**Conflict of Interest Disclosures:** Dr Selvin reported receiving grants from the National Institutes of Health and Foundation for the National Institutes of Health. No other disclosures were reported.

1. McEvoy JW, Chen Y, Rawlings A, et al. Diastolic blood pressure, subclinical myocardial damage, and cardiac events: implications for blood pressure control. *J Am Coll Cardiol*. 2016;68(16):1713-1722. doi:10.1016/j.jacc.2016.07.754

2. McEvoy JW, Daya N, Rahman F, et al. Association of isolated diastolic hypertension as defined by the 2017 ACC/AHA blood pressure guideline with incident cardiovascular outcomes. *JAMA*. 2020;323(4):329-338. doi:10.1001/jama.2019.21402

## Home Noninvasive Positive Pressure Ventilation for Chronic Obstructive Pulmonary Disease

**To the Editor** Dr Wilson and colleagues reviewed bilevel positive airway pressure (BPAP) and home mechanical ventilation for chronic obstructive pulmonary disease (COPD).[1] We are concerned about certain issues related to their methodology.

First, both randomized and nonrandomized studies were pooled together in the same effect estimate. The meta-analysis in support of the European Respiratory Society Task Force Report,[2] which was limited to randomized clinical trials, had a smaller relative risk for mortality of 0.86 (95% CI, 0.58-1.27) for BPAP in individuals with chronic stable COPD. Although the findings from randomized clinical trials and observational studies reported in the review were consistent, the inclusion of observational studies may inflate the odds ratios. In addition, although the sample size was large (51 085 participants), only approximately 1500 were actually pooled.

Second, the authors included studies that examined the role of BPAP after acute hypercapnic respiratory failure alongside studies in patients with chronic stable hypercapnic failure.[3] For clinicians, "Should I *keep* this patient with an acute exacerbation of COPD on BPAP?" is a very different question than "Should I *start* BPAP in this chronic stable hypercapnic COPD patient?" The rationale for combining these heterogenous studies in a meta-analysis is not clear. The absence of statistical heterogeneity alone does not ensure the validity of combining clinically heterogenous studies.

Although BPAP might be beneficial, questions remain that limit its widespread applicability, as highlighted in the accompanying editorial.[4] These include identifying which COPD patients may benefit, timing of initiation, and settings. Although adverse effects with BPAP appear minimal and are probably acceptable to many patients, resource requirements for widespread adoption remain a barrier. Concern has been raised about escalating Medicare billing for ventilators[5]; the present work was commissioned by the Agency for Healthcare Research and Quality and may also affect use of these therapies. In short, this meta-analysis has important methodological limitations that limit the certainty of its results and has the potential to increase confusion and cost in an already confusing area.

**Robert L. Owens, MD**
**Simon Oczkowski, MD**
**Bram Rochwerg, MD**

**Author Affiliations:** Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, La Jolla (Owens); Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Oczkowski, Rochwerg).

**Corresponding Author:** Robert L. Owens, MD, Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, 9444 Campus Point Dr, COB 2-045, La Jolla, CA 92037 (rowens@ucsd.edu).

**Conflict of Interest Disclosures:** Drs Owens, Oczkowski, and Rochwerg reported being members of the American Thoracic Society Clinical Practice Guidelines committee reviewing the use of noninvasive ventilation in individuals with chronic obstructive pulmonary disease, and Drs Oczkowski and Rochwerg were members of a similar group for the European Respiratory Society.

1. Wilson ME, Dobler CC, Morrow AS, et al. Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2020;323(5):455-465. doi:10.1001/jama.2019.22343

2. Ergan B, Oczkowski S, Rochwerg B, et al. European Respiratory Society guideline on long-term home non-invasive ventilation for management of chronic obstructive pulmonary disease. *Eur Respir J*. 2019;54(3):1901003. doi:10.1183/13993003.01003-2019

3. Struik FM, Sprooten RT, Kerstjens HA, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. *Thorax*. 2014;69(9):826-834. doi:10.1136/thoraxjnl-2014-205126

4. Coleman JM III, Gates KL, Kalhan R. Home noninvasive ventilation for patients with chronic obstructive pulmonary disease and chronic respiratory failure. *JAMA*. 2020;323(5):421-422. doi:10.1001/jama.2019.22484

5. Department of Health and Human Services Office of the Inspector General. Escalating Medicare billing for ventilators raises concerns. Published September 2016. Accessed March 24, 2020. https://oig.hhs.gov/oei/reports/oei-12-15-00370.pdf

