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Eur Respir J 2014; 43: 1816–1818 | DOI: 10.1183/09031936.00207313 | Copyright ©ERS 2014

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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Received: Feb 23 2014 | Accepted: Feb 26 2014

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

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Eur Respir J 2014; 43: 1818–1819 | DOI: 10.1183/09031936.00036314 | Copyright ©ERS 2014

What the 4-metre gait speed measures and why it cannot replace functional capacity tests

To the Editor:

In a recent issue of the *European Respiratory Journal*, KON *et al.* [1] explored the responsiveness of the 4-m gait speed (4MGS) test to pulmonary rehabilitation and provided its longitudinal modifications in a sample of chronic obstructive pulmonary disease (COPD) patients. That article may be considered complementary to a previous one published by the same group of authors a few months ago, in which the reliability and validity of the physical performance test were determined in older persons referred to an outpatient respiratory clinic [2]. Consistent with previous evidence from different medical specialties and settings [3], the 4MGS was confirmed to be a robust, clinically friendly instrument capable of improving the patient's assessment and monitoring over time. We strongly believe that both studies by KON and co-workers [1, 2] are extremely interesting and meritorious for proposing the widely studied 4MGS test in the field of respiratory medicine. Nevertheless, in both contributions, the authors tend to present the 4MGS as an alternative to endurance/functional capacity walking tests currently used in respiratory medicine (*i.e.* the 6-min walking test (6MWT) and the incremental shuttle walk (ISW)) by indicating "learning effects" and the need for space as primary limitations of these. We strongly disagree with these statements because such parallelism is mainly unfair and potentially flawed from a methodological viewpoint. It is like considering, for example, the heart rate assessment as an alternative to a stress ECG just because it is easier, more convenient and still clinically informative.

The designs of the 6MWT, ISW and 4MGS are responsive to completely different aims. The 6MWT and the ISW stress the cardiorespiratory capacities of the individual in order to quantify their physiological reserves and exercise tolerance. The results indicate the capacity of the subject to cope with challenging and prolonged stressors. Moreover, it is noteworthy that both the 6MWT and the ISW have no established goal of distance to cover (*i.e.* the subject walks as far as they can). In contrast, the 4MGS test is conducted at the individual's usual pace over a short track with the only objective of obtaining a measure of physical performance under comfortable conditions. Here, although the goal (*i.e.* crossing the 4-m finish line on the floor) may be veiled to the patients, the nature of the test makes it unlikely push them to the limit of their physiological reserves.

During the last two decades, the increasingly demonstrated capacity of the usual gait speed to predict major health-related events in older persons [4] and its strong relationships with key pathophysiological mechanisms of ageing [5] have made this tool of particular interest in the clinical setting. It is now well established that gait speed should not be considered a mere measure of mobility, but indeed represents a more global marker of well-being. Not surprisingly, gait speed has been repeatedly indicated as a potential additional "vital sign" specific to older persons [5–7]. In other words, the 4MGS results may resemble those obtained in the clinical setting when measuring the basal respiratory rate, heart rate, temperature or blood pressure.

By taking into account its strengths (*i.e.* ease of assessment and implementation, objectivity, reliability and inexpensiveness) and weaknesses (*i.e.* being potentially affected by a wide spectrum of confounders, abnormal results possibly having heterogeneous explanations, and arguable use as primary outcome in the clinical and research settings), we believe that the 4MGS represents a useful screening tool to grossly