EDITORIAL

β-blockers in heart failure – are all created equal?

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The authors of a systematic review recently published in the *American Journal of Cardiology* concluded, "Carvedilol, as compared against atenolol, bisoprolol, metoprolol and nebivolol in randomized direct comparison trials, significantly reduced all-cause mortality in systolic HF [heart-failure] patients".[1] The claim is supported by biological rationale: carvedilol, in contrast to other β_1-blockers, blocks not only myocardial β but also α_1 receptors,[2] and in addition has antioxidant action not shared by other β-blockers that could have an impact on disease progression.[3]

However, another systematic review that used a network-meta-analysis concluded, "The benefits of β-blockers in patients with heart failure with reduced ejection fraction seem to be mainly due to a class effect, as no statistical evidence from current trials supports the superiority of any single agent over the others".[4] What is responsible for these apparently discrepant conclusions and what is the bottom line for clinicians treating patients with heart failure?

A network meta-analysis is an extension of the traditional meta-analysis. It compares multiple interventions for a given condition, providing a broad and inclusive picture of the evidence regarding all available treatments.[5] To do so, a network meta-analysis combines the results of direct comparisons (A vs. B) with indirect comparisons (A vs. C and B vs. C) to make inferences about treatment effects. For instance, in considering carvedilol vs. metoprolol, we might have direct comparisons of the two agents, but we could also infer the relative merits of the two agents on the basis of how each agent fared against placebo (e.g., carvedilol does better against placebo than metoprolol; therefore, carvedilol is superior).

The main limitations of network meta-analysis are related to its vulnerability to additional underlying assumptions. In general, we trust direct comparisons more than indirect comparisons. This is because indirect comparisons will be misleading if there are important differences in patients, cointerventions, measurement of outcomes, or risk of bias in the A vs. C and B vs. C comparisons. Thus, we lose confidence in the results of a network meta-analysis if, for a particular comparison, there is disagreement between the estimates of effects obtained from the direct and indirect evidence.[6] We label such disagreement "inconsistency".

Inconsistency between direct and indirect evidence may be the cause of disagreement between the results of the two systematic reviews of β-blockers in heart failure. The first systematic review used a traditional meta-analytical approach, in which they pooled the results from 8 randomized trials comparing carvedilol vs. any selective β-blocker. They found a pooled risk ratio for all cause mortality of 0.85 (95% confidence interval [CI], 0.78–0.93). The confidence in the estimates of effects assessed (judged using the GRADE approach)[7] was high.

The network meta-analysis compared all β-blockers against each other. The authors reported an odds ratio for mortality of carvedilol vs. metoprolol of 0.80 (95% CI, 0.59–1.08). Point estimates suggested carvedilol was also superior to the other drugs but, as with metoprolol, CIs included a small increase in mortality with carvedilol. The confidence in these estimates of effect is therefore moderate due to imprecision.

The point estimates of carvedilol vs. metoprolol are thus consistent in the two meta-analyses; the difference is in the width of the CI. The increased width of the CI in the network meta-analysis is likely due to inconsistency between the direct and indirect comparison (as in a conventional meta-analysis, variation in results between studies widens CIs). If we follow the general rule that direct comparisons are more trustworthy, we would conclude that the findings of a clear benefit of carvedilol in reducing mortality from the conventional meta-analysis are more credible.

Unfortunately, a complication arises. Differences in results from direct and indirect comparisons may be related to variations in population,

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Received: May 14, 2013.
Accepted: May 15, 2013.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2013; 123 (5): 204-205

intervention and outcome measurement.[8] In this case, the main difference between trials is the mean dosage of metoprolol consumed by patients.

One trial (COMET)[9] accounted for 94.3% of the weight in the conventional meta-analysis of direct comparisons between carvedilol and metoprolol. This trial has been criticized for having a target dosage of metoprolol of 100 mg/d and achieving a mean dosage that was 85 mg/d.[10] The three trials comparing metoprolol against placebo that contribute to the estimation of the treatment effect in the network meta-analysis reached mean dosages of metoprolol of 159 mg/d,[11,12] 156 mg/d,[13] and 108 mg/d.[14] Could the apparent difference in effect in the direct vs. indirect comparisons be due to different dosages? Maybe so, and if that is the case, perhaps the general rule does not apply here, and the indirect comparisons in this instance provide the more credible results of the relative merit of carvedilol and metoprolol.

This possibility raises another complication: are the higher doses of metoprolol tested in the metoprolol vs. placebo trials regularly achieved in clinical practice, or are lower dosages, closer to what was reached in the COMET trial, the general standard? A survey in a hospital in the United States found that more than two-thirds of the patients receiving metoprolol were potentially underdosed, and that only 40% of the patients took the drug as prescribed.[15] However, this observation leaves open the possibility that the COMET carvedilol doses are also seldom achieved!

Is there any simple conclusion that could arise from all these considerations? Carvedilol is very unlikely to be inferior to other β-blockers, and it remains plausible that it results in an additional mortality reduction. Clinicians might reasonably choose carvedilol on this basis. Carvedilol skeptics might, however, reasonably point to the criticisms of the COMET trial, and defend the use of other β-blockers with advantages such as β_1 selectivity. In any case, an understanding of the reasons for the differences between the two meta-analyses leaves clinicians in a position to weigh the considerations and, on behalf of their patients suffering from heart failure, make a reasoned choice in the selection of the optimal β-blocker.

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