**In Reply** The issue of combining randomized clinical trials and nonrandomized studies in a meta-analysis is a common challenge faced during evidence synthesis. When an abundance of well-done randomized clinical trials does not exist, clinical decision-making has to proceed based on the available evidence. In our systematic review[1] about home noninvasive positive pressure ventilation (NIPPV) in COPD, we judged that combining these 2 types of studies was appropriate. For transparency purposes, we presented estimates separately from each study design. When examining the 2 designs, we observed similar trends, consistent results (overlapping CIs of relative estimates of mortality, need for intubation, and hospitalization), and no significant heterogeneity. A methodology study by the Cochrane Collaboration that examined 1583 meta-analyses covering 228 different medical conditions concluded that there was little evidence for significant effect estimate differences between observational studies and randomized clinical trials (ratio of odds ratios, 1.08; 95% CI, 0.96-1.22).[2] This should not be interpreted as equating inferences from the 2 designs, and there are many examples of misleading observational studies. It simply means that the totality of evidence needs to be considered when not enough trials are available.

The meta-analysis cited by Dr Owens and colleagues, which formed the basis for the 2019 European Respiratory Society guidelines, also recognized several important benefits of home NIPPV for patients with COPD.[3] These benefits formed, at least in part, the basis for the conditional recommendations by the European Respiratory Society to recommend NIPPV for patients with chronic stable hypercapnia as well as for patients with persistent hypercapnia following an acute exacerbation of respiratory failure. Benefits cited by these guidelines included improvements

in health-related quality of life, dyspnea, and exercise tolerance, with "the possibility of reductions" in mortality and hospitalizations. As with our meta-analysis, the overall strength of evidence was low to moderate, owing to risk of bias of individual studies.

While starting NIPPV in patients with chronic stable hypercapnia is different than starting NIPPV in patients with persistent hypercapnia following an exacerbation of acute respiratory failure, there may be considerable overlap in the benefits (as well as adverse events) in both groups. In the European Respiratory Society guidelines, presumed and similar benefits were cited as part of the justification for recommending NIPPV for patients following an acute exacerbation.[3] When analyzed separately, important benefits for both patients with or without acute exacerbation were noted in our meta-analysis.[1]

In summary, our systematic review, along with several others, documents important benefits and relatively few adverse events for home NIPPV in patients with COPD and persistent hypercapnia. Systematic reviewers do not make guideline recommendations or coverage decisions because such decisions require additional information beyond comparative effectiveness evidence.

**Michael E. Wilson, MD**
**M. Hassan Murad, MD, MPH**
**Zhen Wang, PhD**

**Author Affiliations:** Mayo Clinic Evidence-Based Practice Center, Rochester, Minnesota.

**Corresponding Author:** Michael E. Wilson, MD, Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (wilson.michael1@mayo.edu).

**Conflict of Interest Disclosures:** Drs Wilson, Murad, and Wang reported receiving grants from the Agency for Healthcare Research and Quality.

1. Wilson ME, Dobler CC, Morrow AS, et al. Association of home noninvasive positive pressure ventilation with clinical outcomes in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2020;323(5):455-465. doi:10.1001/jama.2019.22343

2. Anglemyer A, Horvath HT, Bero L. Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials. *Cochrane Database Syst Rev*. 2014;(4):MR000034. doi:10.1002/14651858.MR000034.pub2

3. Ergan B, Oczkowski S, Rochwerg B, et al. European Respiratory Society guidelines on long-term home non-invasive ventilation for management of COPD. *Eur Respir J*. 2019;54(3):1-18. doi:10.1183/13993003.01003-2019

## Guidelines for Letters

Letters discussing a recent *JAMA* article should be submitted within 4 weeks of the article's publication in print. Letters received after 4 weeks will rarely be considered. Letters should not exceed 400 words of text and 5 references and may have no more than 3 authors. Letters reporting original research should not exceed 600 words of text and 6 references and may have no more than 7 authors. They may include up to 2 tables or figures but online supplementary material is not allowed. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters not meeting these specifications are generally not considered. Letters being considered for publication ordinarily will be sent to the authors of the *JAMA* article, who will be given the opportunity to reply. Letters will be published at the discretion of the editors and are subject to abridgement and editing. Further instructions can be found at http://jamanetwork.com/journals/jama/pages/instructions-for-authors. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment are required before publication. Letters should be submitted via the *JAMA* online submission and review system at https://manuscripts.jama.com. For technical assistance, please contact jama-letters@jamanetwork.org.

**Section Editor:** Jody W. Zylke, MD, Deputy Editor.