JCSM
Journal of Clinical Sleep Medicine

LETTERS TO THE EDITOR

Keep Calm and Debate On

Reply to Johnson and Johnson. ASV in CHF recommendations too restrictive. *J Clin Sleep Med* 2016;12(9):1313–1314.

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We read with interest the reply by Drs. Johnson and Johnson to "Updated Adaptive Servo-Ventilation (ASV) Recommendations for the 2012 AASM Guideline."[1] The concerns that they raise, along with other commentaries[2,3] in response to Cowie et al.[4] are reminiscent of the controversy following the publication of the CanPAP study in 2005.[5] The SERVE-HF study was a large randomized controlled trial utilizing intention to treat analysis which found that ASV had no impact on the primary endpoints (the first event of lifesaving cardiovascular intervention, unplanned hospitalization for worsening heart failure, or death from any cause). However, there was an increase in all-cause and cardiovascular mortality associated with ASV therapy.[4]

The updated recommendation[6] was not based exclusively on the SERVE-HF study as asserted by Johnson and Johnson; rather, it was based on a current systematic review of the literature and subsequent meta-analysis. The outcome data for cardiac death was based exclusively on the SERVE-HF, for reasons further detailed below. However, the quality of the evidence for all outcomes, as assessed by the GRADE approach, in conjunction with the values and tradeoffs of using ASV, served as the basis for the updated recommendation.

It is certainly true that the SERVE-HF trial is hampered by several critical limitations but it is not appropriate to weigh this trial, as suggested by Johnson and Johnson against "many other studies which show improved oxygenation and measures of cardiac function." The end-point of concern here is mortality. In fact, at the time the updated review was completed, there were a total of four studies which purported to include mortality analysis, including Cowie et al. The other three studies reported improvement in mortality with ASV treatment.[7–9] Unfortunately, these studies were not directly comparable because the total of 176 subjects had left ventricular ejection fraction (LVEF) values ranging from 34% to 56%. Furthermore, these studies included substantially fewer subjects that all originated from the same institution, thus raising the concern that individual patients may have been represented more than once. Additionally these studies had a relatively shorter follow-up period and did not use an intent to treat approach. Indeed, in one of the studies, the "non-ASV" group of 37 patients included 14 patients who were randomized to the ASV group but either chose not to use or were intolerant of ASV treatment.[7]

Many of the "study flaws" in Cowie et al. are probably more likely to result in a decrease in the differences between study groups. The "adequacy of titration" was criticized, although review of adherence and efficacy of ASV treatment in other studies of patients with heart failure reveals similar findings. Among 26 studies reporting data on the effects of ASV on AHI, only 12 demonstrated normalization of the AHI to < 5 events/h. Thus, the response to ASV in the SERVE-HF trial may well reflect real world expectations. However, there is merit in pointing out that there was a higher proportion of patients taking antiarrhythmic medications in the ASV group. Hopefully, this will be a focus of future post hoc analyses.

Johnson and Johnson emphasize the SERVE-HF study post hoc analyses found no difference in cardiovascular mortality among patients with LVEF ≥ 30% and a lower risk of cardiovascular mortality in subjects with Cheyne-Stokes respiration (CSR) < 20% of the recording time. It should be pointed out that these analyses were actually a sub-analysis of secondary end points from a single study and may be subject to low certainty. Furthermore, the investigators did not include these analyses in their report. They can only be found with a particularly sedulous review of the figures in the Supplementary Appendix. At this time, there is clearly insufficient evidence to justify liberalizing warnings to include use of ASV with caution and close monitoring only on those patients with LVEF < 30% and CSR > 20% of the recording time.

There is evidence that ASV is effective in the minority of patients whose treatment-emergent CSA fails to resolve spontaneously. It is likely that heart failure may contribute to development of treatment-emergent CSA. But the unreferenced statement that ASV benefits chronic heart failure (CHF) patients with LVEF ≤ 45% with treatment-emergent CSA is unjustified based on currently available limited evidence.

With evidence-based medicine, it is not appropriate to discount findings because a particular study is not perfect, particularly in the absence of other data which would lead to an opposing

conclusion. The purpose of practice guidelines is to provide practitioners and patients appropriate guidance to make challenging decisions based on all of the available evidence. With the understanding that clinical research is an ongoing endeavor, the AASM Board of Directors felt that the concerns regarding patient safety warranted review, and commissioned the task force to update the recommendations based on available evidence. As indicated in the guideline, these recommendations will be reviewed and updated as new information becomes available.

The authors of the updated guideline join with all of our colleagues in the call for additional studies to better define the indications, and yes, contraindications, of ASV and similar advanced technologies in the management of some of our sickest patients.

CITATION

Aurora RN, Bista SR, Casey KR, Chowdhuri S, Kristo DA, Mallea JM, Ramar K, Rowley JA, Zak RS, Heald JL. Keep calm and debate on. *J Clin Sleep Med* 2016;12(9):1315–1316.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication July, 2016
Accepted for publication July, 2016
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DISCLOSURE STATEMENT

Drs. Kristo and Ramar serve on the American Academy of Sleep Medicine's Board of Directors. Mr. Heald is employed by the American Academy of Sleep Medicine. The authors have indicated no financial conflicts of interest.