Use of tiotropium Respimat *versus* HandiHaler and mortality in patients with COPD

To the Editor:

Verhamme *et al.* [1] recently compared the possible mortality effect of two delivery systems of tiotropium in their Dutch observational cohort study of 11 287 chronic obstructive pulmonary disease (COPD) first-time users of tiotropium in primary care. They concluded that "until further data become available, physicians should be aware that patients with arrhythmia or a history of cardiovascular disease might be particularly at risk" when using tiotropium Respimat [1]. Although arrhythmia, renal disease and certain cardiac diseases are relative contraindications of tiotropium and, clinically, it may be important to consider whether an increased mortality risk in such patients with these relatively contraindicative comorbidities overrides the additional well-being of the bronchodilatation effect of tiotropium therapy. The evidence on this question is sparse or not available; thus independent randomised trials may be needed. Several publications have considered the pro-arrhythmogenic character and possible detrimental dose-dependent effects of anticholinergics in COPD patients with co-incident cardiac disease or renal disease (assigned to decreased drug excretion). A recent publication found that a large proportion of real life COPD patients (38%) may have such comorbidity and, therefore, be ineligible for inclusion in the previously performed randomised controlled trials [2].

In the Dutch study [1], no statistical significant difference in mortality rate was found in patients without co-existing cardiovascular disease (adjusted HR 1.02), but mortality was higher with Respimat use in patients with cardiovascular disease (adjusted HR 1.36). The author's statistical modelling was adjusted for, among others, age, smoking, recent pneumonia, recent systemic corticosteroid use, recent hospitalisation for exacerbation of COPD, and the number of general practitioner and respiratory physician visits in the previous year.

This does not seem to conflict with the results of the recently published large randomised controlled TIOSPIR (Tiotropium Safety and Performance in Respimat) trial including >17 000 COPD patients, which also did not find a statistically significant device-related, or possibly dose-related, difference in mortality risk when comparing Respimat with the Handihaler device in patients without moderate or severe cardiac or renal comorbidity [3].

In their real life cohort, Verhamme *et al.* [1] described a small but significantly increased proportion of not only cardiovascular disease, but also of the comorbidities of diabetes, cancer and Parkinsonism in the Respimat group, which was seemingly not adjusted for in the analyses. Thus some degree of possible confounding or bias relating to the observational study design cannot be denied, as mentioned by the authors in the discussion.

A relevant matter to consider in this Dutch cohort study, and in the real life treatment of COPD patients, relates to the possible selection bias and also confounding by therapist awareness (and therapist reaction) to the known and accepted relative contraindications to inhalation treatment with long-acting muscarinic antigonists (LAMAs). Several of these relative contraindications are identical to the cardiovascular comorbidities analysed by Verhamme *et al.* [1], and their presence may increase mortality unnecessarily if alternative drugs with a very similar clinical and preventive effect in COPD, without as many precautions and without mortality signals in randomised controlled trials, are actually available (*e.g.* long-acting β-agonists (LABAs)) [4]. Although precautions of LABAs may also include arrhythmia, ischaemic heart disease and renal disease. In the Dutch cohort [1], the prevalence of arrhythmia (9.7%), myocardial infarction (7.4%), ischaemic heart disease (8.1%), heart failure (11%) and renal failure (8%) did not seem to be negligible, and, thus, should probably not be ignored. The question as to whether the physicians treating the patients thought of these precautions or considered not treating such COPD patients with tiotropium Respimat or tiotropium Handihaler may not be easily answered in the Dutch cohort.

To try and answer this question, in 2013 we performed a national email-distributed questionnaire to all clinically active physicians and physicians in training of the three Danish societies of respiratory medicine, cardiology and of geriatrics [5]. For each separate type of COPD inhalation therapy (LAMA, LABA and

TABLE 1 The proportion and number of doctors stating the use of absolute or relative contraindications to long-acting muscarinic antigonist prescription, according to medical specialty#

	Respiratory medicine	Cardiology	Geriatrics	Other specialty	Physician in training	Total
None	13 (19.4)	74 (73.3)	8 (44.4)	14 (53.8)	104 (61.5)	238 (57.2)
Absolute contraindications	24 (35.8)	12 (11.9)	3 (16.7)	6 (23.1)	39 (23.1)	86 (20.7)
Relative contraindications	43 (64.2)	19 (18.8)	8 (44.4)	7 (26.9)	42 (24.9)	129 (31.0)
Total number of doctors	67	101	18	26	169	416

Data are presented as n (%) or n.The individual doctors could specify both absolute and relative contraindications. #: data from general practice participants (n=11) and other doctors (n=24) or very incomplete answers (n=81) are not presented, but complete results from these doctors and a copy of the questionnaire are available from the corresponding author.

