27th ERS Congress

European Respiratory Society

9-13 SEPTEMBER 2017 • MILAN • ITALY

PEER-REVIEWED CONFERENCE REPORT

Resistance in Tuberculosis
Researchers analysed the independent predictors for unsuccessful treatment outcomes in multidrug-resistant tuberculosis.

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Disinfectants Use Increases COPD Risk
A novel hypothesis: an observational study in nurses showed that the risk of COPD is increased in those who use disinfectants at least once a week compared with those who do not.

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Editor Prof. Dr. Richard Dekhuijzen, Radboud University Medical Center, Nijmegen, The Netherlands

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ISSN 2468-8762 17:16

Letter from the Editor

Prof P.N. Richard Dekhuijzen

Dear Reader,

This year's International Congress of the European Respiratory Society (ERS) was again the place to be to get the most recent update in important areas of pulmonary diseases.
The burden of respiratory infections remains significant worldwide, resulting in high rates of morbidity and mortality. Identifying risk factors aids adequate diagnosis and treatment, although resistance - especially in tuberculosis - can be a complicating factor. These factors were presented, as well as survival rates after NTM infections.
The field of airway diseases continues to evolve. Growing insight into aetiology, the role of large and small airways and the interaction between the two have been key in understanding and developing adequate treatment options for patients. There are increasing data on the effects and safety of biologicals in very severe asthma. Modulators of IL-5 activity and of TSLP activity show important clinical effects. New data and comparisons between these compounds were presented. Another development entering the clinic is a triple inhaler containing an ICS, LABA and LAMA. This might benefit COPD patients who have an indication for treatment with all three components.
Pulmonary rehabilitation has shown to be indispensable for pulmonary patients, improving the physical as well as the mental wellbeing of patients. There are many different types of pulmonary rehabilitation that enable physicians and patients to choose the most appropriate program to fit in the patients' daily life activities. Increasing data become available, enabling a more personalised and targeted rehabilitation programme.
Idiopathic Pulmonary Fibrosis (IPF) is slowly revealing its secrets. Timely and accurate diagnosis remains particularly important, especially now that the therapeutic options continue to improve. Data on the long-term effects of new drugs and combinations of efficacious drugs were presented.
Immunotherapy is widely recognised as a 'game changer' in lung cancer, offering patients significantly better perspectives than ever before. It can even be stated that some of metastatic patients have curable diseases. Nevertheless, there are still many challenges to overcome, either diagnostic or therapeutic by nature. Data on long-term effects, side effects and safety were presented, as well as a updated algorithm in advanced NSCLC.
Besides the topics indicated above, interesting findings regarding pulmonary arterial hypertension, respiratory failure and sleep were presented.
While you may not have been able to experience these aspects of the ATS yourself, this report outlines the most significant advancements discussed and practical advice disseminated. So, we hope that you will enjoy reading this Conference Report!

Kind Regards,
Prof. Richard Dekhuijzen

Biography

Prof P.N. Richard Dekhuijzen (Amsterdam, the Netherlands, 1956) is Professor of Pulmonology at the Radboud University Medical Centre in Nijmegen, the Netherlands. His specific area of research interest is in asthma, COPD and inhalation technology.
He studied medicine at the Free University in Amsterdam and completed his training in pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam and in the academic hospital Nijmegen. In 1989 he finished his PhD thesis on training of the respiratory muscles in COPD, followed by a PhD thesis on steroid-induced myopathy of the diaphragm in 1994 at the Catholic University Leuven, Belgium.
He is author/co-author of over 320 peer-reviewed papers and many textbook chapters on respiratory medicine. Until 2016, he was chair of the department of pulmonary diseases and chair of the heart-lung centre Nijmegen, and he was head of the department of cardiology in 2008-2010. Until 2016 he was chair of the medical staff of the Radboudumc. Currently, he is chair of the medical ethical committee of the Radboudumc.

Respiratory Infections

The burden of respiratory infections remains significant worldwide, resulting in high rates of morbidity and mortality. Identifying risk factors aids adequate diagnosis and treatment, although resistance – especially in tuberculosis – can be a complicating factor.

Risk factors for mortality in immunocompetent tuberculosis patients identified

The main risk factors for mortality among immunocompetent patients with tuberculosis are older age, comorbidities and disseminated tuberculosis, according to a retrospective analysis study. A total of 403 patients (median 40 years, 61.3% men) who were diagnosed with pulmonary tuberculosis between 2010 and 2015 were enrolled. All patients had pulmonary tuberculosis, furthermore associated extrapulmonary localisations were observed in 16% of patients (pleural n=31, lymph nodes n=10, osteo-articular n=5, parietal n=5, urinary tractus n=4, cerebral n=3, endobronchial n=2, laryngeal n=2, thyroid n=2, peritoneal n=1 and ovarian n=1). A total of 3% of patients died (9 men and 3 women, median age 49 years). The causes of death were massive haemoptysis (n=4), acute respiratory failure (n=2), fulminant hepatitis (n=2), hypoglycaemia (n=1), and unknown causes (n=3). Multivariate analysis showed that independent factors associated to death among tuberculosis patients were age ≥65 years (P=0.042; odds ratio 2.13; 95%CI 1.17-4.3), diabetes mellitus (P=0.003, OR 3.56; 95%CI 1.56-8.12), extra-respiratory symptoms (P=0.013, OR 2.70; 95%CI 1.23-5.4) and disseminated tuberculosis (P=0.045, odds ratio 1.95; 95%CI 1.14-3.78). [1]

Independent predictors of unfavourable tuberculosis treatment outcomes

Resistance to tuberculosis drugs is an increasing problem worldwide, which complicates treatment significantly. Researchers in Japan assessed the treatment outcomes of multidrug-resistant tuberculosis and determined predictors of unfavourable treatment outcomes among 159 patients who were resistant to various tuberculosis drugs. They conducted a nationwide questionnaire survey. The mean age of the patients was 51.8 years, and 63.5% of enrolled patients was male. In total, 52.2% were new cases and 30.2% were foreign-born, mostly coming from high-tuberculosis-burden Asian countries. Patients were treated with different types of treatment with varying outcomes (Table 1).

The frequencies of resistance to levofloxacin, to kanamycin, and to both drugs were 28.1%, 24.6%, and 15.5%, respectively. The multivariable logistic regression analysis revealed that older age (odds ratio 1.04; 95%CI, 1.02-1.06; P<0.001), being foreign-born (OR 6.47; 95%CI, 1.71-24.40; P=0.01) and treatment without surgical resection (OR 9.03; 95%CI, 1.97-41.4; P=0.005) were independent predictors for unfavourable treatment outcomes. In conclusion, about two-third of patients were successfully treated, but the return of foreign-born multidrug-resistant tuberculosis patients to their home countries before completion of treatment appeared to be a problem. Unsuccessful treatment outcomes of multidrug-resistant tuberculosis were associated with older age, foreign nativity and non-operable cases. [2]

Table 1 Treatments and treatment outcomes in multidrug-resistant tuberculosis patients registered during 2011-2013 in Japan. [2]

	Japan-born (n=111)		Foreign-born (n=48)		Total (n=159)	
Duration of therapy (days	645		595		630	
LVFX prescribed	73/105	69.5%	36/48	75.0%	109/153	71.2%
KM prescribed	35/105	33.3%	31/48	64.6%	66/153	43.1%
LZD prescribed	617/111	15.3%	3/48	6.3%	20/159	12.6%
DLM prescribed	3/111	2.7%	1/48	2.1%	4/159	2.5%
Thoracic surgery	20/111	18.0%	11/48	22.9%	31/159	19.5%
Treatment outcome						
Favourable	71	63.9%	33	68.8%	104	65.4%
Cured	37	33.3%	14	29.2%	51	32.1%
Treatment completed	34	30.6%	19	39.6%	53	33.3%
Unfavourable	40	36%	15	31.3%	45	34.6%
Died	31	27.9%	0	0.0%	32	20.1%
Failed	4	3.6%	1	2.1%	4	2.5%
Lost to follow-up	3	2.7%	3	6.3%	6	3.8%
Transferred out	2	1.8%	11	22.9%	13	8.2%

LVFX = levofloxacin; KM = kanamycin; LZD = linezolid; DLM = delamanid

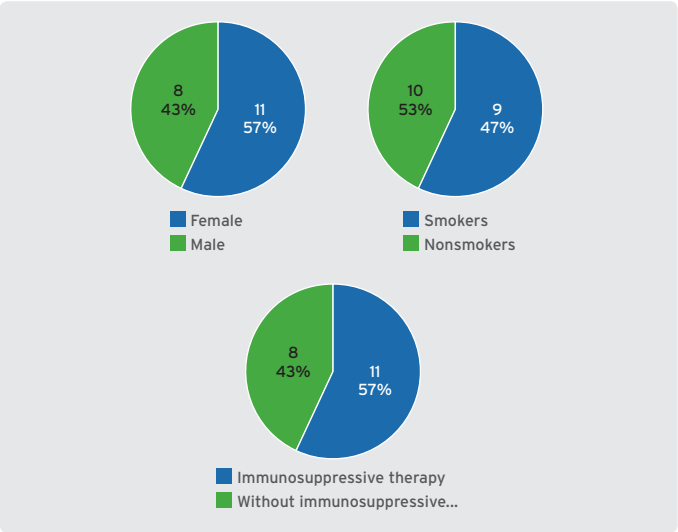
Survival rates NTM differ according to microbiological criteria

