28th ERS Congress

European Respiratory Society

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PEER-REVIEWED CONFERENCE REPORT

Phenotyping Asthma and Its Therapeutic Consequences
State-of-the-art review on asthma, the role of type2 inflammation, and its targeted therapy.

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Endoscopic Solutions for Difficult-to-Treat Patients
In the last 15 years, several endoscopic procedures have been developed to offer patients with advanced COPD, emphysema, or asthma further therapeutic options, which are complementary to medical treatment.

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PAH: Risk Stratification, Drugs, and Angioplasty
Multi-parameter risk assessment is essential to determine prognosis and to define optimal treatment strategy for patients with PAH. The ultimate treatment goal should be to achieve a low risk profile.

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

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Letter from the Editor

Prof. Richard Dekhuijzen

Dear Reader,

This year's European Respiratory Society (ERS) Congress was, as always, the place to be to get the most recent update in important areas of pulmonary diseases.

Data on the effects and safety of biological agents in the short and long term are accumulating and may guide to further personalise pharmacological treatment. Modulators of IL-5 and IL-4/IL-13 activity show important effects on exacerbation rates, hospitalisations, and dose of oral corticosteroids. Insights in careful patient selection are increasing.

The main changes in the GOLD 2018 recommendations for COPD have been discussed. The 2017 way to categorise patients by splitting level or airflow limitation and levels of complaints and exacerbations connects better to the daily clinical practice than the previous one. Also, increasing data on LABA/LAMA combinations and when they are preferred to LABA/ICS combinations were presented.
Treatment options in lung cancer are increasingly expanding and provide better outcomes for patients. Data on long-term effects are accumulating. The occurrence of sometimes serious adverse events is being more easily recognised. Simultaneously, screening remains an important early stage diagnostic tool. It should be considered in a large number of individuals who may be at high risk of developing cancer.
Treatment options in Idiopathic Lung Fibrosis (IPF) are increasing, including combined treatment modalities. Interesting data have been presented.

If you have not been able to experience these aspects of the ERS yourself, this report will outline the most significant advancements discussed at the conference, and practical advice disseminated there. Besides the topics indicated above, interesting findings regarding lung cancer and pulmonary hypertension are also presented. 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 Center in Nijmegen, the Netherlands. His specific area of clinical and research interest includes asthma, COPD, and inhalation technology.
He studied medicine at the VU 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 330 peer-reviewed papers and many text book 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 between 2008-2010. Until 2016, he was chair of the Medical Staff of the Radboudumc. He is the scientific chair of the Aerosol Drug Management Improvement Team (ADMIT) and chair of the Dutch Inhalation Technology Working Group. Currently, he is chair of the Medical Ethical Committee of the Radboudumc.

Conflict of Interest Statement:
In the last three years, Richard Dekhuijzen and/or his department received research grants, unrestricted educational grants, and/or fees for lectures and advisory board meetings from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sandoz, Teva, and Zambon.

COPD: Triple Therapy, MABA, and Antibiotics

During the session 'Clinical trials in COPD: new results', the results of several newly developed combination therapies, a drug with an overlapping mechanism of action, and new findings of an older drug were presented. These findings might provide new hope for COPD patients.

State-of-the-art

By 2020, chronic obstructive pulmonary disease (COPD) is projected to become the third leading cause of death worldwide [1]. Every year, more than 3 million people worldwide die due to this chronic condition. Patients with COPD have a significantly shorter survival than comorbidity-matched controls [2]. Most common causes of death in patients with COPD are non-respiratory, particularly cardiovascular diseases (myocardial infarction and stroke) and cancer [2]. Previous exacerbations and hospitalisations, comorbidities, reduced lung function, and poor health status are the strongest predictors of death in patients with COPD [3]. Although the treatment of symptoms and prevention of acute exacerbations has improved, few advances have been made to stop disease progression or prevent mortality. To reduce disease burden, smoking cessation, increasing physical activity, and early detection and treatment of comorbidities are essential. A global political and economic effort to reduce tobacco use, to regulate environmental exposure, and to find alternatives to the massive use of biomass fuel are urgently needed, so that COPD will not remain a major healthcare problem. To date, no pharmacological treatment has convincingly demonstrated a significant survival benefit in patients with COPD [4]. For the maintenance treatment of adult patients with moderate-to-severe COPD who are not adequately treated by a combination of an inhaled corticosteroid (ICS) and a long-acting β-agonist (LABA), several triple combinations are in development. Some of them became available recently.

