulant drug has initially typically been tested for efficacy and safety in the orthopaedic surgery setting in 3–4 phase III trials to support approval. Based on the data from these pivotal studies the additional analyses that will follow are shown in Table 1.

Table 1: The analyses that commonly follow after the original trials.

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Health economic analysis</th>
<th>Pooled analysis</th>
<th>Meta-analysis</th>
<th>Systematic review</th>
<th>Network meta-analysis</th>
</tr>
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</table>

Subgroup analyses are useful to understand if there are certain patient characteristics or clinical setting where the drug will have less effect or cause more harm than in the average population studied. Due to smaller numbers it is usually necessary to combine several or all the trials performed with the drug in for example orthopaedic surgery.

The regulatory authorities usually require a health economic evaluation to be included in the file submitted for approval. For dabigatran in orthopaedic surgery at least four health-economic analyses have been published (1–4). In addition, a number of national institutes for assessment of health technology have probably performed unpublished analyses.

A pooled analysis of the data from the phase III trials can give a more precise estimate of the efficacy and safety outcomes but without further sophistication. It also provides a tool to summarise data from several trials using a limited word count. Subgroup analyses are often based on pooled data.

The meta-analysis includes a weighting of the studies, usually of the inverse of the variance to give larger trials more influence. The analysis is then often a component of a systematic review of the literature. Data from meta-analyses are considered to provide a high level of evidence for the purpose of clinical practice guidelines. If the meta-analysis is based on several small studies with similar flaws the results may not be helpful. A new large trial may provide results in a different direction than the meta-analysis. A recent example is the THINRS trial on self-testing for patients on warfarin, which failed to confirm any benefit regarding reduction of thromboembolic events (5).

In recent years we have also seen the network meta-analysis (NETMA) emerging as a tool for indirect comparisons between drugs. This is evoking considerable interest since all novel anticoagulants are being tested against a “standard” of low-molecular-weight heparin (LMWH) or warfarin. Head-to-head comparisons between the new anticoagulants will require large numbers, which will be costly and unlikely to be sponsored by any of the manufacturers. The NETMA uses comparisons by statistical inference and the risk of errors is therefore higher than in a standard meta-analysis. A question is, however, how much further all these analytical efforts bring us to the truth?

Network meta-analyses on dabigatran

In this issue of Thrombosis and Haemostasis, Harenberg et al. present a NETMA on the new anticoagulants in hip- or knee arthroplast (6). They have attempted to reduce the risk for error in the NETMA by first performing a cluster analysis to identify which trials were homogeneous and to exclude the heterogeneous studies from the following steps. Unfortunately, most characteristics (age, bodyweight, type of surgery, dose of anticoagulant and time of start of prophylaxis) were heterogeneous and they could only analyse for homogeneous treatment duration, i.e. 10 ± 5 days and 34 ± 5 days. This is perhaps surprising since Cohen et al. in another recent NETMA on the same topic did analyse separately for hip and knee arthroplasty (7). They also excluded studies with the higher North American dose of LMWH to achieve homogeneity for the comparator. Ultimately, Harenberg et al. excluded two of 16 trials; Record 2 due to different treatment duration for rivaroxaban and LMWH (8) and a small phase II study on rivaroxaban due to open-label design (9).

In the second step they meta-analysed the remaining trials to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for the different drug combinations and outcomes. Finally the NETMA was performed but there is no information on the methods used to preserve trial randomisation and to reduce bias. The outcomes analysed are confined to venous thrombosis.
boembolism (VTE, primary efficacy outcome), major bleeding and death. In the Methods section of their paper it is stated that the primary efficacy outcome consisted of symptomatic, objectively verified deep vein thrombosis or pulmonary embolism or death related to pulmonary embolism, but the data analysed is consistent with “all VTE”, i.e. also asymptomatic, which actually was the primary outcome in the studies.

The results of the NETMA can be summarised as follows:

- Both doses of dabigatran (150 mg daily and 220 mg daily) were inferior to rivaroxaban 10 mg daily and also to apixaban 2.5 mg twice daily for the primary efficacy outcome (not tested for apixaban for the 10-day treatment duration).
- There was a trend to better safety regarding major bleeding for apixaban versus rivaroxaban.
- For all other comparisons there was no statistically significant difference.

Figures 1–3 show the ORs for the efficacy or bleeding outcome versus LMWH obtained by simple pooling of data from the same studies as evaluated in the NETMA. The ORs are actually identical with the ones presented by Harenberg et al. from the meta-analysis. From Figures 1 and 2 it is easy to appreciate that rivaroxaban and apixaban are more effective than LMWH and that dabigatran is similar to or slightly worse than LMWH for the efficacy outcome. By making inferences one can also appreciate that both doses of dabigatran are inferior to rivaroxaban or apixaban. From Figure 3 it can be similarly understood that apixaban shows a trend to better safety against rivaroxaban.

**Which NETMA is closest to the truth?**

There are two additional NETMA publications on the same topic – although not including exactly the same trials. In the analysis by Cohen et al. the indirect comparisons were made only against apixaban, and the studies were separately analysed for hip and knee arthroplasty (7). In the analysis by Maratea et al. only efficacy, defined as all VTE and all death, was evaluated (10). The ORs for efficacy from these three NETMAs are shown in Table 2. Furthermore, there is a publication on indirect comparisons by Gomez-Outes et al., who expressed the results as risk differences (11), and therefore

### Table 2: Odds ratios (ORs) and 95% confidence intervals (CIs) for the primary efficacy outcome in three studies on indirect comparisons.