Survival rates of patients with non-tuberculosis mycobacterium (NTM) isolate and/or NTM pulmonary disease (NTM-PD) were calculated by Jankovic et al. This was done by means of a retrospective analysis of all Croatian residents with pulmonary NTM isolated from 2006 to 2016. Researchers assessed the 5-year survival regarding fulfilment of American Thoracic Society (ATS) microbiologic criteria and the level of species' clinical relevance. For those with clinically diagnosed NTM-PD, the survival rate was calculated regarding the received therapy (adequate therapy; short-duration adequate therapy; inadequate or no therapy; tuberculosis therapy). Of a total of 2,007 patients with pulmonary NTM isolate, 21.7% met the ATS/Infectious Diseases Society of America microbiologic criteria. The 5-year survival rate for those meeting the criteria was 60%, compared to 70% in those who did not (P<0.001). Patients meeting the microbiologic criteria had a lower survival rate compared to those who did not, but the difference was lost in the case of species of high-clinical relevance. Adequate treatment of NTM-PD significantly reduces the all-cause mortality indicating a high morbidity of the disease. NTM-PD was diagnosed in 29.4% of patients with available medical records. With respect to the treatment, no differences regarding the NTM caused mortality were found, but the all-cause mortality was 17% in adequately treated, compared to 36% in those receiving no treatment (hazard ratio (HR) 3.04; p=0.018). Thus, patients meeting the microbiologic criteria had lower survival rate compared to those who did not, but the difference was lost in case of species of high clinical relevance. Adequate treatment of NTM-PD significantly reduced all-cause mortality indicating a high morbidity of the disease. [3]

Focus on IPAF diagnosis and management

Interstitial lung disease (ILD) patients may have features of connective tissue disease not fulfilling the regular criteria of connective tissue disease. The ERS and ATS recently proposed the term interstitial pneumonia with autoimmune features (IPAF) to define these patients and standardise

Figure 1 Characteristics of IPAF patients [4]



classifying criteria. Alvarenga et al. applied IPAF criteria to a cohort of 279 ILD patients and described their clinical phenotype. A retrospective analysis of patients who were evaluated between February 2012 and December 2016 was performed. IPAF patients (6.8% of all ILD patients) were selected and characterised regarding clinical, serologic and morphologic criteria. Their mean age was 69.7 (14.2) years. Other characteristics include gender, smoking status, and immunosuppressive therapy (Figure 1). [4]

It emerged that a considerable proportion of patients evaluated fulfil IPAF criteria particularly serologic and morphologic (both 95%). These were more frequently females, non-smokers, with non-specific interstitial pneumonia pattern on a computed tomography (CT) scan and positive antinuclear antibody. Based on these findings, researchers called for prospective studies to guide management of IPAF. [4]

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3. Jankovic M, et al. 5-year survival of patients with nontuberculous mycobacteria pulmonary disease (NTM-PD)–data from Croatian national registry. PA2733.
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Chronic Airway Diseases, Asthma and COPD

The field of airway disease has been evolving for many decades, and will continue to do so. Growing insight into aetiology, the role of large and small airways and the interaction between the two have been key in understanding and developing adequate treatment options for patients.

Tezepelumab reduces asthma exacerbations independent of baseline blood eosinophil counts

Results from a phase 2 study showed a reduction of asthma exacerbations in patients with moderate-to-severe, uncontrolled disease independent of baseline blood eosinophil counts with tezepelumab [1]. Tezepelumab is a human IgG2 monoclonal antibody which targets the thymic stromal lymphopoietin (TSLP) cytokine. TSLP activates multiple pathways which are involved in asthma induction, persistence, and flare-ups. A total of 584 patients was randomised to subcutaneous injections of tezepelumab 70 mg every 4 weeks mg (n=145), 210 mg (n=145) every 4 weeks, 280 mg every 2 weeks (n=146), or placebo every 2 weeks (n=148). These were current non-smokers aged 18-75 years with poorly controlled asthma despite treatment with long-acting β-agonists combined with a medium-to-high dose of inhaled glucocorticoids for at least 6 months before enrolment. Placebo was administered at the intermediate visits in those patients receiving 4-week dosing regimens. The results showed that exacerbation rates at week 52 were lower in the low- (61%), medium- (71%), and high-dose (66%) tezepelumab groups than in the placebo group. At all doses, tezepelumab was associated with a longer time to the first asthma exacerbation; the risk for any exacerbation was lower with treatment compared with placebo by 34% (HR, 0.66; 95%CI, 0.41-1.05; P=0.08), 54% (HR 0.46; 95%CI, 0.27-0.78; P=0.003), and 45% (HR 0.55; 95%CI, 0.34-0.90; P=0.02) in the low-, medium-, and high-dose groups, respectively.

The change from baseline in the prebronchodilator forced expiratory volume in 1 second (FEV_1) was greater in the low-, medium-, and high-dose tezepelumab groups than in the placebo group by 0.12 L (95%CI, 0.02-0.21L; P=0.01), 0.11 L (95%CI, 0.02-0.20L; P=0.02), and 0.15 L (95%CI, 0.06-0.25L; P=0.002). Adverse events (AEs) occurred in a similar rate in both tezepelumab and placebo groups, with similar levels of discontinuations, regardless of asthma-related AEs. At least one AE was reported by 62.2% of the placebo group, 66.2% of the low-dose tezepelumab group, 64.8% of the medium-dose group, and 61.6% of the high-dose group. For serious AEs (SAEs), this was 12.2%, 11.7%, 9.0%, and 12.3%, respectively. It was noted that the limited pool of at-risk patients combined with a study period of 1 year only need to be considered when assessing the possibility of infections arising as a result of TSLP inhibition. Thus, confirming the safety of tezepelumab should be prioritised in future studies.

Benralizumab response greater with higher baseline blood eosinophilic counts

In phase 3 studies benralizumab – a humanised anti–interleukin-5 receptor anti-eosinophil monoclonal antibody – significantly reduced asthma exacerbations and improved asthma control for patients with severe, uncontrolled asthma. Evaluation of the effect of baseline blood anti-eosinophil counts and exacerbation history on benralizumab response showed that severe, uncontrolled asthma, greater baseline blood anti-eosinophil counts and more frequent exacerbations were associated with greater treatment effects. In a post-hoc analysis of pooled data from SIROCCO (48 weeks (n=1,204)) and CALIMA (56 weeks (n=1,091)) the annual exacerbation rate was evaluated using the baseline blood anti-eosinophil count and exacerbation history for patients with severe, uncontrolled asthma receiving benralizumab 30 mg every 4 weeks, every 8 weeks, every 4 weeks for the first 3 doses, or placebo. [2,3] These patients had ≥2 exacerbations in the previous year. The annual exacerbation rate was reduced by benralizumab versus placebo at every eosinophil threshold, with a response/eosinophil threshold relationship for dosing every 8 weeks. More exacerbations in the past year were associated with a greater response to benralizumab. Similar trends emerged for lung function and asthma symptom improvements (Table 2). [4]

Table 2 Annual exacerbation rate data from pooled studies [4]

AER comparisons by cumulative baseline blood eosinophil counts and prior exacerbations for pooled data from SIROCCO and CALIMA studies				
Eosinophil counts/ exacerbations and treatments*	**Estimated AER**	**Estimated difference in AER vs placebo**	**AER ratio vs placebo (95% confidence interval)**	**P-value**
≥0 cells/μL[b]				
Placebo (n=770)	1.16			
Benralizumab Q4W (n=748)	0.73	-0.43	0.63 (0.54, 0.74)	<0.001
Benralizumab Q8W (n=751)	0.75	-0.41	0.64 (0.55, 0.75)	<0.001
≥150 cells/μL[b]				
Placebo (n=648)	1.14			
Benralizumab Q4W (n=647)	0.69	-0.45	0.61 (0.51, 0.72)	<0.001
Benralizumab Q8W (n=646)	0.72	-0.42	0.63 (0.53, 0.74)	<0.001
≥300 cells/μL[b]				
Placebo (n=511)	1.14			
Benralizumab Q4W (n=511)	0.68	-0.46	0.59 (0.49, 0.72)	<0.001
Benralizumab Q8W (n=499)	0.65	-0.49	0.57 (0.47, 0.69)	<0.001
≥450 cells/μL[b,c]				
Placebo (n=306)	1.25			
Benralizumab Q4W (n=295)	0.73	-0.51	0.59 (0.46, 0.75)	<0.001
Benralizumab Q8W (n=298)	0.62	-0.63	0.50 (0.38, 0.64)	<0.001
Two exacerbations in the year prior to study entry and ≥300 cells/μL[c,d,e]				
Placebo (n=299)	0.80			
Benralizumab Q4W (n=318)	0.52	-0.28	0.65 (0.49, 0.85)	0.002
Benralizumab Q8W (n=302)	0.56	-0.24	0.70 (0.53, 0.92)	0.010
≥3 exacerbations in the year prior to study entry and ≥300 cells/μL[c,d,e]				
Placebo (n=212)	1.85			
Benralizumab Q4W (n=193)	1.07	-0.78	0.58 (0.44, 0.76)	<0.001
Benralizumab Q8W (n=197)	0.80	-1.05	0.43 (0.32, 0.58)	<0.001

AER, annual exacerbation rate; Q4W, every 4 weeks; Q8W, Q4W for the first 3 doses followed by every 8 weeks thereafter.
[a] In combination with high-dasage inhaled corticosteroid plus long-acting bronchodilator.
[b] Estimates via negative binomial model with adjustment for treatment, region, oral corticosteroid use, and prior exacerbations.
[c] Estimates were re-weighted to account for 2:1 stratification for blood ≥300 to <300 cell/μL.
[d] Estimates via negative binomial model with adjustment for treatment, region, and corticosteroid use.
[e] Asthma exacerbations were defined as deterioration requiring systemic corticosteroids or hospitalisation for athma.