Three landmark triple therapy trials

The fixed-dose combination of an extrafine inhalation solution formulation of the ICS beclomethasone dipropionate, the LABA formoterol fumarate, and the long-acting muscarinic antagonist (LAMA) glycopyrronium is EMA-approved since July 2017 for maintenance treatment of patients with moderate-to-severe COPD who are not adequately treated by ICS/LABA [5]. In three landmark phase 3 randomised controlled trials (RCTs; TRILOGY, TRINITY, and TRIBUTE) this triple therapy reduced moderate-to-severe COPD exacerbations compared to the LAMA tiotropium, the combination of the ICS beclomethasone dipropionate plus the LABA formoterol fumarate, and the combination therapy of the LABA indacaterol and the LAMA glycopyrronium in patients with (very) severe airflow limitation at risk of exacerbations, i.e. with ≥1 exacerbation in the previous year [6-8]. However, the effect of this triple therapy on mortality in patients with COPD remains unexplored.

Pooled analysis

A pooled analysis of fatal adverse events (AEs) in the safety populations from TRILOGY, TRINITY, and TRIBUTE, was conducted by Prof. Leonardo Fabbri (University of Modena and Reggio Emilia, Italy) and others. Time to death was analysed using a Cox proportional hazards model, including only the effect of treatment. Hazard ratios (HRs) of all comparisons between extrafine ICS-containing regimens and ICS-free treatments were calculated [6-9]. The pooled results suggest that treatment with extrafine ICS-containing medications compared to ICS-free treatments may be associated with a lower rate of mortality, which is driven by non-respiratory events, in symptomatic patients with COPD and (very) severe airflow limitation who are at risk for exacerbations. Only with respect to the incidence of non-respiratory deaths, the difference was statistically significant. A lower rate of mortality was also observed in ICS-containing treatment arms compared to non-ICS containing treatment in the IMPACT study [10] and in a pooled analysis from 7 previous RCTs involving more than 5,000 patients with stable COPD [11].

Reason for more optimism

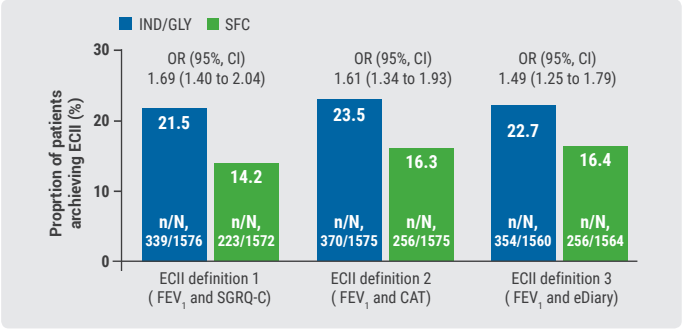
Nevertheless, given the unidirectional effects seen in the analysis of TRILOGY, TRINITY, and TRIBUTE [6-9], there may be reason for more optimism regarding the effect of more intense ICS-containing treatments on survival in

symptomatic patients with (very) severe COPD. Particularly considering that combination therapy, and especially triple therapy, is almost invariably required in these patients either to improve symptoms, quality of life, and/or to reduce exacerbations and hospitalisations [12]. Prof. Fabbri ended his lecture by mentioning that a properly designed and powered new study with mortality as primary outcome in these patients is required for this optimism to be confirmed.

