**Medical Insider COPD Podcast, Season 3
The impact of triple therapy: Mortality in COPD**

Richard Russell (00:00):

Welcome to the Medical Insider COPD by Boehringer Ingelheim, a podcast offering a breath of fresh air to clinicians treating COPD across the globe. My name is Dr. Richard Russell. I'm a Consultant Chest Physician at Lymington New Forest Hospital in the United Kingdom. I'm a Senior Clinical Researcher at the University of Oxford, and I'm the Editor-in-Chief of the *International Journal of COPD*. I'm delighted to be your moderating host for this season of the Medical Insider COPD podcast series. I'm here to bring you news and insights in COPD right from the source, to you, our listener. So, thank you for joining us today. Be sure to subscribe and follow Medical Insider COPD podcast to ensure you do not miss any of the exciting topics in this series.

Richard Russell (01:07):

Today, we're going to delve into publication, which I believe is worth reading and is brand new. This is entitled the ‘Significance of FEV3/FEV6 in recognition of early airway disease in smokers at risk of developing COPD: Analysis of the American SPIROMICS Cohort’.

Richard Russell (01:24):

I'm also going to look into an emerging exciting topic from social media called *Lacing Up for Your Lungs*. But first, I am really pleased to introduce today's guest, my friend, Dr. Marc Miravitlles, who's going to discuss with us the topic of mortality analysis in COPD and treating COPD. Marc, welcome to the podcast.

Marc Miravitlles (01:43):

Hello, Richard. It is my pleasure to talk to you today. I am Marc Miravitlles, Chest Physician working in Vall d'Hebron Hospital in Barcelona. And my main interest is COPD and also alpha one trypsin deficiency.

Richard Russell (01:58):

So, Marc, we're going to be talking about mortality and the benefits and risks of using treatment for mortality, and understanding these studies of mortality. But before we look at that, let's talk briefly about guideline recommendation of treatment for initiation of follow up of COPD. Can you unpack that very briefly for us?

Marc Miravitlles (02:17):

Most guidelines agree that patients with COPD should be on long-acting bronchodilators. Long-acting bronchodilators are the basis for treatment of COPD because they relieve symptoms. They improve dyspnoea, improve exercise capacity and also reduce the risk of exacerbations. And only patients who despite bronchodilation are still having exacerbations, they may require other treatments such as anti-inflammatories and in particular, inhaled corticosteroids.

Richard Russell (02:47):

Do you feel that the guidelines, you are someone who's been very involved in guidelines, really are lined up on this – ERS, ATS as well as the GOLD strategy?

Marc Miravitlles (02:58):

Yes. And all guidelines recognise that bronchodilators are the basis of treatment. In fact, the GOLD strategy in the four categories in which they divide patients with COPD for initial therapy, in all four categories, they indicate that bronchodilators are the main option or the first option for treatment. And only in those more symptomatic and with higher risk of exacerbations, if they have a particular type of inflammation, more eosinophilic inflammation, they may start therapy also with an inhaled corticosteroid.

Richard Russell (03:32):

This has been a theme from several podcasts in the past, and we'll come on I'm sure to talk about personalised medicine. But let's now talk about mortality and the importance of mortality as an outcome and mortality analysis. Marc, can you tell us a little about how easy or difficult this is?

Marc Miravitlles (03:48):

Well, it is really very difficult. Because studies design and powered for mortalities as a main outcome, need to be very large studies with huge populations and also followed for long periods of time, usually three to four years. And it is easy to understand that these largest studies are difficult to conduct and very expensive, and therefore we only have a few of such studies in the field of COPD.

Richard Russell (04:17):

We've also looked at the role of randomised controlled trials and real-world data. When looking at outcomes, Marc, I believe there's a new mortality pooled analysis, which will help us.

Marc Miravitlles (04:28):

Yes. In fact, we have conducted and presented recently at the ATS, a pooled analysis of the clinical trials with two bronchodilators, long-acting beta 2-agonists and a long-acting anti muscarinic agent, a LABA and LAMA, compared with triple therapy. In this case, it was tiotropium/olodaterol compared with tiotropium/olodaterol plus an inhaled corticosteroid. And this pooled analysis was carefully conducted to match for the clinical characteristics of the patients in order to avoid bias as much as possible. And the results show no difference in mortality between patients treated with the two bronchodilators or patients on triple therapy.

Richard Russell (05:13):

So very importantly, you actually controlled very tightly for those variables in the patients, which actually might influence the mortality outcome.

Marc Miravitlles (05:20):

That's true. I mean, it is clear that a pooled analysis is not a randomised clinical trial, and it may be subjected to some kinds of biases. Some of them can be controlled, and some others may be unknown. But to the best of our possibilities, we match for the baseline characteristics that we know that can influence survival. And even after this careful matching, there was no difference in mortality between the two treatment arms.