Thus, for patients with severe, uncontrolled asthma, greater baseline blood eosinophilic counts and more frequent exacerbations were associated with greater treatment effects. The researchers stressed that these results should help refine patient selection for benralizumab treatment. [4]

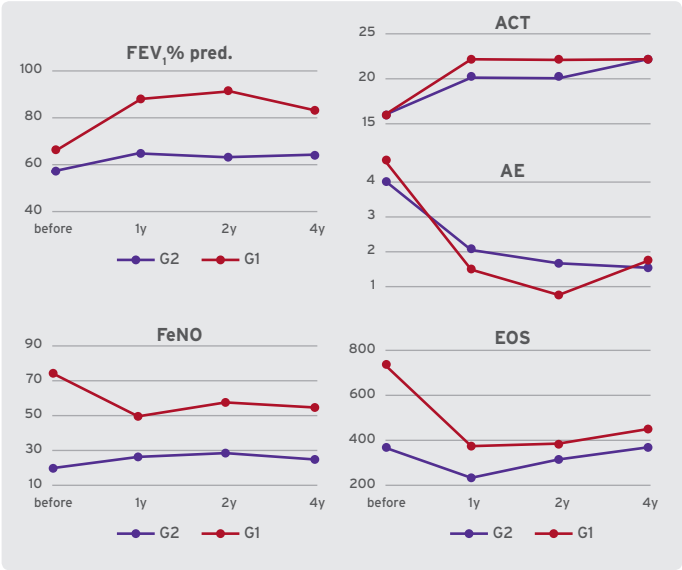
Direct comparison of reslizumab and benralizumab in eosininophilic asthma

The relative treatment effect of reslizumab was compared to benralizumab using prespecified eligibility criteria and a systematic literature review, which identified randomised controlled trials (RCTs). The base case population included severe asthma with blood eosinophils ≥300 cells/μL and ≥2 clinical asthma exacerbation in the previous year. A total of four RCTs (n=1,855) were included. Compared to benralizumab every 4 weeks and benralizumab every 8 weeks, reslizumab reduced clinical asthma exacerbation by 47% (relative risk = 0.53 [95%CI: 0.09-3.09]) and 47% (0.53 [0.09, 3.15]); it improved FEV_1 by 111 mL (-10, 230) and 90 mL (-30, 210), Asthma Control Questionnaire score by -0.37 (-0.63, -0.10) and -0.27 (-0.53, 0.00), and Asthma Quality of Life Questionnaire score by 0.32 (0.03, 0.60) and 0.22 (-0.07, 0.50), respectively. Similar results were found in the sensitivity analyses. The Bayesian probability for reslizumab having fewer total AEs than benralizumab exceeded 92%, yet was not statistically significant. Moreover, reslizumab was significantly associated with fewer discontinuations due to asthma exacerbations vs benralizumab. Despite the fact that the results were always in favour of reslizumab, some endpoints were not statistically significant due to small sample sizes in the base case analysis. [5]

Long-term use of omalizumab effective in severe asthma

The assessment of the effect over four years of omalizumab on severe asthma demonstrated its long-term efficacy of omalizumab on exacerbations and symptoms in these patients. In a subgroup of patients who were identifiable with higher circulating eosinophils and fractional exhaled nitric oxide (FeNO), omalizumab attenuated airway inflammation and reversed airway obstruction, which is suggestive of an effect on airway remodelling. A total of 29 patients (19 female/10 male) with allergic severe asthma and FEV_1 <80% predicted with a mean age of 57 years (range 38-75 years) were evaluated one year before and after treatment with omalizumab. Patients were divided into two groups: group 1 showing persistent FEV_1 normalisation after omalizumab and group 2 had persistent airway obstruction. In all 29 patients, omalizumab treatment was followed by significant improvement in FEV_1, symptoms, exacerbations, and circulating eosinophils. At baseline, group 1 had higher FEV_1 (67 vs 57 %), FeNO (75.8 vs 26.6 parts per billion), circulating eosinophils (738 vs 339 10^6/L), while total IgE (434 vs 343 UI/L), symptoms (16 vs 16) and exacerbations (4.6 vs 4.2)

Figure 2 FEV_1, symptom, FeNO and circulating eosinophils [6]



ACT = asthma control test

were similar to group 2. In group 1, all variables improved during treatment, while in group 2, only symptoms and exacerbations improved (Figure 2). [6]

Extrafine triple therapy reduces exacerbations in GOLD B COPD patients

The current GOLD management strategy recommends the use of a triple combination in group D patients. However, group B includes a significant portion of exacerbating subjects that may also benefit from this treatment. In TRILOGY and TRINITY studies, fixed triple combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium (BDP/FF/G) showed to significantly reduce moderate-to-severe exacerbations compared with inhaled corticosteroids (ICS) or long-acting beta-2-agonists (LABA; BDP/FF) and long-acting muscarinic antagonists (LAMA; tiotropium) in symptomatic, severe-to-very severe COPD (chronic obstructive pulmonary disease) patients with an exacerbation history. In TRILOGY, the pre-dose FEV_1 improved compared to BDP/F by 0.08L and the 2-hour post-dose FEV_1 improved by 0.117L versus BDP/F. The number of exacerbations decreased with 23% on triple therapy versus ICS/LABA. [7] The TRINITY trial also showed beneficial effects of triple therapy, this time compared to tiotropium in patients with symptomatic COPD, FEV_1 <50% and a history of exacerbations. The moderate-to-severe exacerbation rates for patients were 0.46 for triple therapy and 0.57 for tiotropium; resulting in triple being superior to tiotropium (rate ratio=0.80 [95%CI 0.69-0.92]). [8] Singh et al. re-categorised the distribution of these study populations into current GOLD groups and conducted a post-hoc analysis of both studies in which the effect of triple therapy was evaluated in the subgroup of GOLD B patients with 1 exacerbation in the previous year. In TRILOGY, out of 1,367 patients, 55% were classified as B vs 45% as D patients. In TRINITY, out of 2,689 patients, 49% were group B, whereas 51% were group D (≥2 moderate exacerbation and/or ≥1 hospital/emergency room admission). In B patients, triple therapy significantly reduced moderate-to-severe exacerbations by 23% vs ICS/LABA in GOLD B patients in TRILOGY (adjusted risk reduction = 0.77, 95%CI: 0.59-0.99, P=0.042); this was 22% vs LAMA in TRINITY (adjusted risk reduction = 0.78, 95% CI: 0.62-0.97, P=0.023). These findings were consistent with the overall populations. These results demonstrate that BDP/FF/G extrafine triple therapy reduces moderate-to-severe exacerbations also in GOLD B patients with 1 exacerbations in the previous year. [9]

Mepolizumab for high-risk eosinophilic COPD

Mepolizumab, a humanised anti-IL-5 monoclonal antibody which is already approved for the treatment of severe asthma, has shown beneficial effects in COPD patients with high blood eosinophil counts. Mepolizumab reduced exacerbations by approximately 20% overall in patients with high-risk eosinophilic COPD, who were receiving optimal standard-of-care treatment. Whereas in patients with blood counts of at least 300 eosinophils/mm³, exacerbations were decreased by at least 38%. This reduction is comparable to what has been observed in patients with asthma treated with mepolizumab. The METREX trial assessed efficacy and safety of mepolizumab in patients with eosinophilic COPD, and the METREO trial evaluated dosing. Initially, the results in both trials were moderate with mepolizumab consistently lowering the annual rate of moderate-to-severe exacerbations by 18% compared to placebo in the METREX trial and 20% in the METREO trial. No significant differences between 100-mg and 300-mg doses were observed in the latter study, but when data from both trials were combined, the numbers for patients with higher blood eosinophil counts became clinically significant. Patients assessed were classified as having an eosinophilic phenotype (≥150 eosinophils/mm³ at baseline screening or ≥300 eosinophils/mm³ during the previous year). [10,11]

Exposure to disinfectants increases COPD risk

A preliminary observational study of a large cohort of female nurses showed that the COPD risk is higher in those who use disinfectants at least once a week than in those

who do not. Data from the prospective Nurses' Health Study II (n=116,430) was used, participants completed a survey every 2 years from 2009 to 2017. In the cohort – which consisted of 55,185 women with a mean age of 54 years – 663 reported incident physician-diagnosed COPD during the follow-up period of approximately 8 years. An association between incident COPD and high-level exposure to glutaraldehyde, bleach, hydrogen peroxide, alcohol, and quats was found (odds ratio 1.24-1.32; P<0.05 for all). Of those nurses diagnosed with COPD, 37% reported the weekly use of disinfectants to clean surfaces (adjusted odds ratio, 95%CI: 1.22, 1.04-1.43) and 19% reported weekly use to clean instruments (adjusted odds ratio: 1.18, 0.98-1.43). Regression models demonstrated that the risk for COPD was 22% higher for nurses who cleaned instruments and 32% higher for nurses who cleaned surfaces. These results support the existence of an association between exposure to disinfectants and higher COPD incidence in nurses and as a novel hypothesis, merit further investigation. [12]