Early clinical important improvement

Exacerbation frequency is relatively low in RCTs, even in studies including exacerbating COPD patients [13]. "So, we need large patient numbers and trials of long duration to show a treatment effect on exacerbations", mentioned Dr Konstantinos Kostikas (Novartis Pharma, Basel, Switzerland). It would be valuable to identify which patients will likely benefit in terms of exacerbation prevention. The FLAME investigators developed a composite endpoint, called early clinical important improvement (ECII), which is defined as the clinically relevant improvement in both lung function (trough FEV_1) and one in seven patient-reported outcomes (PROs), determined at 4 or 12 weeks. The current analysis evaluated whether this novel composite endpoint would be a valuable predictor of exacerbation risk during the subsequent follow-up [14]. The FLAME study directly compared the LABA indacaterol (110 µg) plus the LAMA glycopyrronium (50 µg) once-daily with the LABA salmeterol (50 µg) plus the ICS fluticasone (500 µg) twice-daily [13]. Approximately 18-21% of patients achieved ECII at week 4 or 12 post-randomisation, which was dependent on the ECII definition. More patients achieved ECII during treatment with indacaterol/glycopyrronium compared with salmeterol/fluticasone according to the three evaluated ECII definitions at week 4 (Figure 1).

Figure 1 Percentage of patients who achieved ECII with indacaterol/glycopyrronium compared with salmeterol/fluticasone according to ECII definitions at week 4 [14]



Abbreviations: IND/GLY, indacaterol/glycopyrronium; SFC, salmeterol/fluticasone. n, number of patients who achieve ECII; N, number of patients corresponding to the respective treatment group included in the analysis.

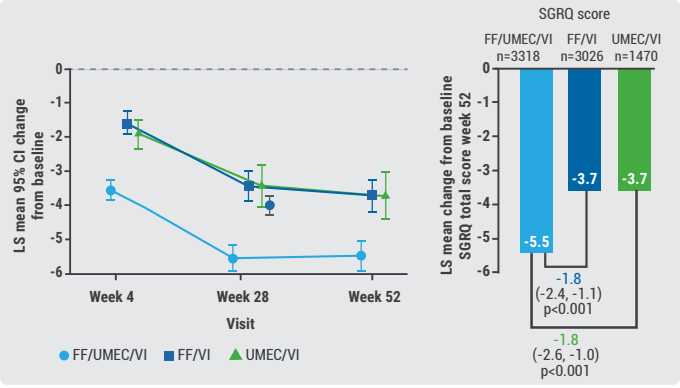
Novel endpoint needs further validation

ECII is a novel composite endpoint based on the clinically relevant improvement in lung function and a patient-reported outcome in the early phase of a treatment intervention that may predict subsequent exacerbation risk. ECII may be useful both in clinical trials and in clinical practice as an early objective measure of how patients will respond to specific treatments in terms of exacerbations. Dr Kostikas indicated that further validation of ECII in other datasets and in prospective trials is needed in order to define the potential clinical application of this composite endpoint.

Another triple therapy combination

IMPACT is a phase 3, 52-week, randomised, double-blind, three-arm parallel group study in symptomatic COPD patients, in which once-daily inhaled triple therapy with the ICS fluticasone furoate, the LAMA umeclidinium, and the LABA vilanterol was compared with once-daily dual therapies of fluticasone/vilanterol and umeclidinium/vilanterol. IMPACT demonstrated that this triple therapy reduced moderate-to-severe exacerbations, and improved lung function and health status, measured by the St George's Respiratory Questionnaire (SGRQ), compared with both mentioned dual therapies. The safety profile of fluticasone/umeclidinium/vilanterol triple therapy was consistent with the profiles of the component drugs. These results were published earlier this year in the *NEJM* [10]. In the IMPACT trial, SGRQ and Patient Global Impression of Change (PGIC) were used to measure health-related quality of life and patient impression of change. Through mapping change in SGRQ total score against PGIC, these synchronised measurements of SGRQ and PGIC allowed different levels of response to be defined. Triple therapy demonstrated clinically meaningful benefits in SGRQ total and domain scores vs both dual therapies (Figure 2). Both moderate and major responder rates also favoured triple therapy [15].

Figure 2 Least squares mean (95% CI) change from baseline in SGRQ total score over time [10]



Abbreviations: FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol

ICS: to use or not to use?

