Treatment benefit cannot be excluded on the basis of mean difference alone

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Background

When a continuous outcome is included in a Cochrane review, the pooled mean difference (MD) and its 95% confidence interval (CI) need to be assessed for statistical significance and clinical importance. Statistical significance is tested by checking whether one end of the 95% CI crosses the line of no difference on the Forest plot, and it is tempting to assess the clinical importance of the outcome by comparing the other end of the 95% CI with the Minimal Important Difference (MID) for that outcome. So, for example, the St George's Respiratory Questionnaire (SGRQ) measures quality of life on a scale of 100 points, with a high score indicating worse outcomes; the MID on this scale is a reduction of four units, which represents a noticeable improvement in the patient's quality of life.

However, comparing the 95% CI of the MD with the MID in this way is not a safe approach to rule out a clinically important effect of treatment. It is important to check the MD and also to look at individual responses to treatment.

Objective

To contrast the results of assessing clinical importance using a pooled mean difference versus individual responses from a Cochrane review comparing tiotropium with placebo in people with chronic obstructive pulmonary disease (COPD)*.

Methods

The Cochrane review contained nine trials which randomised 11,672 participants with COPD to tiotropium or placebo, for an average duration of 12 months. The pooled MD and 95% CI were compared with the MID of four units. The same outcome was also modelled at a population level using the mean from each group and a standard deviation of 14 units. The RR and 95% CI from a responder analysis were converted to absolute differences using Visual Rx and the results shown as a Cates plot (www.nntonline.net). This poster compares the results of the responder analysis and the population model of individual responses.

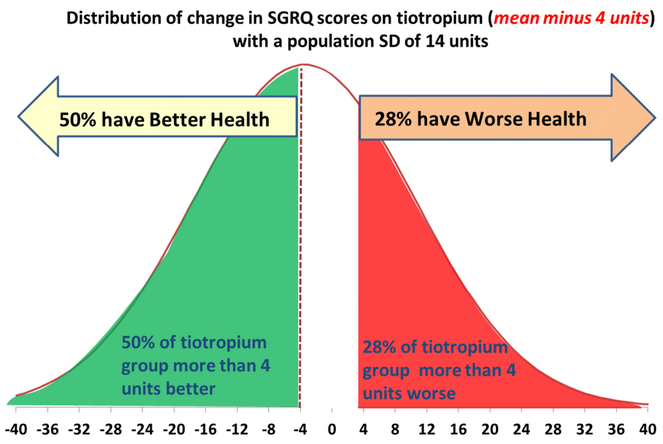
Results

The pooled MD from the Cochrane review was a reduction of 2.89 units (95% CI: 2.44 to 3.35 units) which is statistically significant but does not reach the MID of a four unit reduction. However, when modelled at a population level there were 9% more people who would be expected to experience a 4 unit improvement on tiotropium. When we converted the responder analysis from these trials into a Cates plot we find that 10% (95% CI: 8-12%) more people benefited on tiotropium (awaiting publication).

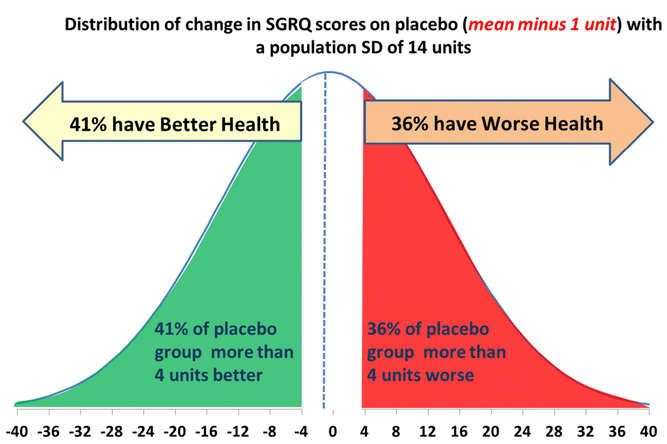
Conclusion

There is good agreement between the population model and the responder analysis ; both indicate a population benefit of treatment even though the MD is less than four units.

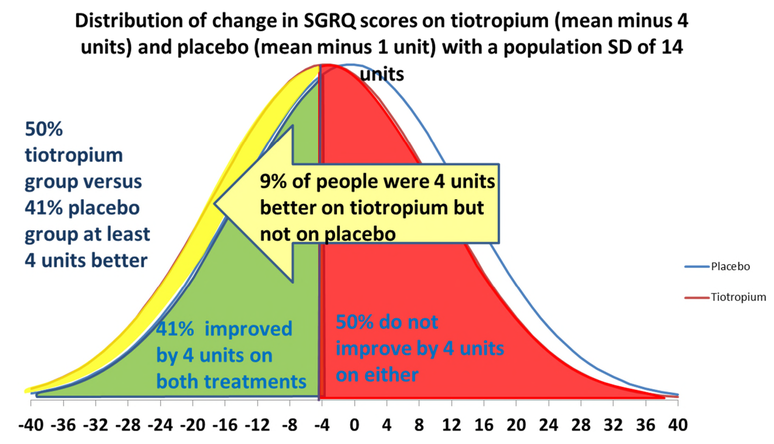
Clinical importance should not be assessed on the basis of the MD alone.



Model results of the distribution of people given tiotropium who are expected to change by more than 4 units in SGRQ. Those who are better are shown in green and those who are worse are shown in red.



Model results of the distribution of people given placebo who are expected to change by more than 4 units in SGRQ.



Comparing the two populations, the model predicts that 9% more people on tiotropium than on placebo are expected to improve by at least 4 units.

- **On tiotropium an additional 10 people (95% CI: 8-12) out of 100 achieved an improvement of 4 units in SGRQ compared to baseline. These are the yellow faces.**

- **On placebo 39 out of 100 people achieved an improvement of 4 units in SGRQ compared to baseline. These are the green faces.**
- **51 out of 100 people did not achieve an improvement of 4 units in SGRQ compared to baseline on either tiotropium or placebo. These are the red faces.**

Cates Plot showing 10% more people actually improved on tiotropium than on placebo

*Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 2012;7:CD009285 doi: 10.1002/14651858.CD009285.pub2.

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