Olofsen,[2] multiple analyses found that the absence of plasma concentration data did not significantly affect the estimate for the interindividual variability of the effect site concentration of remifentanil at which half-maximal ventilatory depression was observed, so it is unlikely our conclusion was affected. We agree with Overdyk *et al.* that our findings should not be extrapolated to other clinical scenarios where patients with obstructive sleep apnea may be at increased risk of opioid-induced ventilatory depression.

### Competing Interests

The authors declare no competing interests.

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# Chlorhexidine Inefficacy in Ventilated Patients: Comment

## To the Editor:

The recent article by La Combe *et al.* is timely, directly challenging the practice of using oral chlorhexidine in intubated patients to reduce oral bacterial counts and ventilator-associated pneumonia.[1] While documenting a lack of efficacy of chlorhexidine to reduce bacterial load in the oropharynx, they failed to address the specific known pulmonary toxicity of chlorhexidine or evaluate the direct toxic impact of chlorhexidine "silent aspiration" into the lung, leaking between endotracheal tube cuff and tracheal mucosa. This would have been of great interest, as specific toxicology concerns remain discounted and with their administration of the 15-ml volumes and 0.12% concentrations applied. The authors did indicate some studies that specifically linked oral chlorhexidine use to increased mortality.

I previously published concerns regarding the silent aspiration of chlorhexidine and toothpaste used in clinical ventilator-associated pneumonia bundles, when my wife nearly succumbed to "silent aspiration" pneumonia in 2015. Ventilator-associated pneumonia and aspiration pneumonia occurred only after a motor vehicle trauma with immediate intubation after 24 to 48 h of normal pulmonary and radiological findings.[2] Progressive and severe aspiration pneumonia then developed postoperatively and in conjunction with the prevailing ventilator-associated pneumonia bundle (chlorhexidine and toothpaste), until tracheostomy performed on the ninth day of intubation led to improvement, as secretions now exited onto the anterior neck above the cuff, instead of draining into the lungs.

I was astonished to find during my review of the literature that in animal studies, chlorhexidine greater than 0.1% concentrations exhibit significant pulmonary toxicity.[3,4] However, toxicity has not been specifically addressed in intubated humans, where "silent" pulmonary aspiration is a recognized and expected risk. Toothpaste (inorganic silicates) is also a particulate material used in ventilator-associated pneumonia with known pulmonary implications and should be similarly concerning, as well as the scandal involving chlorhexidine and the National Quality Forum's (Washington, DC) guidelines for sterile skin prep: The U.S. Justice Department settled a $40 million whistleblower lawsuit in early 2014, alleging that CareFusion (USA), the maker of ChloraPrep, had inappropriately influenced the National Quality Forum.[5] Thus, business interests and guidelines do not ensure patient safety. Both toothpaste and chlorhexidine have found support as ventilator-associated pneumonia bundle quality parameters to a large degree, because of dental hygiene use in nonintubated daily living care—without concerns specific to pulmonary dangers from laryngeal incompetence and silent aspiration, a problem known to be inherent in intubated patients.

Minimization of ventilator-associated pneumonia in 2019 may require specific investigations regarding "silent aspiration" as causative and the importance of (1) elimination of all pulmonary toxins introduced into the oral cavity, (2) maximally effective oral hygiene using pulmonary tolerated aqueous and antibiotic solutions *via* electrical power brushing,[6] and (3) early tracheostomy to allow egress of secretions from above the cuff and return of glottic protective closure mechanisms, where indicated.

## Competing Interests

The author declares no competing interests.

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# Chlorhexidine Inefficacy in Ventilated Patients: Reply

## In Reply:

We thank Dr. Kempen for his interest in our work.[1] Dr. Kempen states that we "failed to address the specific known pulmonary toxicity." Dr. Kempen failed to understand that this was not the objective of our study. Dr. Kempen has forgotten that high-quality research recommends to address one question at a time in a study. So the question of chlorhexidine pulmonary toxicity is a completely different question from the one we wished to answer. We would, however, be delighted if Dr. Kempen addresses this interesting issue in a clinical study. Of note, however, we have recently alerted clinicians on the risk of excess mortality linked to chlorhexidine exposure.[2]

We thank Dr. Kempen for mentioning the article regarding the hidden financial ties and the Health Quality Group. This reminds us of the utmost importance of disclosing potential conflicts of interest.