The role of ICS in COPD is an area of intense interest, said Dr Gary Ferguson (Pulmonary Research Institute of Southeast Michigan, USA) at the beginning of his lecture [16]. The recently updated GOLD guidelines recommend initiation of ICS treatment for patients with high exacerbation risk only [17], due to concerns over the risk:benefit ratio of chronic ICS use compared to other therapies. However, real-world studies have shown that ICS are prescribed across the spectrum of disease severity [18]. The benefits of ICS/LAMA/LABA triple therapy are not well studied in certain patient populations, such as patients who are considered to have a lower risk of exacerbations. Budesonide/glycopyrronium/formoterol metered-dose inhaler (MDI), formulated using an innovative co-suspension delivery technology, is a fixed-dose triple combination in development for patients with COPD. "KRONOS was partly a regulatory study to evaluate triple vs dual combination therapy", stated Dr Ferguson. In symptomatic patients with moderate-to-severe COPD, mostly GOLD B, budesonide/glycopyrronium/formoterol (320/14.4/10 µg) MDI provided clinically meaningful improvements in lung function vs budesonide/formoterol, delivered as MDI or dry powder inhalers (DPI, Figure 3). This treatment effect was independent of exacerbation history.

An important endpoint, according to Dr Ferguson, was the rate of moderate-to-severe COPD exacerbations over 24 weeks. Triple therapy resulted in significant, clinically meaningful reductions in exacerbation rates vs glycopyrronium/formoterol MDI, with numerical reductions vs budesonide/formoterol, delivered as MDI or DPI. There was a significant difference between triple and dual therapy with glycopyrronium/formoterol (rate ratio 0.48; 95% CI 0.37-0.64; P<0.0001). The time to first moderate-to-severe COPD exacerbation was also significantly different, again in comparison with glycopyrronium/formoterol (HR 0.593; 95% CI 0.37-0.64; P<0.0001, measured with Cox regression analysis). All treatments were well tolerated with no new or unexpected safety findings. The incidence of pneumonia was similar across treatment groups.

Favourable risk:benefit profile

According to Dr Ferguson, the favourable risk:benefit profile of budesonide/glycopyrronium/formoterol MDI challenges current recommendations for ICS use in COPD. "It raises a question of whether a broader patient population than just those with frequent exacerbations benefit from triple therapy. KRONOS supports the potential use of triple therapy in symptomatic patients with COPD who are not adequately controlled by dual therapy, irrespective of exacerbation risk." The results of KRONOS were published online in *The Lancet Respiratory Medicine* [19].

MABA: dual mechanism of action

"The newly developed compound AZD8871 works both as a LABA, and as a LAMA", declared Dr Ioannis Psallidas (Medical Science Director, AstraZeneca, and University of Oxford, UK) [20]. It is a long-acting, bi-functional bronchodilator agent, combining muscarinic antagonist and β2-adrenoceptor agonist activities in a single molecule (MABA, Figure 4) [21].

Figure 4 MABA: molecular structure concept with 3 elements [20]

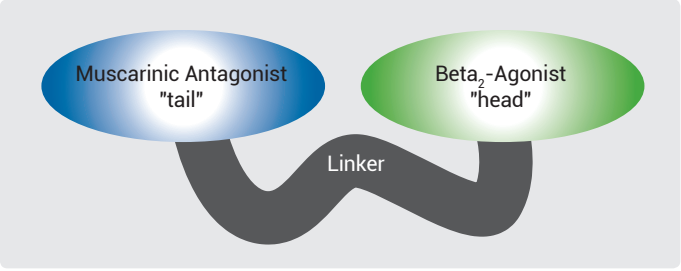
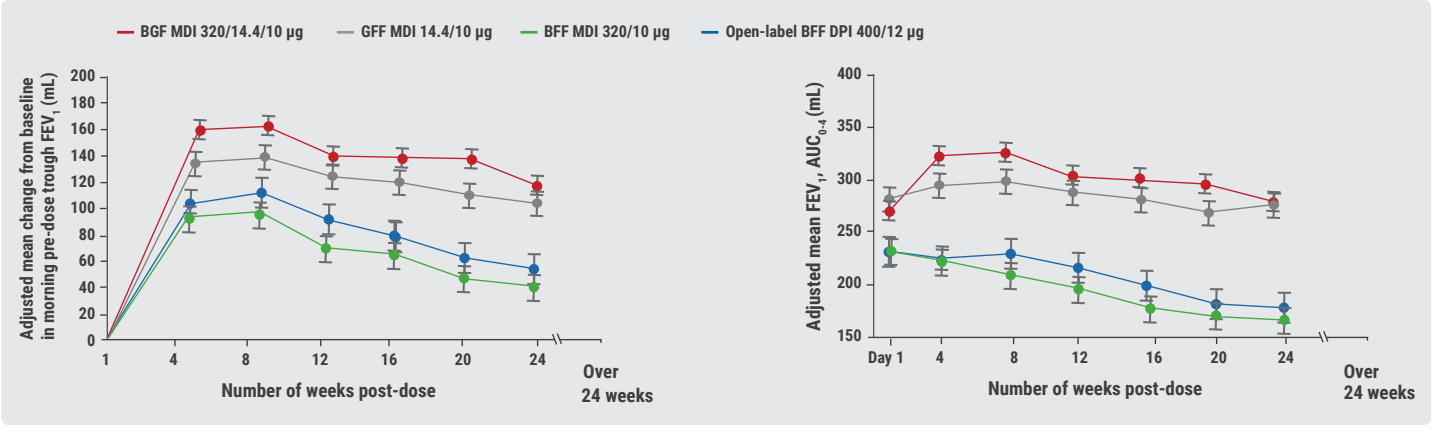