Higher effectiveness indacaterol/glycopyrronium for COPD exacerbations prevention than salmeterol/fluticasone

In an analysis of the 52-week FLAME study, the number needed to treat for indacaterol/glycopyrronium compared with salmeterol/fluticasone in preventing COPD exacerbations was calculated in patients with a moderate-to-very severe airflow limitation. A total of 5,328 patients were screened of which 63.1% were randomised to each group (indacaterol/glycopyrronium, n=1,680; salmeterol/fluticasone, n=1,682). Of the randomised patients, 3,354 were included in the full analysis set (indacaterol/glycopyrronium n=1,675; salmeterol/fluticasone n=1,679). The number necessary to prevent one exacerbation (mild, moderate and severe) was estimated to be 2.00, for every 2 patients treated over one year with indacaterol/glycopyrronium rather than salmeterol/fluticasone. On average, one exacerbation could be avoided. For the prevention of one moderate-and-severe exacerbation, the number needed to treat was estimated to be 4.76. It was estimated to be 50 in order to prevent one severe exacerbation. The number needed to treat in order to prevent one case of repeat exacerbation (patients presenting with ≥3 COPD exacerbations over a one-year trial period) was estimated to be 32 (Table 3).

Table 3 Number needed to treat with indacaterol/glycopyrronium to prevent one exacerbation of any severity versus salmeterol/fluticasone based on annualised event rates during one year treatment period (FAS population). [13]

Exacerbation severities	Indacaterol/ glycopyrronium 110/60µg o.d. N=1675		Salmeterol/ fluticasone 50/600µg b.i.d. N=1679	NNT
All (mild, moderate or severe) exacerbations, total number*, n(%)	4843 (100		5438 (100)	
Annualised (95% CI)*	3.59 (3.29 to 392)		4.09 (3.75 to 4.45)	2.00
ARR		0.5		
Moderate and severe exacerbations (combined), total number, n(%)	1285 (25.8)		1452 (26.7)	
Annualised (95% CI)*	0.98 (0.88 to 1.10)		1.19 (1.07 to 1.32)	4.78
ARR		0.21		
Mild exacerbations [1] total number, n(%)	3678 (74.4)		3986 (73.3)	
Annualised (95% CI)*	2.46 (2.20 to 2.74)		2.72 (2.43 to 3.03)	3.85
ARR	-	0.26		
Moderate exacerbations [2] total number, n(%)[c]	1056 (21.4)		1211 (22.3)	
Annualised (95% CI)*	0.81 (0.72 to 0.91)		0.98 (0.87 to 1.10)	5.88
ARR		0.17		
Severe exacerbations [1] total number, n(%)[3]	209 (4.2)		241 (4.4)	
Annualised (95% CI)*	0.15 (0.11 to 0.19)		0.17 (0.13 to 0.22)	50.00
ARR		0.02		

ARR = absolute risk reduction; NNT = number needed to treat.

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Exercise, Rehabilitation and Physiology

Pulmonary rehabilitation has shown to be indispensable for pulmonary patients, improving the physical as well as the mental wellbeing of patients. There are many different types of pulmonary rehabilitation that enable physicians and patients to choose the most appropriate program to fit in the patients' daily life activities.

Need for innovative methods of pulmonary rehabilitation

Alternative models for pulmonary rehabilitation have shown short-term benefits on limited outcomes, but results should be cautiously interpreted and not be generalised. Physical activity is effective but its role as adjunct to pulmonary rehabilitation has not been demonstrated. The impact of pulmonary rehabilitation on COPD hospitalisations remains unclear, as results from RCTs suggest; it reduces the number of admissions. Although cohort studies did not confirm this as was recently demonstrated by Moore et al. They compared rates of hospital and general practice-treated acute exacerbations of COPD, prior to and following pulmonary rehabilitation in almost 70,000 eligible COPD patients. It was found that <10% of patients who were eligible for pulmonary rehabilitation were actually referred. Patients who were eligible and referred for – but not necessarily completed – pulmonary rehabilitation did not have less general practice visits or hospitalisations for acute exacerbations of COPD in the year following pulmonary rehabilitation, compared with those who were not referred or compared with the year prior to pulmonary rehabilitation. [1] Thus, there is a clear need for optimalisation of maintenance programs and/or development of novel interventions. [2]

COPD phenotypes

With regard to COPD patients, several phenotypes have been described but the influence of physical activity, skeletal muscle strength and body composition has so far remained unclear. Xavier et al. investigated the phenotypes in 152 COPD patients according to physical activity, body composition and muscle strength in a cross-sectional study. Patients were assessed by lung function, clinical control, Health-related Quality of Life (HrQoL), physical activity, skeletal muscle strength and body composition. The researchers identified three distinct clusters of phenotypes (Table 4).

Differences between the phenotypes concerned the level of activity, with phenotype 1 patients being more physically active compared to phenotype 2 and 3. Phenotype 1 patients also presented a better body composition with 68% of muscle mass and 18% of fat mass. Although phenotypes 2 and 3 were also less physical active, patients in phenotype 2 were older (73 years [68-78]), while patients in phenotype 3 presented a worse QoL (51 Chronic Respiratory Disease Questionnaire total score [46-61]), clinical control (3 Clinical COPD Questionnaire total score [3-4]) and body composition (54% of muscle mass [51-60] and 34% of fat mass [28-38]). No difference in lung function between the three phenotypes was identified. These results suggest that COPD patients present distinct phenotypes according to body composition, skeletal muscle strength and physical activity independent of lung function. [3]

Table 4 COPD phenotypes according to activity level [3]

Phenotype	Number of steps per day
Phenotype 1	6,108 (3,749 - 7,468)
Phenotype 2	1,543 (1,741 - 3,344)
Phenotype 2	2,919 (2,117 - 3,639)

1-min sit-to-stand test score no predictor for long-term outcome after pulmonary rehabilitation

Individual COPD patient benefits in long-term pulmonary rehabilitation are variable and the reasons for this patient variation are still not properly understood. Therefore, a German study investigated whether the 1-min sit-to-stand test as a measure of functional exercise capacity was associated with long-term treatment outcomes after pulmonary rehabilitation. A total of 129 COPD patients were included; they underwent a 3-week inpatient pulmonary rehabilitation program. They were assessed for HrQoL by using the St. George's Respiratory Questionnaire (SGRQ) at baseline and 1 year after pulmonary rehabilitation (scale 0-100, higher scores indicating more limitations). It was found that the 1-min sit-to-stand test score at baseline was (mean±SD) 25.1±7.7 and increased by 4.2±4.4 after pulmonary rehabilitation. The SGRQ total score at baseline

was 48.7±17.3; at 1-year follow-up this was 43.0±21.7. Baseline 1-min sit-to-stand test score (odds ratio = 1.00, 95% CI 0.95 to 1.10) and change in 1-min sit-to-stand test score after pulmonary rehabilitation (1.06, 0.97 to 1.16) were not significantly associated with an improvement in SGRQ total score of 4 or more points after 1 year. The results were similar for baseline and change in 6-min walk distance (6MWD) as predictors in separate analyses. [4]

Pulmonary rehabilitation positively affects QoL

Until recently, the effect of pulmonary rehabilitation on the QoL of COPD patients had not been quantified. In the first study to do so, British researchers showed that the City and Hackney PR service (CHPR) program was effective in improving a patient's experience of living with COPD, with an association between patient experience, symptom burden and psychological well-being.

Within the study period, 36 participants with COPD completed the CHPR program. The majority was male (61%), the mean age was 65.6 years and mean FEV_1 was 53.4%. There was a statistically significant decrease in mean pre-pulmonary rehabilitation to post-pulmonary rehabilitation COPD patient reported experience measure (PREM) 9 scores in the study population (Table 5). [5]

Of the study population 66.67% reported an improved experience of living with COPD following a course of pulmonary rehabilitation. A correlation between primary and secondary outcomes pre and post pulmonary rehabilitation scores was also demonstrated. [5]

Weekend pulmonary rehabilitation program successful

As COPD accounts for a significant number of lost working days per annum, combined with the fact that pulmonary rehabilitation has shown to be very cost effective, it is important to enable patients to take part as much as possible. Nevertheless, patients who are unable to attend weekday classes due to working commitments, often miss out on the benefits of pulmonary rehabilitation. The Adult Respiratory Care and Rehabilitation Team of St. Barts Hospital in London, assessed the feasibility and efficacy of a multidisciplinary pulmonary rehabilitation program for these patients during the weekend. It was demonstrated that a weekend pulmonary rehabilitation program worked well for younger participants who have weekday work commitments. It was well-received by the participants – feedback by questionnaire showed high levels of perceived experience – and the program improved physical endurance of participants. [6]

Table 5 Primary Outcome Data: COPD PREM 9 Score difference [5]

	Pre PR Mean total score (SD)	Post PR Mean total score (SD)	Mean total difference (SD)	95% CI of mean difference	P value
COPD PREM 9	20.8 (8.43)	14.72 (10.59)	5.36 (9.70)	2.08 to 8.64	0.002*

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Interstitial Lung Disease and Vascular Disease

Fuelled by significant advances in understanding pathogenesis as well as the influence of various external and internal factors, Idopathic Pulmonary Fibrosis (IPF) is slowly revealing its secrets. Timely and accurate diagnosis remains particularly important, especially now that the therapeutic options continue to improve.

Favourable outcomes long-term use of pirfenidone

In the PASSPORT study, a 5-year post-authorisation safety registry collected real-world data in European patients who initiated pirfenidone. Patients were followed for up to 2 years.

Table 6 ADRs in safety population (n=1,009) [1]

ADR	Patients with event, n (%)	Exposure-adjusted event rate of ADRs* PEY = 1252.8	Patients with event in first 30 days, n (%)	Patients with event resulting in discontinuation of pirfenidone, n (%)
Any ADR	741 (73.4)	-	379 (37.6)	290 (28.7)
Most common ADRs (≥5% 0f patients)				
Nausea	208 (20.6)	181.2	113 (11.2)	41 (4.1)
Fatigue	187 (18.5)	154.9	101 (10.0)	15 (1.5)
Decreased appetite	163 (16.2)	137.3	69 (6.8)	17 (1.7)
Decreased weight	161 (16.0)	137.3	59 (5.8)	32 (3.2)
Rash	123 (12.2)	107.8	15 (1.5)	32 (3.2)
Diarrhoea	96 (9.5)	88.6	44 (4.4)	21 (2.1)
Dizziness	65 (6.4)	55.1	30 (3.0)	5 (0.5)
Photosensitivity reaction	59 (5.8)	48.7	5 (0.5)	15 (1.5)

PEY = person exposure years

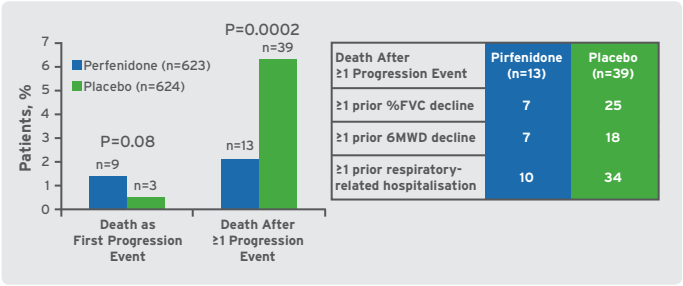
The analysis of this study showed that dose adjustments had a favourable effect on treatment persistence. In general, the results on safety were consistent with the known safety profile of pirfenidone, based on RCT data and post-marketing experience (no new safety signals were observed). Adverse drug reactions (ADRs) occurring during the study were self-reported by patients at follow-up visits every 3 months. In total, 1,009 patients (mean age 69.6 years and 80.0% being male) were enrolled. The median duration of pirfenidone exposure was 14.25 months. The percentage of patients surviving at 1 year and 2 year was 89% and 76%, respectively. The 10th and 20th percentiles of time to death were 0.88 years and 1.63 years. The proportion of patients who had a dose adjustment was 37.0%. ADRs were recorded in 73.4% of patients, 51.1% of whom had an ADR in the first 30 days of treatment (Table 6). [1]

Serious ADRs were reported in 5.5% of patients and ADRs of special interest were reported in 68.7% of patients. In total, 64.9% patients discontinued the study early. ADRs that led to discontinuation of pirfenidone were recorded in 28.7% of patients. [1]

Discontinuation patterns pirfenidone

Patterns of premature discontinuation in patients being treated with pirfenidone in the RECAP study showed that the majority of discontinuations due to AEs were unrelated to IPF progression. AEs were most frequent in patients initiating pirfenidone and in the first year of treatment, suggesting that close monitoring of patients during this time is important to reduce the risk of discontinuation. A total of 1,058 patients was assessed, the median duration of pirfenidone exposure was 88 weeks. Of these, 59.2% of patients discontinued pirfenidone due to AE other than IPF (23.0%), AE related to IPF progression (10.9%), death (9.0%), lung transplant (4.2%) or other reason (e.g. withdrawn consent; 12.2%). The discontinuation rate generally decreased over time for all categories, regardless of prior treatment group. Researchers noted the study had some limitations such as an open-label, uncontrolled design with no applicable sample size or power calculations, survivor bias towards patients who did not die

Figure 3 Incidence of death as a progression event up to 12 months in pirfenidone treated patients versus placebo [3]



Death After ≥1 Progression Event	Pirfenidone (n=13)	Placebo (n=39)
≥1 prior %FVC decline	7	25
≥1 prior 6MWD decline	7	18
≥1 prior respiratory-related hospitalisation	10	34

in the previous phase III studies, and no adjustments were made for patient mortality in discontinuation rates over time as well as results presented derived from a post-hoc analysis. [2]

Multiple progression events reduced with pirfenidone treatment

Nathan et al. determined the incidence of multiple progression events and the proportion of patients with death subsequent to a progression event in the first 12 months of pirfenidone treatment vs placebo. This was done by analysing data from all patients from the pooled phase 3 trials (pirfenidone n=623; placebo n=624) for incidence of events, defined as relative decline in forced vital capacity (FVC) ≥10%, an absolute decline in 6MWD ≥50 m, respiratory-related hospitalisation and all-cause mortality. It emerged that the incidence of progression events was driven by declines in FVC (total events, 202 pirfenidone vs 304 placebo) and 6MWD (265 pirfenidone vs 348 placebo). A lower proportion of patients had >1 event with pirfenidone vs placebo (17.0% vs 30.1%; P<0.0001). Death following ≥1 progression event occurred less often with pirfenidone vs placebo (2.1% vs 6.3%; P=0.0002) (Figure 3). [3]

In conclusion, pirfenidone treatment significantly reduced the incidence of multiple progression events compared with placebo and continued treatment with pirfenidone may confer a benefit despite the occurrence of any single disease progression event. Besides, a multiple events-driven approach may allow for shortening the duration and reducing the number of patients in clinical trials. [3]

Fatigue is a significant issue in IPF which needs to be addressed

Costabel et al. compared fatigue in 1,247 patients with IPF receiving pirfenidone (n=623) or placebo (n=624) in the CAPACITY and ASCEND trials. Fatigue-related AEs occurred in 26.0% of pirfenidone-treated patients and in 19.1% of those receiving placebo. It was found that 80.2% of patients who received pirfenidone and 86.6% who received placebo had only 1 episode of fatigue. Moderate and severe fatigue occurred in 10.8% whereas in 1.1% pirfenidone patients, versus 4.2% and 0.8% in placebo patients. Fatigue-related AEs resulted in dose modification in 17.6% of pirfenidone patients and in 7.0% of those on placebo. Moreover, fatigue occurred sooner after randomisation (median 30.5 vs 36.0 days) and for shorter duration (64.0 vs 109.5 days) in the pirfenidone vs placebo groups, respectively. Researchers concluded that Fatigue-related treatment-emergent AEs (TEAEs) tended to be more frequent yet shorter in duration in patients with IPF who received pirfenidone vs placebo. More patients who received pirfenidone reported fatigue-related TEAEs of moderate severity than patients receiving placebo. A higher proportion of patients with fatigue had a history of depression compared to patients without fatigue and a higher proportion of patients with fatigue also had nausea and other gastrointestinal-related TEAEs. Fatigue in patients in the pirfenidone group required dose modification more often than patients in the placebo group. As fatigue is a common event in patients with IPF, the use of a fatigue questionnaire to quantitatively assess fatigue in IPF patients should be considered in future trials. [4]

No effect of metformin on outcomes in IPF

A post-hoc analysis demonstrated that metformin has no effect on clinically relevant outcomes in patients with IPF. Spagnolo et al. categorised patients randomised to placebo (n=624) in 3 trials of pirfenidone by baseline metformin use. The primary outcome was disease progression (FVC decline ≥10%, 6MWD decline ≥50 m or death). Other outcomes were all-cause and IPF-related mortality, all-cause hospitalisation, absolute and relative ≥10% and ≥5% FVC decline and 6MWD decline ≥50 m. In total, 11.4% patients were metformin users. In unadjusted 1-year analyses, there were no significant differences in disease progression (40.8% vs 40.9%, P=0.997), all-cause mortality (4.2% vs 7.1%, P=0.371) or IPF-related mortality (2.8% vs 4.7%, P=0.470), all-cause hospitalisation (21.1% vs 18.8%, P=0.639), absolute ≥10% (18.3% vs 18.1%, P=0.963) and ≥5% FVC decline (50.7% vs 39.8%, P=0.078), relative ≥10% FVC decline (39.4% vs 28.4%, P=0.055) and 6MWD decline ≥50 m (29.6% vs 26.2%, P=0.547). A significantly higher proportion of metformin users versus those who did not use metformin had relative ≥5% FVC decline (63.4% vs 50.6%, P=0.043). Multivariate analyses

yielded similar results. Nevertheless, it was emphasised that these results did not directly address the potential role of glucose metabolism in IPF and that further research is needed to understand the role of diabetes in IPF and any potential impact on disease outcomes. [5,6]

Safety and tolerability of combination therapy nintedanib/pirfenidone assessed for first time