Regarding toothbrushing, there is—to date—no clear clinical effect of toothbrushing to reduce ventilator-associated pneumonia in ventilated patients. Indeed, the most recent Cochrane systematic review regarding oral hygiene care[3] clearly indicates: "We are uncertain as to the effects of toothbrushing (± antiseptics) on the outcomes of [ventilator-associated pneumonia]." So, Dr. Kempen's recommendation regarding toothbrushing is purely speculative. In addition, the reference Dr. Kempen used to support his claim[4] has nothing to do with ventilator-associated pneumonia prevention and does not address intensive care unit patients but individuals of any age with no reported disability that might affect toothbrushing. Importantly, authors of this systematic review cited by Dr. Kempen state: "The clinical importance of these findings [*i.e.*, the greater removal of dental plaque by powered toothbrushing compared with manual toothbrushing] remains unclear."[4]

Finally, Dr. Kempen is wrong when he mentions early tracheostomy as a means to reduce ventilator-associated pneumonia. Large single- or multicenter trials have all failed to show any benefit of early tracheostomy on ventilator-associated pneumonia reduction.[5–7]

Although we welcome all contributions to the debate regarding ventilator-associated pneumonia prevention, scientific accuracy is mandatory for the contribution to be seriously considered.

## Acknowledgments

Drs. La Combe and Ricard have provided this Reply to the Letter to the Editor on behalf of all authors of the original article.[1]

## Competing Interests

The authors declare no competing interests.

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# Cardiac Events after Electroconvulsive Therapy: Comment

## To the Editor:

We read the recent paper "Major Adverse Cardiac Events and Mortality Associated with Electroconvulsive Therapy" by Duma *et al.*[1] published in Anesthesiology with great interest. We recently wrote an article entitled "The Mortality Rate of Electroconvulsive Therapy: A Systematic Review and Pooled Analysis,"[2] which has a very similar focus to that of Duma *et al.*, but the results are strikingly different. According to Duma *et al.*, "All-cause mortality was 0.42 (0.11 to 1.52) deaths per 1,000 patients and 0.06 (0.02 to 0.23) deaths per 1,000 electroconvulsive therapy treatments,"[1] which is substantially different from the results from our analyses "…yielding an [electroconvulsive therapy]–related mortality rate of 2.1 per 100,000 treatments (95% CI, 1.2 to 3.4)."[2] The main reason for this discrepancy (there are also differences in the statistical approach) is that we focused exclusively on deaths that were plausibly causally related to electroconvulsive therapy, *i.e.,* taking the timing (during or relatively soon after electroconvulsive therapy) and cause (*e.g.,* cardiac arrest or aspiration pneumonia) into account, while Duma *et al.* focused on all deaths that were reported in studies of electroconvulsive therapy—irrespective of the timing and cause of death. As evident from the mortality estimates previously noted, this distinction has important consequences.

In order to understand how the distinction between "[electroconvulsive therapy]—related mortality"[2] and "mortality associated with electroconvulsive therapy"[1] has resulted in the very different mortality estimates reported in the review by Tørring *et al.*[2] and Duma *et al.*,[1] respectively, let us look at the study by Shiwach *et al.*[3] In this study, it was reported that "Only one death, which occurred on the same day as the electroconvulsive therapy, could be specifically linked to the associated anesthesia. An additional four deaths could plausibly have been associated with the anesthesia."[3] These five deaths were included in the analyses by Tørring *et al.*,[2] while Duma *et al.* included all 30 deaths occurring within 14 days of an electroconvulsive therapy session, irrespective of the cause[1]—for example, eight suicides (suicidal ideation/intent is among the prime indications for electroconvulsive therapy—so these death are highly unlikely to be caused by electroconvulsive therapy), a death due to cancer, and a death due to an auto accident that took place 4 days after the last electroconvulsive therapy session.[3] As related examples, Duma *et al.*[1] included data from the relatively small studies by Tecoult and Nathan.[4] and Martinez *et al.*[5] in their assessment of mortality associated with electroconvulsive therapy. We did not include data from these studies in our review[2] because we required a study to report on at least 3,000 electroconvulsive therapy treatments in order to avoid inclusion of deaths due to chance findings or selection or publication bias.[6,7] However, even without this sample size restriction, we would not have included the deaths reported in these two studies in the calculation of electroconvulsive therapy–related mortality, as their causal relation to electroconvulsive therapy is highly doubtful. In the study by Tecoult and Nathan,[4] the one death that occurred was described as follows: "One patient aged 42 years, died at home from