<table>
<thead>
<tr>
<th></th>
<th>Harenberg 10 days</th>
<th>Harenberg 34 days</th>
<th>Maratea</th>
<th>Cohen THA</th>
<th>Cohen TKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95%CI</td>
<td>OR</td>
<td>95%CI</td>
<td>OR</td>
<td>95%CI</td>
</tr>
<tr>
<td>D150:D220</td>
<td>1.16 (0.88 – 1.52)</td>
<td>1.48 (0.96 – 2.30)</td>
<td>1.20 (0.98 – 1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D150:R10</td>
<td>2.26 (1.58 – 3.23)</td>
<td>4.26 (2.24 – 8.11)</td>
<td>2.86 (2.27 – 3.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D220:R10</td>
<td>1.95 (1.39 – 2.73)</td>
<td>2.87 (1.57 – 5.23)</td>
<td>2.38 (1.85 – 3.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D150:A5</td>
<td>3.88 (2.26 – 6.67)</td>
<td>2.00 (1.61 – 2.50)</td>
<td>3.74 (2.12 – 6.60)</td>
<td>2.04 (1.46 – 2.86)</td>
<td></td>
</tr>
<tr>
<td>D220:A5</td>
<td>2.62 (1.61 – 4.26)</td>
<td>1.66 (1.33 – 2.08)</td>
<td>2.51 (1.50 – 4.21)</td>
<td>1.72 (1.22 – 2.42)</td>
<td></td>
</tr>
<tr>
<td>R10:A5</td>
<td>0.91 (0.46 – 1.80)</td>
<td>0.70 (0.53 – 0.90)</td>
<td>0.69 (0.38 – 1.25)</td>
<td>0.83 (0.57 – 1.19)</td>
<td></td>
</tr>
</tbody>
</table>

THR – total hip arthroplasty; TKA – total knee arthroplasty; OR – odds ratio; CI – confidence interval; D150 – dabigatran 150 mg daily; D220 – dabigatran 220 mg daily; R10 – rivaroxaban 10 mg daily; A5 – apixaban 2.5 mg twice daily.
that study was not included in this table. The results that are statistically significant are in bold – and are the same from all three analyses although the ORs differ.

It is evident that depending on how we select our populations the ORs will vary, suggesting anything between 166% and 426% increased risk for thromboembolic events on dabigatran compared to rivaroxaban or apixaban. For the clinician it is only the symptomatic events that really matter, and this was reflected by the methodology in the latest version of the American College of Chest Physicians (ACCP) practice guidelines (12). Let us then take the worst case from the NETMA of Harenberg et al., which is dabigatran 150 mg versus rivaroxaban in the extended treatment (OR 4.26).

The symptomatic events and related deaths were in the RE-NOVATE study – 10 on dabigatran 150 mg and four on enoxaparin (14) and in RECORD 1 – six on rivaroxaban and 11 on enoxaparin (15), resulting in similar ORs and a similar relationship between these ORs of 4.51 (as for all VTE in the NETMA). The absolute risks for such events in these studies were 0.9% and 0.3% for dabigatran 150 mg and rivaroxaban, respectively, which is perhaps less impressive than the ORs.

Table 3: Odds ratios for the primary efficacy outcome from the NETMA and by dividing crude pooled odds ratios.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Duration, days</th>
<th>OR, NETMA</th>
<th>OR, crude pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>D150:D220</td>
<td>10 ± 4</td>
<td>1.16</td>
<td>1.19</td>
</tr>
<tr>
<td>D150:R10</td>
<td>10 ± 4</td>
<td>2.26</td>
<td>2.28</td>
</tr>
<tr>
<td>D220:R10</td>
<td>10 ± 4</td>
<td>1.95</td>
<td>1.93</td>
</tr>
<tr>
<td>D150:D220</td>
<td>34 ± 4</td>
<td>1.48</td>
<td>1.48</td>
</tr>
<tr>
<td>D150:R10</td>
<td>34 ± 4</td>
<td>4.26</td>
<td>4.25</td>
</tr>
<tr>
<td>D220:R10</td>
<td>34 ± 4</td>
<td>2.87</td>
<td>2.87</td>
</tr>
<tr>
<td>D150:A5</td>
<td>34 ± 4</td>
<td>3.88</td>
<td>3.88</td>
</tr>
<tr>
<td>D220:A5</td>
<td>34 ± 4</td>
<td>2.62</td>
<td>2.62</td>
</tr>
<tr>
<td>R10:A5</td>
<td>34 ± 4</td>
<td>0.91</td>
<td>0.91</td>
</tr>
</tbody>
</table>

THR – total hip arthroplasty; TKA – total knee arthroplasty; OR – odds ratio; CI – confidence interval; D150 – dabigatran 150 mg daily; D220 – dabigatran 220 mg daily; R10 – rivaroxaban 10 mg daily; A5 – apixaban 2.5 mg twice daily.
Is the NETMA giving us new information?

NETMAs have been appearing prolifically in the various journals with the new anticoagulants, even for non-VTE (16–19), where they have been proposed as some (albeit weak) evidence in the absence of head-to-head trials (20).

As mentioned above, the NETMA should be based on a method to reduce errors or bias but it is interesting that virtually the same results can be reached in a much simpler way. ►Table 3 shows the odds ratios for the primary outcome as published in the NETMA and by simply dividing the crude pooled ORs that were shown in ►Figures 1 and 2.

With the risk of being called a disbeliever or even a cynic, I feel that we are processing data from original studies over and over with increasingly sophisticated methods but the incremental knowledge has become very small.

Conflicts of interest

None declared.

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References