The first international study of the addition of nintedanib to pirfenidone treatment in patients with chronic IPF provided important information on the safety and tolerability of combination treatment. A total of 89 patients were included in a single-arm, open-label study assessed safety and tolerability of 24 weeks pirfenidone (1602–2403 mg/day) and nintedanib (200–300 mg/day) in patients with IPF with mean predicted FVC percentage of 71.8% and a mean predicted percentage of carbon monoxide diffusing capacity (DLco) of 48.4%. Patients had received pirfenidone for a mean duration of 20.4 months prior to entering the study. A total 82.0% completed 24 weeks of combination treatment at any dose and of these, 77.5% met the primary endpoint. The mean daily doses during combination treatment were 2339.3 mg/day pirfenidone and 255.4 mg/day nintedanib (including titration period doses). It was shown that 25.8% had treatment interruptions; 1.1% had interruption of pirfenidone alone, 18.0% had interruption of nintedanib alone and 6.7% had interruption of combination treatment. Interruptions of combination treatment lasted an average duration of approximately 4 days. Discontinuation of treatment occurred in 18.0% of patients receiving combination treatment, of these, 14.6% discontinued due to a TEAE which were considered treatment related in 12.4%. Discontinuation of combination treatment occurred throughout the trial period and there was no clear pattern in the timing of early discontinuation over 24 weeks of treatment. Overall, 98.9% experienced a total of 670 TEAEs; these TEAEs were considered treatment related in 83.1%. The most common TEAEs were diarrhoea, nausea and vomiting. Severe TEAEs occurred in 20.2% and these were considered treatment related in 6.7%. Serious TEAEs occurred in 18.0% of patients, of which 2.2% experienced one serious treatment-related TEAE, both of which were attributed to nintedanib. No fatal TEAEs were reported during the study. In an exploratory analysis of efficacy, mean (standard deviation) percent predicted FVC and DLco declined by 0.37% (4.44) and 1.86% (6.40) from baseline, respectively, in patients who completed 24 weeks of treatment. It needs to be noted that the patients in this study were already tolerating a stable dose of pirfenidone prior to the initiation of nintedanib, which may explain the higher incidence of TEAEs judged by investigators to be related to nintedanib compared with pirfenidone. [7]

Baseline characteristics different in severe emphysema

Comparing the baseline characteristics in 455 patients with IPF and emphysema ≥15% vs <15% showed differences between these groups. These may impact on whether a patient is likely to be at risk of reduced FVC decline due to emphysema. The majority of patients were male (70.5%), and the mean age was 65.1 years. Emphysema was present in 38.2% of patients of which 118 had emphysema extent 0-15% and 56 had emphysema extent ≥15%. Compared with patients with emphysema 0-15%, those with emphysema ≥15% had significantly higher mean percent predicted FVC (P=0.0009) and significantly lower mean FEV_1/FVC (P<0.0001). No significant differences in baseline FEV_1, DLco, FVC/DLco, University of California-San Diego Shortness of Breath Questionnaire or composite physiologic index were observed. Further research is needed to determine if baseline lung function can predict emphysema extent in patients with IPF. [8]

Biomarkers for lung function decline in development

Jia et al. aimed to identify genetic pathways and gene biomarkers which are associated with lung function decline and other potentially important clinical outcome measures in IPF. This was done by using peripheral blood mononuclear cells (PBMCs) of 122 well-characterised patients with IPF. Researchers used different approaches to identify and select possible biomarkers. The first approach was weighted gene co-expression network analysis constructing 51 gene co-expression network modules. Of these, 4 modules were identified as significantly associated with changes in %FVC from baseline to 52 weeks, with r>0.2 and P<0.05. Approach 2 consisted of mixed-effects models for repeated measures (MMRM) analysis using gene expression as a continuous variable, identifying 265 candidate biomarkers associated with %FVC decline (P<0.05). Approach 3 used MMRM analysis for gene expression as a categorical variable and identified 186 candidate biomarkers associated with %FVC decline (P<0.05). Subsequently, genes correlated with %FVC decline identified by approaches 1, 2 and 3 were compared and the overlap between these sets of genes was used to select 9 genes as candidate biomarkers for further evaluation. Hierarchical clustering of patients with IPF based on gene expression levels of the 9 selected candidate biomarkers

associated with %FVC decline identified 2 dominant clusters of patients (cluster 1, n=57; cluster 2, n=65). Clusters identified by hierarchical clustering of gene expression of these 9 selected candidates biomarkers had significant differences in %FVC decline over 52 weeks. Of the 9 selected candidate biomarkers, 6 were expressed at significantly lower levels, and 1 was expressed at significantly higher levels at baseline in the PBMCs of patients who experienced disease progression compared with those who did not. It was stated that the candidate biomarkers identified in these analyses merit further scrutiny and assessment in an independent cohort to test their reproducibility and robustness in prognosticating lung function decline. [9]

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Lung Cancer

The diagnostic possibilities and the treatment of lung cancer have seen some significant breakthroughs in the last decade, which have impacted the survival rates as well as quality of life of patients. Immunotherapy is widely recognised as a 'game changer', offering patients significantly better perspectives than ever before. It can even be stated that some of metastatic patients have curable disease. Nevertheless, there are still many challenges to overcome, either diagnostic or therapeutic by nature.

Treatment algorithm for advanced disease continues to evolve

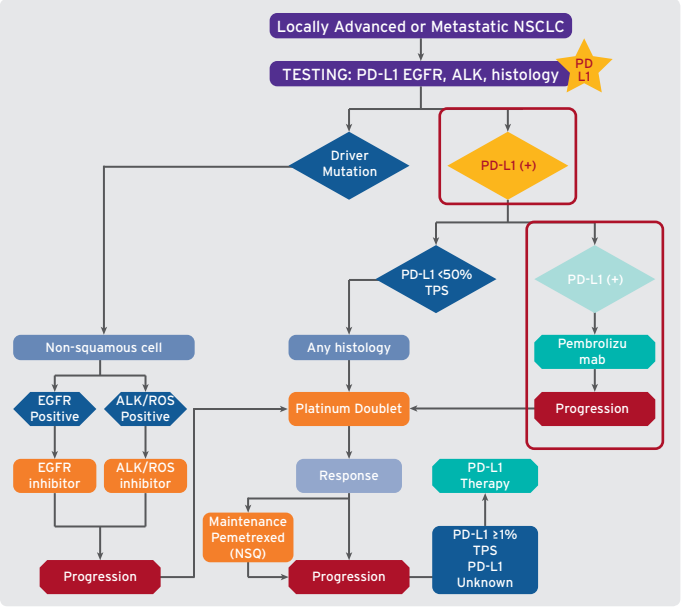
The most significant advancements in lung cancer have been screening which reduced lung cancer mortality by 20%, predicting response to therapy (genetic/proteomic), immunotherapy in 1st and 2nd lines and as adjuvant treatment, crossing blood brain barrier with molecules such as alectinib and uncovering resistance mechanisms to tyrosine kinase inhibitors and circulating tumorous DNA technology. These advances have also meant a shift in therapy algorithm with regard to advanced non-small-cell lung carcinoma (NSCLC) (Figure 4).

However, this year's treatment algorithm will be changed soon too, as the combination of chemotherapy and pembrolizumab will become available.[1]

Poor performance score and pleural dissemination response to nivolumab treatment

A poor performance score (ECOG-PS ≥2) and pleural dissemination are negatively associated with disease control rate by nivolumab. This was shown by a retrospective review of electronic medical records of 216 NSCLC patients who

Figure 4 Treatment algorithm in advanced NSCLC



ALK = anaplastic lymphoma kinase; ROS = proto-oncogene tyrosine-protein kinase

were treated with nivolumab. The mean age was 69 years, 71% was male, 79% was a current or former smoker and 81% had advanced disease. In total, 46% of patients achieved disease control. Current or former smoking, higher serum albumin and squamous cell carcinoma were positively associated with disease control, whereas poor PS, epidermal growth factor receptor (EGFR) mutation, positive anaplastic lymphoma kinase (ALK) translocation, current steroid therapy, tumour involvement in 3 or more organs and metastasis to the central nervous system or pleura, were negatively associated with disease control. In the multivariate analysis, only poor performance score and pleural dissemination indicated a significantly negative association with disease control. The researchers concluded that treatment with nivolumab should be initiated when performance score remains to be deteriorated or has been improved by other treatments such as anamorelin. Also, further prospective studies to investigate the impact of performance score on response with nivolumab should be conducted.[2]

Next treatment after progression on nivolumab

The aim of this French multi-centre study was to evaluate the efficacy of the next treatment after progression on nivolumab in patients with advanced NSCLC. The primary end point of the trial was progression free survival (PFS) on the treatment given after nivolumab. A total of 297 patients who were treated with nivolumab were included. Mean age was 65 years, 69% was male, 90% were smokers; 61% had adenocarcinoma, 29% had squamous cell carcinoma and 10% had other histology. In 68% of the patient population, performance score was 0-1. Nivolumab was given in 40%, 29% and 31% in 2nd, 3rd or ≥4th line treatment respectively. With a 22 months median follow-up, PFS on nivolumab was 2.6 months (95% CI [2.1-3.5]); overall survival was 10.9 months [8.5 – not reached]. Before further treatment could be given, 32% of patients had died and 4% were lost to follow-up. Furthermore, 24% were controlled, 5% were progressive but they did not receive a post-nivolumab treatment, whereas 34% received post-nivolumab treatment. The characteristics of these patients did not differ from those of the overall population. The most frequent drugs used as post-nivolumab treatment were gemcitabine (24%), docetaxel (21%) and erlotinib (15%). PFS after nivolumab treatment was 2.7 months [2.1-3.4]; 2.7 months for gemcitabine, 2.7 months for docetaxel and 1.8 months for erlotinib. The treatment duration was >5 months for gemcitabine and >4 months for docetaxel in 25% of patients. It was thus concluded that nivolumab produced similar efficacy as was seen in phase III trials. Although only 34% of patients received post-nivolumab treatment, 25% of patients had longer treatment duration on gemcitabine or docetaxel.[3]