Figure 3 Peak and trough FEV_1 over 24 weeks in KRONOS study [16]



Abbreviations: BGF, budesonide/glycopyrronium/formoterol; GFF, glycopyrronium/formoterol; BFF, budesonide/formoterol; MDI, metered-dose inhaler; DPI, dry powder inhaler

Until now, four phase 1 studies have been performed to study this new MABA. Single and multiple doses of AZD8871 administered in healthy volunteers and patients with asthma or COPD showed that AZD8871 is safe and efficacious in terms of lung function. Especially in COPD patients, a single dose of AZD8871 (400 µg or 1800 µg) demonstrated a sustained bronchodilation after 36 hours. AZD8871 1800 µg showed greater bronchodilation compared to market products (indacaterol and tiotropium) for both peak and trough FEV_1. These results were already presented last year at the ERS 2017 meeting [22].

Improved lung function and symptoms

During the ERS 2018 meeting, Dr Psallidas and others reported results from a phase 2a randomised, double-blind, placebo-controlled trial of repeated doses of AZD8871 100 µg and 600 µg in COPD patients. Patients were treated for 14 days. The primary objective was to evaluate the efficacy of inhaled AZD8871 in patients with moderate-to-severe COPD. Repeated once-daily doses of AZD8871 100 µg and 600 µg exhibited statistically significant and clinically relevant dose-ordered differences vs placebo in trough FEV_1 (primary endpoint). The bronchodilation was sustained over 24 hours with both AZD8871 doses after 14 days of repeated administration. Peak FEV_1 with both doses was clinically and statistically significantly greater than placebo. Furthermore, there was a significant improvement in symptoms for AZD8871 600 µg on days 8 and 14 and a significant reduction of daily rescue medication usage for both doses. The safety and tolerability outcomes were not shown during this presentation, but Dr Psallidas reassured that the overall observed safety and tolerability profile was good for both dose levels.

Novel LAMA under development

Revefenacin is a novel once-daily, lung-sensitive LAMA under development for the nebulised long-term maintenance treatment of COPD. Increased trough FEV_1 has been demonstrated for nebulised revefenacin 88 µg and 175 µg once-daily in patients with moderate-to-severe COPD over 12 weeks [23]. Safety and tolerability were also demonstrated for nebulised revefenacin 88 µg and 175 µg once-daily for up to 52 weeks in patients with moderate-to-severe stable COPD [24]. At ERS 2018, Dr James Donohue (University of North Carolina at Chapel Hill, USA) presented a post-hoc analysis assessing COPD exacerbation data associated with revefenacin 88 µg and 175 µg once-daily in patients with moderate-to-severe COPD who participated in the phase 3 revefenacin clinical trial program [25]. In total, 40-51% of patients in these trials were on LABA or ICS/LABA. