SERVE-HF on-treatment analysis: does the on-treatment analysis SERVE its purpose?

T. Douglas Bradley[1,2]

Affiliations: [1]Dept of Medicine, University of Toronto, Toronto, ON, Canada. [2]Sleep Research Laboratories, University Health Network Toronto Rehabilitation Institute and Toronto General Hospital, Toronto, ON, Canada.

Correspondence: T. Douglas Bradley, University Health Network Toronto General Hospital, 9N-943, 200 Elizabeth Street, Toronto, ON, M5G 2C4, Canada. E-mail: douglas.bradley@utoronto.ca

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The randomised clinical trial (RCT) is the best-accepted means to assess the effectiveness of a treatment for a given disease because treatment allocation is not influenced by non-random factors such as patient or physician preference. Conversely, observational trials, in which treatment allocations are not randomised, can be, and often are, subject to patient or physician preference. For this reason, the results of observational trials of various interventions are not considered to carry as much weight as those of RCTs, and results of such trials are often considered to be only suggestive or hypothesis generating, rather than definitive. Indeed, in several instances, the positive treatment results of observational trials have not been borne out by RCTs. For example, in the field of sleep apnoea and cardiovascular diseases, several non-randomised observational studies reported reduced fatal and non-fatal cardiovascular events rates among obstructive sleep apnoea (OSA) patients who elected to be treated by, and to continue on, continuous positive airway pressure (CPAP) compared to those who elected not to be treated by, or who discontinued, such treatment [1–3]. In contrast, several large-scale RCTs of treatment of OSA by CPAP demonstrated no beneficial effect of CPAP on fatal or non-fatal cardiovascular events [4–6]. Nevertheless, the reliability of the results of an RCT depends on the degree of adherence to the treatment allocation: the greater the adherence, the more reliable the results, and *vice versa*. For these reasons, there are various means by which RCTs can be analysed that take into account treatment adherence.

In intention-to-treat (ITT) analyses, clinical outcomes are assessed according to the original treatment allocation, irrespective of adherence to that treatment. The assumption underlying this approach is that in clinical practice, when a physician prescribes a treatment, he/she intends that the patient will adhere to it. However, in reality, adherence is seldom 100%, so that any overall clinical effect of a treatment will be diluted by those who refuse therapy or discontinue it prematurely. Accordingly, the ITT analysis takes into account such a diluting effect of non-adherence to provide an estimate of the overall effect size of an intervention. However, if adherence to random treatment allocation in a RCT is relatively poor, especially for an unblinded intervention, any potential beneficial or detrimental effect of an intervention may be diluted significantly, and influenced by factors similar to those affecting observational trials.

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When adherence to a randomly allocated intervention is relatively poor, one can undertake a per-protocol, or on-treatment (OT) analysis. In such an analysis, outcomes are assessed on the basis of what treatment the patient actually received, irrespective of the original randomisation. The intent of such an analysis is to determine whether being on, or not being on a treatment is associated with a particular outcome. However, such an analysis reduces the power of randomisation, and is, to some extent, subject to the same limitations as observational studies because patient and/or physician preferences for treatment come into play. This raises the important question: what meaningful results can arise from a trial with relatively poor adherence to randomly assigned interventions?

In this issue of the *European Respiratory Journal*, Woehrle *et al.* [7] describe the results of an OT analysis of the adaptive servo-ventilation for central sleep apnoea in heart failure (SERVE-HF) trial. This was an unblinded RCT in which 1325 patients with a combination of heart failure with reduced ejection fraction (HrEF) and predominantly central sleep apnoea (CSA) were assigned either to a control group who did not receive minute ventilation triggered adaptive servo-ventilation (ASV_{MV}) or a treatment group who did. In the original ITT analysis [8], there was no difference in the primary outcome of the composite of all-cause mortality, life-saving cardiovascular intervention or unplanned hospitalisation for worsening chronic heart failure, but all-cause and cardiovascular mortality rates were significantly greater in those assigned to $ASV_{MV.}$ However, adherence to assigned treatments was relatively poor: 29% of those assigned to ASV_{MV} either did not start or discontinued it prematurely, and mean usage was only 3.7 h per night over the course of the trial, while among those assigned to control, 17% crossed over to ASV_{MV} prior to completion of the trial. One interpretation of these observations could be that the adverse effects of ASV_{MV} were so great that even with such a high ASV_{MV} drop-out rate, it still increased mortality. Another interpretation could be that exposure to ASV_{MV} per se was not responsible for increased mortality, but that withdrawal from it increased mortality risk. In either case, poor adherence to randomly assigned therapy needs to be taken into account in interpreting the outcomes of this trial.