Real-word immune-related adverse events on nivolumab similar to randomised control trials

Recent real-world data regarding nivolumab use in routine NSCLC treatment, shows promising efficacy which is consistent with results observed in randomised clinical trials. Despite a similar spectrum of immune-related AEs, therapy-related deaths occurred which supports the need for good selection and close monitoring in routine care patients. These findings were obtained from data of 148 patients in 5 lung cancer centres in Berlin. The majority of patients was male, median age was 64 years; 41.9% had adenocarcinoma, 56.1% had squamous cell carcinoma and 2.0% had other histology. Nivolumab was given as 1st line treatment in 1.4% of patients, as 2nd line treatment in 55.4%, as 3rd line treatment in 25.7%; later lines accounted for 17.6% of patients. The responses according to RECIST 1.1 were: complete response (0%), partial response (18.8%), stable disease (36.7%) and progressive disease 44.5%. The overall response rate was 18.8% and the disease control rate 55.5%. The most common immune-related AEs were dermatitis (max. common terminology criteria (CTC) Grade 3), endocrinological disorders (max. CTC Grade 2), pneumonitis (max. CTC Grade 5), colitis (max. CTC Grade 3) and hepatitis (max. CTC Grade 4). Probable therapy-related deaths occurred in 2.7% of patients. [4]

Lower dose afatinib as effective as higher dose

Afatinib has become one of the first-line therapies for patients with stage IV lung adenocarcinoma and EGFR mutation. Although the initial dose was 40 mg daily in most clinical trials, from 28% to 53.3% of patients required a dose reduction due to intolerable side effects. The first retrospective study compared the clinical efficacy and ADRs of different initial doses (40 mg vs. 30 mg daily) of afatinib. The study suggested that the initial dose of 30 mg daily to treat stage IV lung adenocarcinoma shared a similar response rate and PFS as the initial dose of 40 mg daily, but exerted fewer ADRs. A total of 48 patients were included of which 60.5% and 39.5% patients received 30 mg and 40 mg daily as the initial dose of afatinib, respectively. A similar response rate (P=0.0862) was observed, as was a similar disease control rate, and a similar PFS (P=0.8418). Patients in the 30 mg group had significantly lower incidences of ADRs, such as diarrhoea and Grade 3 skin rash. The researchers

indicated that further prospective studies are now required to confirm these findings.[5]

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Pulmonary Arterial Hypertension

Management of pulmonary arterial hypertension (PAH) and its related/underlying conditions have recently seen some significant advances. New drugs have impacted on patients' perspectives and will continue to do so, as insight into the condition steadily grows.

Macitentan yields positive results in inoperable CTEPH

Simoneau et al. evaluated efficacy and safety of macitentan – an endothelin receptor antagonist – in primary inoperable chronic thromboembolic pulmonary hypertension (CTEPH) in the randomised, double-blind MERIT study. Eligible patients were classified as WHO functional class II–IV with pulmonary vascular resistance ≥400 dyn•sec/cm^5 and 6MWD of 150-450 m. Patients with WHO functional class III–IV were allowed treatment with phosphodiesterase type-5 inhibitors (PDE-5i) or oral/inhaled prostanoids. A total of 80 patients were randomised to placebo (n=40) or macitentan 10 mg (n=40) once daily for 24 weeks. The results showed that the primary endpoint and 6MWD significantly improved in the macitentan group compared with placebo. Patients in the macitentan group were less likely to experience WHO functional class worsening compared to placebo. Pulmonary hypertension-related disease progression occurred in 5.0% (macitentan) and 17.5% (placebo) of patients. The most common AEs were peripheral oedema (22.5% for macitentan and 10.0% for placebo) and decreased haemoglobin/anaemia (17.5% vs 2.5%, respectively). Five patients on placebo prematurely discontinued treatment. There were two deaths in the placebo group. It was concluded that macitentan, which was well-tolerated by patients, led to significant improvements in cardiopulmonary haemodynamics and clinical parameters in inoperable CTEPH patients. [1]

Switching to riociguat is safe

Gall et al. examined safety of switching to riociguat which is approved for the treatment of PAH and inoperable or persistent/recurrent CTEPH, from other PAH-targeted therapies. [2,3] This was done by using interim results of the EXPosurE Registry RiociguaT in patients with PAH, an ongoing, international, multicentre, prospective, non-interventional, post-approval study linked with an academic pulmonary hypertension registry (COMPERA). In this analysis, patients with PAH or CTEPH (n=1,201) were combined. A total of 658 riociguat-pretreated and 543 riociguat-newly treated patients were included with the newly treated group containing 105 switched and 438 non-switched patients. No patient received a concomitant PDE5i and among switched patients, 7.6% had switched from an endothelin receptor antagonists (ERA) (bosentan), 1.9% from a prostanoid (iloprost) and 90.5% from a PDE5i (sildenafil or tadalafil). With regard to safety, 48% of patients experienced AEs; 13% experienced drug-related AEs and 27% experienced SAEs (Table 7).

The numbers of AEs of special interest were small with a low rate of study drug discontinuation due to these events. Overall, 82 patients (24 with PAH and 58 with CTEPH: 6.8%) died during the observation period, including 26 non-switched patients and 11 switched patients. The most frequent causes of death were right ventricular failure (n=19) and cardiac failure/congestive cardiac failure (n=4). When compared with the overall population, switched and non-switched.

Patients experienced higher exposure-adjusted AE rates, possibly because they were all newly treated. The researchers concluded that AEs and SAEs reported to date on approximately 1,200 patients from EXPERT are consistent

Table 7 AE and SAE rates

Any AE, n (%)	575 (48)
Discontinued riociguat due to AE, n (%)	59 (5)
AEs experienced in ≥2% of patients, n (%)	
Dizziness	86 (7)
Dyspnoea	71 (6)
Peripheral oedema	65 (5)
Cough	51 (4)
Right ventricular failure	48 (4)
Oedema	42 (3)
Syncope	40 (3)
Pneumonia	39 (3)
Dyspepsia	32 (3)
Epistaxis	32 (3)
Hypotension	31 (3)
Headache	29 (2)
Diarrhoea	27 (2)
Infection	26 (2)
Nausea	26 (2)
Haemoptysis	24 (2)
Iron deficiency	24 (2)
Palpitations	24 (2)
Any drug-related AE, n (%)	152 (13)
Drug-related AEs experienced in ≥2% of patients, n (%)	
Dizziness	40 (3)
Dyspepsia	26 (2)
Any SAE, n (%)	323 (27)
SAEs experienced in ≥2% of patients, n (%)	
Right ventricular failure	47 (4)
Dyspnoea	37 (3)
Pneumonia	31 (3)
Syncope	27 (2)
Any drug-related SAE, n (%)	42 (3)
Discontinued riociguat due to SAE, n (%)	42 (3)

with the known safety profile of riociguat. [4-10] No new safety signals were identified and the rates of haemoptysis and symptomatic hypotension remained low. The tolerability of riociguat appears to be comparable between patients who switched to riociguat from other pulmonary arterial hypertension-targeted therapies and non-switched patients. [11]

Treatment has no impact on QoL in CTEPH

It is evident that a serious condition such as CTEPH can have a debilitating effect on the QoL of patients. The accompanying incapacitating symptoms such as dyspnoea, hypoxaemia, fatigue, syncope can lead to right ventricular dysfunction and death. When surgery is not possible, treatment with riociguat

Table 8 Data on 6MWT before and after treatment [13]

	OMWT data	Baseline	Evaluation 1	Evaluation 2
Subject 1	Initial Borg Index	6	6	3
	Final Borg Index	8	7	2
	Walked distance (m)	188	204	256
	Initial O2 sat. (%)	94	93	98
	Final O2 sat. (%)	92	91	96
Subject 2	Initial Borg Index	3	0	
	Final Borg Index	4	3	
	Walked distance (m)	360	354	
	Initial O2 sat. (%)	93%	93%	
	Final O2 sat. (%)	94%	92%	

can be initiated; however, the impact on the QoL of CTEPH patients is poorly described and results are inconsistent. [12] Blanco et al. evaluated the impact of riociguat treatment in QoL of 3 inoperable, persistent or recurrent CTEPH patients. The QoL was evaluated through the SF-36 Health Survey at the first clinic visit after treatment prescription and after every 2 or 4 months of beginning of riociguat use. Patients also performed the (6MWT at the same visit. Follow-up evaluations were obtained from 2 patients (female, mean ages 64 years). The results showed a consistent improvement in the 6MWT distance by 64m, during 5 months of treatment for the first subject and absolutely no change of the distance for the second subject after 3 months of riociguat. Interestingly, for both subjects, Borg dyspnoea scale results were improved (mean change 3 points for pre and 5 points for post 6MWT). Mean peripheral oxygen saturation was increased for the first subject (from 94 to 98% pre-test and from 92 to 96% post-test) but did not change for the second subject (kept 93% pre and 92% post 6MWT) (Table 8). [13]

However, no change in any physical or mental health scale domain of the SF36 was observed for any subjects. [13]

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Respiratory Failure and Sleep

Sleep apnoea is associated with a variety of health-related conditions, including cardiovascular risk. By unravelling the exact aetiology of the condition as well as the associated risk factors, treatment can be significantly improved.

