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Comparison of apixaban, dabigatran, rivaroxaban, and edoxaban in the acute treatment and prevention of venous thromboembolism: systematic review and network meta-analysis

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Objective

- Venous thromboembolism (VTE) represents a substantial personal and economic burden. Effective treatment requires a balance between the prevention of recurrence and the incidence of bleeding complications. Current standard of care (SOC) for acute VTE is either warfarin or intravenous unfractionated heparin, followed by 3-6 months of VTE treatment.

Methods

Systematic literature review

- A systematic review was conducted to identify studies enrolling patients receiving treatment for acute VTE event.
- Studies were reviewed in full and seven publications reporting on six unique RCTs were included.

Meta-analysis

- A Bayesian network meta-analysis (NMA) was conducted following methodology published by the NICE Decision Support Unit.
- Analysis was performed on a dichotomous outcome and the treatment effect was evaluated in terms of relative risk (RR).
- Analyses of efficacy outcome considered the number of events in an interim-to-interim intention-to-treat (ITT) population, whereas the number of safety outcomes were based on the reported safety population.

Results

Systematic literature review

- From the original search, 5,021 citations were identified of which 4,966 were excluded based on the title/abstract. Fifty five papers were reviewed in full and seven publications reporting on six unique RCTs were included.

- The results of the sensitivity analysis using data from the individual EINSTEIN trials are shown in Table 2. As expected, the results using pooled data from the six trials provided a more precise estimate of the treatment effect.

Network meta-analysis

- The network of evidence for the VTE and VTE-related death endpoint comprised 17 comparisons within the ITT population.
- Network analysis was performed using the Bayesian framework of NMA (Markov Chain Monte Carlo). The network meta-analysis was conducted using the package R (version 3.4.3) and the R-INLA package.

- The network meta-analysis demonstrated a statistically significant difference in efficacy between the NOACs and SOC for acute VTE treatment.

- Treatment with NOACs resulted in a lower incidence of VTE compared with SOC.
- The efficacy of NOACs was consistent across all subgroups.

Conclusions

- All NOACs demonstrated a similar reduction in VTE or VTE-related death and all-cause mortality.

- Apixaban demonstrated the narrowest 95% confidence intervals and was consistently associated with a lower risk of VTE or VTE-related death compared with SOC.

- Apixaban was associated with a significantly lower risk of major or clinically relevant non-major (CRNM) bleeding compared with SOC.

- Apixaban also had a significantly lower risk of major bleeding compared with rivaroxaban, dabigatran, and SOC.

- Apixaban was associated with a significantly higher risk of serious bleeding compared with SOC.

- Apixaban treatment was associated with a significantly lower risk of VTE or VTE-related death and all-cause mortality.

- The results of this systematic review provide evidence that NOACs are superior to SOC for the treatment of acute VTE.

Table 1. Selection criteria for meta-analysis

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adult patients (≥18 years of age) with an objectively confirmed VTE (DVT and/or PE), who were receiving treatment for acute VTE</td>
</tr>
</tbody>
</table>

Table 2. Patient characteristics at baseline across treatment arms for the included studies

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Mean age (SD)</th>
<th>Female, %</th>
<th>Unprovoked VTE</th>
<th>Major bleeding</th>
<th>CRNM bleeding</th>
<th>All-cause mortality</th>
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<tr>
<td>Warfarin (standard dose)/VKA</td>
<td>71.5 (15.2)</td>
<td>39.8</td>
<td>3.9</td>
<td>0.47</td>
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<td>Apixaban vs. VKA</td>
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<td>Dabigatran vs. VKA</td>
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<td>Rivaroxaban vs. VKA</td>
<td>2.00</td>
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Network meta-analysis

- The network of evidence for the VTE and VTE-related death endpoint is illustrated in Figure 1. Due to the small number of studies in this network, the MA was not subjected to a fixed-effect model only.

- Results from the fixed-effect NMA are shown in Table 3. While, double-blind RCTs may be less prone to bias than open-label studies, such a design is not always feasible in anticoagulant trials.

- Time on treatment: Treatment times varied from 3–12 months between the trials.

- Unprovoked VTE: Unprovoked VTE varied from 35.0–48.8% between the trials. 1 Patients with an unprovoked VTE may have a higher risk of recurrence, which may result in variations in the baseline risk of VTE events between trials.

- Definitions of primary efficacy outcomes: The VTE and VTE-related death endpoint comprised reported events of VTE final and/or any reported event of VTE-related death. The NNH was calculated as a ratio of outcomes of the NMA (resulting in non-final ITT and VTE and VTE-related death compared with SOC). The VTE or death associated with VTE was defined as a composite endpoint of a VTE-related death or VTE event, as a composite of VTE-related death and death "at risk" of VTE. All studies reported a consistent definition of bleeding outcomes as defined by the International Society on Thrombosis and Haemostasis.

- Network meta-analysis: The network meta-analysis was conducted using the package R (version 3.4.3) and the R-INLA package.

- Results from the fixed-effect NMA are shown in Table 3. Treatment effects were estimated using a random-effects model, assuming a gamma distribution for the treatment effects and a normal distribution for the random-effects distribution.

- Significant results are indicated by an asterisk (*). "P" represents 5% significance level for the fixed-effect model only.

Figure 1: Network diagram of available evidence

Table 3: Results of fixed-effects NMA

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