Many factors could have played a role in poor adherence to ASV_{MV}, including patient and physician preference, or undesirable side-effects of the intervention. To what extent each of these played a role cannot be determined from the data presented. With respect to cross-overs from control to ASV_{MV}, one can assume that patients' and/or physicians' preferences or lack of equipoise were the major contributors. Whatever the case, it was not clear whether excess mortality in the ASV_{MV} group was occurring while on or not on the intervention. For this reason an OT analysis was undertaken.

Because excess overall mortality was predominantly due to cardiovascular causes, the OT analysis focused on cardiovascular mortality as the outcome of interest. The authors performed two types of OT analyses. In the first, an as-treated analysis compared all treatment periods with ASV_{MV} to all treatment periods without ASV_{MV} irrespective of randomisation. They found that the increased risk of cardiovascular death related to ASV_{MV} observed in the ITT analysis was no longer apparent such that during periods of ASV_{MV} usage, cardiovascular mortality did not differ from periods of non-ASV_{MV} usage. Superficially, this suggests that ASV_{MV} had no adverse effect on cardiovascular mortality. However, on closer examination, the reason for this lack of difference in cardiovascular mortality was that among those randomised to control who remained off ASV_{MV}, cardiovascular mortality was lower than among those randomised to ASV_{MV} who crossed-over to control, whereas among those randomised to ASV_{MV} who remained on ASV_{MV}, cardiovascular mortality was much higher than among those randomised to control who crossed over to $ASV_{MV.}$ These observations suggested the relationship between usage or non-usage of ASV_{MV} and cardiovascular mortality was not random but was being influenced by patient or physician preferences to adhere or not to adhere to treatment assignment, or the influence of significant side-effects of ASV_{MV} that made its usage unacceptable to some randomised to it.

For these reasons, the investigators undertook a rather clever and more sophisticated type of OT assessment: an as-treated-as-randomised analysis which compared only time intervals during which patients used the treatment to which they were randomised, while periods in which randomly assigned treatment was not adhered to were excluded. This type of analysis has the advantage over the simple as-treated analysis of being less influenced by patient or physician treatment decision bias, but has the disadvantage of reducing the number of patients and events analysed and thus reducing statistical power. The outcome of this analysis was similar to the original ITT analysis: there was a strong tendency for those randomised to ASV_{MV} who adhered to it to have higher cardiovascular mortality than those randomised to control who remained on control, but this difference was not quite statistically significant, probably owing to loss of statistical power because of fewer overall observations than in the original ITT analysis.

So, how is one to interpret the overall findings of the SERVE-HF trial in light of these new OT analyses? First, one has to give greatest weight to the results of the ITT analysis that demonstrated a harmful effect

of ASV_{MV} on cardiovascular mortality in HFrEF patients with predominantly CSA [8]. Although the OT as-treated analysis suggested superficially that exposure to ASV_{MV} *per se* was not associated with increased cardiovascular mortality, this analysis is open to bias due to patient and/or physician preferences in treatment decisions [7]. By mitigating the influence of such biases *via* performance of the as-treated-as-randomised OT analysis, the results appear similar to the original ITT analysis, and therefore are consistent with a harmful effect of ASV_{MV} on cardiovascular mortality in this patient population. Therefore, ASV_{MV} should not be used to treat CSA in patients with HFrEF in the clinical setting. However, this does not preclude testing other forms of ASV that use different algorithms to control pressure and flow generation in HFrEF patients with CSA, such as peak flow triggered ASV (ASV_{PF}) in the setting of well monitored RCTs [9]. The findings of the SERVE-HF trial also cannot be extrapolated to the treatment of OSA in patients with HFrEF. Indeed, the effects of ASV_{PF} are being tested in a large-scale RCT, the Adaptive Servo-ventilation for Treatment of CSA and OSA in Patients with HFrEF (the ADVENT-HF trial) [9]. This trial should shed light on whether the adverse effect of ASV_{MV} on mortality in HFrEF and predominantly CSA in the SERVE-HF trial was a class effect of ASV, or was specific to the device used. ADVENT-HF should also provide novel data on whether treating OSA in HFrEF improves cardiovascular morbidity and mortality or not.

In summary, the negative results of SERVE-HF reported in the original ITT analysis [8] should now be considered valid in light of the OT analyses reported by Woehrle *et al.* [7]. Nevertheless, such results should not discourage the performance of other RCTs aimed at determining whether treating CSA or OSA in HFrEF patients can improve cardiovascular outcomes. Indeed, they make more compelling the need to complete such trials, since in most cases, results of a single RCT should not be considered definitive for a particular disease.

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