inhaled corticosteroids), doctors were asked if they used any relative or absolute contraindications, without any detailed or specific suggestions being presented. If they used contraindications, they were asked to specify them. Although the response rate was moderate (538 (35%) out of 1558), we thought the results were informative, and satisfactorily valid and interesting (table 1). To some surprise, 57% of the Danish peers actively informed us that they used no relative or absolute contraindications to LAMAs when treating COPD patients. The proportion of doctors stating no use of contraindications to LAMAs differed considerably between physicians in the fields of respiratory medicine (19%), cardiology (73%) and geriatrics (44%), and in physicians in training (62%) ($p<0.0001$, Chi-squared). This result, to put it bluntly, could be a form of pronounced medical attention deficit syndrome. However, other additional probable explanations for the minor medical attention to the precautions include: 1) a general lack of discussion of the impact of the exclusion of patients with renal or recent cardiac comorbidities in the randomised controlled trials of tiotropium or other LAMAs; and 2) the rather wide variation of mentioned specific precautions of renal or recent cardiac comorbidities when comparing the national drug index, the patients drug data sheet and the regulatory authority's databases, and between countries' databases (including not mentioning single comorbidity precautions as renal disease or recent heart failure).

VERHAMME *et al.* [1] may be able to shed more light on the possible reduced medical attention concerning the relative contraindications among peers in general practice and, in addition, from the Dutch IPCI Project Database they may be able to analyse whether the proportions of COPD patients experiencing renal and cardiovascular comorbidities, but not treated with tiotropium, differ significantly compared to the proportions among the similar (but tiotropium treated) patients included in their published cohort.

The Dutch study and other published large observational non-randomised controlled trials may, to some degree, be able to adjust for possible bias regarding COPD stage, comorbidity and the severity of comorbidity, but may still be affected by confounding [1]. When the previously mentioned precautions seem to be not very widely used in clinical practice and in the present absence of rigorous evidence from randomised controlled trials among the sub-group of COPD patients with renal or recent cardiac comorbidity treated with LAMAs, the time may seem ripe for an independent randomised study with LAMA *versus* LABA among this group of patients, including treatment arms for comparison of the Respimat and Handihaler versions of tiotropium.

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Great variation (27–81%) in the proportion of doctors considering any contraindications to LAMA treatment in COPD http://ow.ly/tiwxA

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From the authors:

C.N. Meyer addresses an important point that might partially explain discordances between findings of classical randomised controlled trials (RCTs) and observational (cohort or database) studies: do physicians take into account absolute and relative contraindications before prescribing a new drug? In their Danish, questionnaire-based study, a substantial proportion of physicians stated that they did not use any contraindications to long-acting muscarinic antagonists when treating patients with chronic obstructive pulmonary disease (COPD). These disturbing findings are in accordance with the relatively high prevalences of arrhythmia, ischaemic heart disease and renal failure in our cohort study on the association between use of tiotropium Respimat *versus* use of tiotropium Handihaler and mortality in COPD patients [1]. As COPD patients with moderate and severe cardiac or renal comorbidity were excluded from the TIOSPIR (Tiotropium Safety and Perfomance In Respimat) RCT, the jury is still out whether tiotropium Respimat is safe in COPD patients with comorbid cardiac or renal disease [2–4]. C.N. Meyer also points out that we did not adjust for other comorbidities such as diabetes, cancer and Parkinsonism, potentially resulting in residual confounding. However, we would like to clarify that, when building the final statistical model, we adjusted for all factors that changed the crude hazard ratio (HR) by >5%. As diabetes, cancer and Parkinsonism did not change the HR by >5%, these comorbidities were not included in the final model.

We welcome the research question, as formulated by C.N. Meyer, to check whether the proportion of COPD patients experiencing renal and cardiovascular comorbidities is different in patients treated with tiotropium compared with patients not being treated with tiotropium. Our data on the association between type of tiotropium device and mortality do not include information on comparator drugs. We do, however, have real-life data on the differences in comorbidity between users of tiotropium Handihaler and users of long-acting β_2-agonists (LABAs), from our case–control study of the use of tiotropium Handihaler and the risk of cardio- and cerebrovascular events and mortality [5]. At the time of first prescription during follow-up, there were no differences between tiotropium and LABA users in terms of myocardial infarction, angina pectoris, stroke or renal failure. There were, however, differences in terms of more peripheral artery disease, lipid disorder and hypertension in tiotropium Handihaler users *versus* LABA users.

In contrast to classical RCTs with strict inclusion and exclusion criteria (encompassing absolute and relative contraindications to the study drug of interest), observational studies allow the investigation of the safety of a drug under real-life circumstances in routine-care settings. Since differential prescribing (channelling) is a concern, this risk of confounding bias needs to be carefully addressed in the design phase (*e.g.* use of pragmatic trials) and in the analysis phase. Ultimately, when developing clinical practice guidelines, the complimentary evidence of classical RCTs, pragmatic trials and observational studies needs to be incorporated.

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Complimentary evidence from RCTs, pragmatic trials and observational studies needs to be incorporated in guidelines http://ow.ly/ugC1O

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