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Comparing new anticoagulants in atrial fibrillation using the number needed to treat

The new oral anticoagulants for patients with atrial fibrillation [1–3] represent a nearly ideal setting for the application of network meta-analysis. The three registration trials (RE-LY, ROCKET AF, and ARISTOTLE evaluating dabigatran, rivaroxaban and apixaban against warfarin, respectively) were quite homogeneous in terms of design, comparators, inclusion criteria, and end-point definition, and this is generally thought to be a prerequisite for undertaking indirect comparisons.

The indirect comparisons between the new agents published thus far have either been purely narrative [1,2] or based on network meta-analysis [3]. Regardless of the method of analysis adopted, all of these papers have examined the effectiveness data of the three new drugs on the basis of relative risk (or hazard ratio or odds-ratio), and in none of these analyses has the number needed to treat (NNT) been considered.

In 2011, we carried out an indirect analysis similar to that of Mantha and Ansell [3], which we published in an Italian journal [4]. At that time, the apixaban trial was not yet available, and so our comparison was restricted to four comparators (dabigatran 110 mg, dabigatran 150 mg, rivaroxaban, and warfarin). Later, we tried the application of an original presentation of this network meta-analysis ("revised figure") in which the values of relative risk were replaced by the corresponding values of NNT [5].

![Revised NNT-based figure presenting the results of direct and adjusted indirect comparisons. Each comparison is associated with its respective value of NNT (with 95% CI). All analyses are based on the occurrence of pulmonary or systemic embolism or stroke in patients with atrial fibrillation. The graph shows three direct comparisons (solid lines) and three indirect comparisons (dotted lines). Superiority is found in the direct comparison of dabigatran 150 mg/d vs. standard treatment and of apixaban vs. standard treatment as well as in the head-to-head indirect comparison of dabigatran 150 mg/d vs. rivaroxaban. For the purpose of our analysis, we employed the same event frequencies published by Mantha and Ansell [3] in their Table 3; in the NNT-based analysis, the warfarin group was assigned an event frequency of 7/328013, i.e. the sum of the numerators and denominators in the three control groups. Symbols: + = more effective at statistical level of p < 0.05; – = less effective at statistical level of p > 0.05; = = no difference; t = indicates which treatment is favoured by a trend in cases of no difference. Cases where the upper limit of the 95% CI for NNT extends to infinity are meant to be not statistically significant at the level of p < 0.05 while the others show a significant difference at this level. Abbreviations: NNT = number needed to treat; CI = confidence interval.](image-url)

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In this paper, we present an update of our previous analysis [5] in which we added the apixaban trial. The "revisited" figure based on the NNT is shown in Fig. 1. In this figure, all values of NNT are greater than 100, while the upper limit of the 95% confidence interval reaches, in some cases, extremely high values (e.g. nearly 2400 in the comparison between dabigatran 150 mg/day vs. rivaroxaban 20 mg/day).

In our view, this revisited presentation of the results is of more immediate understanding than the standard one [3]. More importantly, as compared with the standard approach, the NNT approach conveys in this case a less optimistic message about the incremental benefit determined by the new agents. Likewise, the differences between individual new agents seem to have a quite negligible clinical relevance.

In summary, the overall results of this NNT-based analysis are much less impressive in terms of extent of the benefit than those suggested by the analyses based on relative risks. It has been observed that a new era has started for anticoagulation in atrial fibrillation [6]. Our results instead suggest that the clinical relevance of the incremental benefits in this area is not as large as one could think.

Conflict of interests

The authors state that they have no conflict of interests.

References


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