comparison differs significantly from the setting described in the study protocol.

Aaron *et al* advocate that any intention to treat analysis is superior to other strategies. However, when withdrawal rates are substantial, as in the Optimal Trial, and patients withdrawing from study medication are given medication being tested in the trial, any conclusion on analysis methodology should be made with caution.

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Author's reply

We would like to thank Dr Vestbo for his comments. We agree that in the Optimal Trial more patients originally randomised to the placebo arm prematurely discontinued study medications, and that many of these patients were subsequently put on open label ICS/LABA products.[1] As discussed in our paper, the relative risk reduction decreased from 21% if patients were prematurely excluded once they discontinued study drugs to 15% when an intent to treat analysis was used.[2] We agree with Dr Vestbo that our intention to treat analysis was conservative, and it did slightly reduce the possibility of a difference being found between placebo and active treatment but we would argue that this analysis was necessary in order to prevent bias.

An intention to treat analysis is necessary as it is impossible to know a priori the ultimate direction of the bias when patients who stop study medications early are banished from a clinical trial. Will the bias favour the drug or favour placebo? For example, a similar analysis of a trial assessing tiotriopium for chronic obstructive pulmonary disease (COPD)[3] showed that the bias can work exactly in the opposite direction and instead favour placebo over active drug. In this study, higher incidence rates of fatal events occurred following premature discontinuation of study medication, especially in those patients randomised to the placebo arm. Presumably, patients who were taking placebo in this study were doing poorly and many prematurely stopped study drugs and then, shortly thereafter, they died. In this case, early exclusion of these patients would have introduced bias because the factors which determined whether a patient might have been excluded were also related to the outcome. If these patients had been dropped from the trial after premature discontinuation of study medications, this would have meant that their deaths would not have been discovered, and this would have produced a biased mortality incidence ratio in favour of placebo over tiotropium. The authors of this study concluded that failure to consider outcomes of patients who discontinue study medications early may bias results against effective therapies.[4] Only by ensuring full follow-up of all randomised patients and by using a proper intention to treat analysis was this potential bias eliminated.

There is an old saying in medicine "You can't find a fever if you don't take a temperature". This applies to clinical trials as well; the investigator cannot know what really happened in a clinical trial unless he/she evaluates outcomes in all randomised patients for the full study follow-up period, regardless of patient compliance.

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IL1 may be elevated but is it all bad in ARDS?

Frank *et al* have elegantly demonstrated in animal models of ventilator associated lung injury (VALI) that interleukin 1β (IL1β) may play a role in the development of alveolar barrier dysfunction. However, the ventilation strategy used for these experiments (with a very high tidal volume of 30 ml/kg) induced an increase in IL1β of only 36 pg/ml in lavage as opposed to 7 pg/ml in their control animals, a level that in their in vitro models of epithelial resistance and permeability did not significantly affect permeability.[1]

Our recent study published in *Thorax* has evaluated IL1β levels in bronchoalveolar lavage fluid in patients with adult respiratory distress syndrome (ARDS) as 143 pg/ml.[2] Thus their animal model does not adequately reflect the in vivo situation in patients with established ARDS. We believe this may be important because several lines of evidence suggest that IL1β may play a role in stimulating repair of the alveolar epithelium.

Effective alveolar repair following the development of ARDS is believed to involve the transdifferentiation of alveolar type II cells (ATII), which retain stem cell-like properties, into type I cells via intermediate cell phenotypes. The turnover rate of ATII cells is boosted after acute lung injury and the recovery process is believed to involve cell migration and proliferation in addition to transdifferentiation of ATII epithelial cells.[3]

Geiser *et al* were the first to show that pulmonary oedema fluid, early in the course of ARDS, stimulates repair of wounded monolayers in culture to a greater extent than plasma obtained from the same patients or pulmonary oedema fluid from patients with hydrostatic oedema.[4] The potential of oedema fluid to promote wound repair was associated with a trend towards improved survival and reduction in the duration of ventilation. The enhanced wound repair is IL1β dependent and mediated by autocrine release of epidermal growth factor and transforming growth factor α.[5] Recently, we have further demonstrated that lung lavage fluid from ARDS patients treated with intravenous salbutamol enhanced A549 monolayer wound repair responses compared with placebo treated patients in vitro by an IL1β dependent mechanism.[2]

In conclusion, the data from the study by Frank *et al* clearly demonstrate that increased IL1 signalling may be an early mechanism of alveolar barrier dysfunction in VALI in rats and mice. However, significant evidence suggests that once ARDS is established, elevated IL1 levels may have beneficial effects on epithelial repair. We believe that this may therefore account for the apparent failure of anti-IL1 strategies in humans with ARDS.

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Authors' reply

We appreciate the comments from Drs Thickett and Perkins and welcome the opportunity to further discuss the potential roles of interleukin 1 (IL1) in the pathogenesis and repair of acute lung injury.

Regarding the differences in IL1β levels in bronchoalveolar lavage fluid (BALF) obtained from mice and humans, we do not believe that the differences are surprising. IL1β levels are influenced by the lavage volume and the specific assays used. The primary finding is that IL1β mRNA expression and protein levels are markedly increased in the lung early in the course of ventilator induced lung injury.

We agree that the potential broader role of IL1 in alveolar repair and lung fibrosis should be considered when designing future studies of IL1 blockade for acute lung injury. Because of space limitations, we could not elaborate on this important issue in our manuscript.[1] Previous clinical studies have reported that the majority of the pro-inflammatory activity in BALF is attributable to IL1.[2] Through both neutrophil recruitment and an effect of epithelial cells, IL1 induces an increase in permeability to protein.[1] IL1β also downregulates epithelial sodium channel (ENaC) expression and impairs vectorial fluid transport.[3] Together, these effects favour pulmonary oedema formation, the hallmark of acute lung injury and ARDS. Although we have found that IL1 impairs alveolar barrier permeability, previous work from our group has demonstrated that IL1 promotes alveolar epithelial cell migration.[4 5] It is conceivable that blocking IL1 signalling could interfere with normal alveolar epithelial cell migration over the basement membrane during the repair phase of acute lung injury. However, one recent study found that mesenchymal stem cells prevented both acute lung injury and fibrosis following bleomycin administration in mice. The effect was attributable to IL1 receptor antagonist expression in the stem cells.[6] Additionally, chronic overexpression of IL1β induces acute lung injury followed by pulmonary fibrosis,[7] although the mechanisms for the acute inflammatory response and later fibrosis may be distinct.[8] Together these data show that IL1 signalling may govern a broad spectrum of inflammatory and repair processes in the injured lung. Differences in the timing of IL1 blockade may have different effects on injury and repair. Our hypothesis is that early blockade of IL1 signalling may limit the quantity of pulmonary oedema by preserving barrier function and sodium transport, while later IL1 blockade may affect epithelial repair and fibrosis. Additional studies of transgenic mice and IL1 receptor antagonist in other models of acute lung injury and fibrosis may shed more light on how the timing of IL1 signalling during lung injury influences the diverse effects of this cytokine.

Previous clinical trials have not directly addressed the question of the efficacy of IL1 receptor antagonist in patients with acute lung injury. Given the lack of effective therapies for this syndrome of acute respiratory failure in critically ill patients, we believe that further investigation of IL1 receptor antagonist is warranted.

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Pre-cessation varenicline treatment vs post-cessation NRT: an uneven playing field

The study by Aubin *et al*[1] published in this issue is significant in that it is the first head-to-head comparison of the two smoking cessation pharmacotherapies: varenicline and nicotine replacement therapy (NRT). The results suggest that varenicline yielded higher rates of smoking abstinence than NRT. However, an important flaw in the design hampers the interpretation of the results. An imbalance resulted from the fact that the varenicline group began treatment 1 week before the target quit date whereas the NRT group began treatment on the quit date. Although the authors justified this decision based on current manufacturer's instructions for using NRT, the asymmetrical design is problematic.

The problem with the imbalanced design stems from the finding that initiating NRT before the quit date approximately doubles the efficacy of NRT compared with beginning treatment on the quit date.[2] It is plausible that a similar enhancement of efficacy results from initiating varenicline before the quit date. Therefore, beginning varenicline but not NRT before the quit date may have created an unfair advantage for varenicline. Although most studies of pre-cessation NRT have used pretreatment for 2 weeks as opposed to 1 week, it is conceivable that even pre-cessation exposure to treatment for 1 week augments success rates.

A likely mechanism for the enhancement in efficacy with pre-cessation treatment is behavioural extinction.[3] Extinction results from a reduction in the rewarding effects of cigarettes when they are smoked concurrently with NRT or with a nicotinic antagonist such as mecamylamine,[4] or with the nicotinic receptor partial agonist varenicline.[5] This decrement in smoking reward may, in turn, reduce dependence levels and facilitate quitting smoking.

Pre-cessation NRT is not approved by the Food and Drugs Administration, but this recommendation may change as more studies replicate the positive results with pre-cessation NRT.[6] Moreover, the main concern expressed regarding smoking concurrently with NRT—nicotine overdose—can be obviated by switching patients to denicotinised cigarettes during pre-cessation treatment with NRT.[4]

A comparison of NRT and varenicline using equal pre-cessation treatment regimens will ultimately prove informative in evaluating these two treatments.

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