Richard Russell (05:48):

Well, let's come on now then to discuss a couple of studies that have actually looked at mortality as secondary outcomes, particularly in the randomised control world, which have shown some different results. So, we looked at maybe IMPACT, ETHOS and TRILOGY studies particularly, how do they differ from the study you're just talking about?

Marc Miravitlles (06:06):

Yes, well, these studies were randomised clinical trials compare triple therapy with LABA/LAMA and also LABA/ICS. But I guess the most interesting comparison here is triple versus LABA/LAMA, and they showed a significant reduction in mortality in patients on triple therapy. The first observation is that these studies were not designed and powered for mortality. Nonetheless, a mortality analysis was conducted, and these were the results. However, we need to recognise that these patients included in these clinical trials are very different from the patients included in the previous pooled analysis, between tio/olodaterol and triple therapy.

Richard Russell (06:50):

So, do you think then, that some of these outcomes may well have been due to enrichment and increased risk, which we'd have seen in randomised controlled trials, which in a pooled analysis you're going to lose?

Marc Miravitlles (06:59):

Yes, but not only. In fact, I think the main reason for the different results was that patients included in ETHOS and IMPACT were patients at high risk for exacerbations. These were patients who were already on dual, I mean on LABA/LAMA, LABA/ICS, or even in triple therapy, up to 50% of them were already on triple therapy. And despite of that, they were suffering from frequent or severe exacerbations. So, these are not the majority of patients in the community. So, these are a particular subgroup of patients with severe or very severe COPD and high risk for exacerbations. And in this population, there was a significant effect on mortality and in particular, in a sub-group of these patients, but the patients in the pooled analysis were patients included in bronchodilator trials, and therefore not enriched for high-risk patients.

Richard Russell (07:54):

One area of controversy with regards to these studies is always about ICS, inhaled corticosteroid withdrawal at randomisation. If you're on triple therapy to start with, and you come off inhaled corticosteroids, do you suffer at the beginning an increased risk of problems? Marc, can you explain that for us and maybe see if that's been a problem.

Marc Miravitlles (08:12):

Well, this is another difference between the pooled analysis and the IMPACT and ETHOS trial. In the pooled analysis, there was no ICS withdrawal. All patients in the LABA/LAMA had never been treated before with an ICS. In contrast, patients on IMPACT on ETHOS, up to 50% were on triple before randomisation and more than 70% were on ICS before randomisation. And therefore, when they were randomised, half of them were randomised to LABA/LAMA. Those who were randomised to LABA/LAMA had to discontinue ICS. And we know from clinical trials that discontinuation of ICS in patients at high risk of exacerbations, such as those in IMPACT and ETHOS, they have a high risk of exacerbations, in particularly, they have high blood eosinophils. And therefore, this could explain, at least in part, some of the results seen in these trials.

Richard Russell (09:05):

One of the things that we need to understand when we look at randomised controlled trials is, are they generalisable to the population? So, let me ask you, do you think these trials are generalisable and do you think maybe the pooled mortality analysis may be even better?

Marc Miravitlles (09:21):

Well, this is very important, in fact, and it is important to recognise that these, the results can be extrapolated to the population that are represented in the trials. And the population included in IMPACT and ETHOS is a population basically from Teaching Hospitals, Reference centres and that see patients who are more severe at high risk. So, these patients had an FEV1 below 50%, the mean FEV1 was around 43-44%, and again, on frequent or severe exacerbations, despite therapy. In contrast, we know that in general, in the community, the majority of patients are infrequent exacerbators, and they used to have no or just one exacerbation a year. So, these are the majority of patients that we see in the community and the majority of patients treated by general practitioners. So, the results of ETHOS and IMPACT cannot be extrapolated to the general population with COPD in the community.

Richard Russell (10:22):

You began at the beginning by telling us about baseline therapy of COPD, and we've now discussed how we may want to treat the most severe patients. And we also mentioned eosinophil. So, let's talk about personalising therapy on understanding risk-benefit. So, Marc, can you unpack for us briefly the idea of risk-benefit when prescribing inhaled corticosteroids over perhaps dual bronchodilators LAMA/LABA therapy, and obviously risk of side effects versus benefit of actually the treatment.

Marc Miravitlles (10:50):

Yes, I think the first that we need to acknowledge is that the indication of inhaled corticosteroids is the prevention of exacerbations. And therefore, ICS should be used in patients who are at high risk of exacerbations. In other words, patients who had exacerbations in the past, because this is the best marker of a future risk of exacerbations. And in particular, when we see these patients with frequent exacerbations, we know that those who have high blood eosinophils will be the ones that will respond better to ICS, and the higher the concentration of eosinophils, the better the response to ICS. In contrast, patients who have low blood eosinophil counts will not benefit from ICS. And they will be at increased risk of side effect in particular, infective side effects such as pneumonia.

