Selection bias in on-treatment analyses: results from the Serve-HF study

Christine zu Eulenburg, Karl Wegscheider

The Serve-HF trial investigates the effect of adaptive servo-ventilation (ASV) on prognosis in heart failure (HF) patients with central sleep apnea. One surprising result of the primary intention-to-treat analysis was that ASV increases the risk of cardiovascular and overall mortality[1]. As secondary analyses, a series of on-treatment analyses with various definitions of device usage was pre-specified to investigate the effect of the actual treatment received during the study. Some people trusted that this analysis would make the mortality increase disappear. In fact, different approaches resulted in a wide variety of estimates some of which suggested that the mortality increase was doubtful. An unadjusted analysis of time-varying usage during different follow-up intervals showed no increased cardiovascular risk in ASV use while the fully adjusted analysis was in line with the randomized result. For explanation, a significant self-selection bias could be directly demonstrated in this special case. Generally, an on-treatment analysis is not protected by randomization and may therefore be severely biased. In principle, on-treatment analysis should be performed with full adjustment. They are epidemiologic in nature and cannot reach the validity of intention-to-treat analyses.

1. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;**373**(12):1095-105.