Sleep apnoea and cardiovascular morbidity and mortality

Sleep apnoea syndrome is a well-known factor for cardiovascular morbidity and mortality. It was hypothesised that the severity of sleep apnoea syndrome is reflected by elevated high-sensitive troponin T (hsTnT). This was shown in a retrospective analysis of 563 consecutive sleep apnoea patients with regard to hsTnT, sleep and overnight respiratory parameters, C-reactive protein (CRP), creatinine/glomerular filtration rate, N-Terminal pro-Brain Natriuretic Peptide (NT pro-BNP) as well as pulmonary function test. Of these patients, 73.7% had positive hsTnT (≥14 pg/mL). There was no association with severity of sleep apnoea syndrome as defined by apnoea-hypopnoea-index (AHI), oxygen desaturation index (ODI) or lowest saturation during the night. It emerged that elevated hsTnT was associated with known coronary artery disease, hypertension and chronic kidney disease. Patients without these co-morbidities did not show clinically relevant elevated hsTnT and therefore significant lower hsTnT compared to patients with at least one known co-morbidity (P<0.001), and slightly less severe results with regard to ODI (p=0.039), arousal index (P=0.042), mean saturation (P=0.001), total sleep time <90% saturation (P=0.012). The number of patients with elevated hsTnT did not change during the positive airway pressure therapy (P=0.245). This was true for patients with (P=0.358) and without co-morbidities (P=0.500). Thus, despite the association of sleep apnoea and cardiovascular sequelae, immediate changes as reflected by changes in hsTnT could neither be found at baseline nor with positive airway pressure therapy.[1]

High prevalence of obstructive sleep apnoea syndrome in nocturnal asthma

Ping Lo et al. assessed the prevalence of obstructive sleep apnoea syndrome among patients with nocturnal symptoms and poorly controlled asthma. Eligible patients were those with nocturnal asthma symptoms despite receiving at least moderate dose of ICS and long-acting bronchodilators (Table 9).

Of the 145 patients recruited, 84.1% of patients underwent a sleep study of which 50.8% had AHI ≥ /h while 18.9% and 4.9% had AHI ≥15/h and ≥30/h, respectively. Patients with obstructive sleep apnoea syndrome had a higher body mass index (BMI) (27.4 kg vs 25.1 kg, P=0.016), bigger neck circumference (36.6 cm vs 34.8 cm, P=0.006) and lower minimum SaO2 (80.7% vs 87.2%, P<0.001). BMI and neck circumference were significantly correlated with AHI (r=0.255, p=0.008 and r=0.247, P=0.007, respectively). There were no significant correlations among age, Epworth Sleepiness Score, FEV1, and bronchial hyperreactivity against AHI. It was concluded that a high prevalence of obstructive sleep apnoea syndrome was found among patients with nocturnal asthma despite treatment with at least moderate dose of ICS and long-acting bronchodilators. Therefore, research on the effect of continuous positive airway pressure therapy on asthma control is needed.[2]

Table 9 Patient characteristics [2]

	All patients (n=122)	Patients with AHI ≥10 (n=41)	Patients with AHI <10 (n=81)
Demographic variables			
Age (years)	50.5 ± 12.0	51.7 ± 12.4	49.3 ± 11.9
Gender (M/F)	37 / 85	64.3%	72.5%
BMI (kg/m2)	25.9 ± 4.8	27.4 ± 5.1	25.1 ± 4.5*
Smoking history (pack-years)	0.2 ± 1.2	0.1 ± 0.6	0.3 ± 1.5
Neck circumference (cm)	35.4 ± 3.5	36.6 ± 3.1	34.8 ± 3.6*
Asthma variables			
FEV1	1.89 ± 0.63	1.90 ± 0.61	188 ± 0.65
FEV1 (% predicted)	79.2 ± 20.5	81.8 ± 19.9	77.5 ± 20.9
FVC	2.53 ± 0.77	2.47 ± 0.79	2.57 ± 0.76
FVC (% predicted)	85 ± 18.1	84.8 ± 20.9	85.1 ± 16.2
Morning PEFR	336.9 ± 100.5	344.0 ± 85.6	332.5 ± 109.2
Evening PEFR	338.8 ± 99.4	340.4 ± 86.7	331.3 ± 107.2
PEFR variability (before sleep study)	25.4 ± 12.7	23.8 ± 12.1	26.3 ± 13.2
Bronchial challenge test (PD20)	1.05 ± 1.39[a]	0.42 ± 0.29[b]	1.43 ± 1.66[c]
- Negative result in BCT	46	21	25
- Failed BCT due to Fev1 <60%	26	5	21
- Defaulted BCT	29	8	21
ACT score	15.0 ± 2.8	15.2 ± 2.8	14.9 ± 2.8
AQLQ score	4.3 ± 0.9	4.2 ± 0.9	4.4 ± 0.9
Nocturnal symptoms score	3.7 ± 0.6	3.7 ± 0.6	3.8 ± 0.6
Medication variables			
High dose inhaled steroids	110	37	73
Medium dose inhaled steroids	10	3	7
Use of LABA	121	41	80
Use of montelukast	91	33	58
Use of tiotropium	37	14	23
Sleep variables			
ESS score	8.3 ± 5.4	8.8 ± 5.4	8.1 ± 5.3
AHI (events/hr)	8.9 ± 10.0	19.6 ± 10.3	3.3 ± 2.4*
Supine AHI (events/hr)	13.6 ± 13.6	26.6 ± 13.0	6.1 ± 6.5*
minSA O2 (%)	85 ± 5.8	80.7 ± 6.6	87.2 ± 3.9*
Comorbidities			
Gerd (RDQ) score)	1.8 ± 1.1	2.0 ± 1.2	1.7 ± 1.0
Rhinitis (ARIA) score	9.4 ± 4.2	8.9 ± 3.7	9.7 ± 4.5

Date are mean ± SD
* p<0.05 campared with subjects with AHI ≥ 10/hr
[a] 21 subjects in all participants had PD20 <6μmol/L for analysis
[b] 8 subjects in the CPAP group had PD20 <6μmol/L for analysis
[c] 13 subjects in the control group had PD20 <6μmol/L for analysis

Acute pulmonary embolism more severe in obstructive sleep apnoea patients

As obstructive sleep apnoea is very common among patients who experienced an acute pulmonary embolism, it is key to characterise clinical features of this population. Berghaus et al. aimed to do so by prospectively screening 253 survivors of an acute pulmonary embolism for sleep-disordered breathing by using portable monitoring during hospitalisation. Nocturnal polysomnography was performed in all patients with an AHI >15/h documented by portable monitoring and in all subjects with a portable monitoring AHI ≤15/h as evidence of increased daytime sleepiness. The results showed that 35.1% of patients were diagnosed to have an AHI ≥ 15/h. In contrast to patients with an AHI <15/h, subjects with moderate or severe obstructive sleep apnoea syndrome are significantly older (P<0.001), have significantly impaired renal (P<0.001) and left-ventricular functions (P=0.003), show significantly elevated troponin I (P=0.005) and D-dimer levels (P=0.024), are hospitalised significantly longer (P<0.001), and have significantly elevated acute pulmonary embolism severity scores (P=0.015). Linear regression analysis revealed that pulmonary embolism patients in the AHI ≥15/h cohort were at significant risk for myocardial injury (P=0.006), elevated pulmonary embolism severity scores (P=0.017) and a prolonged hospital stay (P=0.032). Based on clinical risk stratification and models, patients with no relevant obstructive sleep apnoea syndrome tend to be at a lower risk for short-term mortality (P=0.068). Based on these findings, it was stated that acute pulmonary embolism presents more severely in obstructive sleep apnoea patients compared to patients without relevant sleep-disordered breathing, possibly due to obstructive sleep apnoea-related hypercoagulability.[3]

Sleep-disordered breathing associated with objective sleep duration

Matsumoto et al. investigated the association between sleep-disordered breathing and objective sleep duration. The latter was determined by actigraphy and 3% ODI by pulse oximetry. The severity of sleep disordered breathing was defined by 3% ODI levels: normal <5; mild, 5-<15; and moderate to severe, ≥15. Of a total of 8,294 individuals, 70% was analysed. It emerged that in men (n=1,849) but not in women (n=3,965), the objective sleep duration was significantly shorter, with increases in the severity of sleep-disordered breathing (normal, 375.6±65.3; mild, 363.6±60.5; and moderate to severe, 354.2±68.0 min; P<0.001) while subjective sleep duration was not. The difference between

subjective and objective sleep duration increased according to the progression in the severity of sleep-disordered breathing in both sexes. Participants with obesity had a shorter objective sleep duration, which was worsened by the coincidence of moderate-to-severe sleep-disordered breathing in men. After adjusting for covariates, the 3% ODI was independently negatively associated with objective sleep duration as well as BMI. The researchers concluded that in addition to obesity, sleep-disordered breathing with intermittent hypoxaemia was significantly associated with reduced objective sleep duration in men. Sex difference in the association between sleep-disordered breathing and objective sleep duration might be one reason for differences in the association between sleep-disordered breathing and cardiovascular events in men and women.[4]

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