Richard Russell (11:43):

That's very helpful. Now I'm going to leave you with the hardest task Marc. Perhaps you can summarise two or three points that you think the audience should take away from this discussion we've had.

Marc Miravitlles (11:53):

Well, this is not easy. But well, the first would be that the basis of treatment is long-acting bronchodilators, and most patients will require two and will do better with two than with one. Patients who despite two bronchodilators is still having exacerbations, we need to look at blood eosinophils. Patients with high blood eosinophil counts must be on ICS in combination to long-acting bronchodilators. Patients with low levels of blood eosinophils should not be on ICS. And patients with intermediate levels of blood eosinophils are perhaps the most difficult to manage, because in them we need to make individual decisions based on other characteristics, such as the frequency of exacerbations, the smoking habits and the type of exacerbations. So, exacerbations that are more infective are less likely to be prevented with ICS.

Richard Russell (12:45):

Thank you, Marc. That's very helpful. In just a minute, I'm going to talk about an important new publication and also a really hot topic from social media. But before I do that, I want to thank Dr. Marc Miravitlles for joining me today on the Medical Insider COPD podcast. Marc, thank you for unpacking this really important subject for us.

Marc Miravitlles (13:05):

Thank you. It was a pleasure, Richard.

Richard Russell (13:12):

I'm going to unpack for you now, a really new and interesting paper that I found in the literature on COPD. This is entitled ‘The Significance of FEV3/FEV6 in Recognizing Early Airways Disease in Smokers at Risk of Development of COPD.’ This is analysis of this SPIROMICS cohort published in Chest, November 9th, 2021, by Yee, et al. The question here is, if we look at small airways in COPD, do they really matter? Does small airways dysfunction actually make a difference? And this paper was able, using the cohort, to look at FEV3 to FEV6 ratio, to identify early abnormalities of the small airways and ask the question, did these abnormalities predict future problems, the development of COPD and even exacerbations?

Richard Russell (14:00):

So, what this group did was take 832 current and former smokers with normal FEV1 to FVC ratios, so no airways obstruction, and then measured their FEV3 to FEV6 ratios and followed them. Well, what did they find? Well, they found if you defined an abnormal ratio of FEV3 to FEV6, using a lower limit of normal, that these patients had lower FEV1s, impaired quality of life, as measured by a higher St. George's Respiratory Questionnaire, increased levels of emphysema, and also an increased level of small airways disease as found on CT scan. They also found an increased odds ratio of having exacerbations and hospitalisations at one year. These people were more likely to develop COPD and have problems with their COPD. What was nice was, compared with the spirometry alone, this FEV3 to FEV6 ratio was reproducible and repeatable. So, it's something we can do out in practice.

Richard Russell (15:02):

So, what does this mean? Well, this means we may well be able to identify an early cohort of COPD using easy and simple measure of spirometry at risk of developing COPD. This also makes me think that we need to ask our patients the right questions. These patients had abnormalities, but did they think they had breathlessness or not? Well, maybe they didn't, but maybe if we asked about breathlessness, we may find more of them as triggered by the FEV3 to FEV6 measurement. And then finally, should we be treating these patients earlier, intervening with bronchodilators, doing rehabilitation with them and keeping them well and preventing them from developing COPD, obviously stopping them smoking. So, an interesting paper, and I would commend it to you. Have a read and have a think about its findings.

Richard Russell (15:57):

So now, let's talk about the hot topic on social media at the moment. Let's talk hashtag *Lacing Up for Lungs*. This is about wearing an orange ribbon or an orange color, lacing up your shoes and getting active for COPD. This has also been tagged with hashtag COPD awareness. So, look out for it. The goal of this from the COPD Foundation, veterans’ organisations, celebrities, and even COPD news today is really to have an active and healthy lifestyle for all, but particularly focusing on COPD. Their messages that breathing should not be taken for granted. 380 million people in the world have COPD and are struggling. So, there's a whole load of promotional videos, tweets, and also the idea behind lacing up and get moving for COPD. The COPD foundation is also providing a COPD awareness toolkit, which will tweet out and also engage the whole community to get laced up for your lungs and become aware of COPD.

Richard Russell (17:01):

I hope you've enjoyed today's podcast. We've unpacked the importance of mortality analysis in COPD and how we should treat COPD. We've looked at a new paper in COPD looking at lung function and spirometry. And then finally, we've laced up for our lungs to get active for COPD. So, thank you for joining me today on Medical Insider COPD podcast, and look out for the next in our exciting podcast series. And remember, let's lace up for lungs and become aware of COPD and not take breathing for granted.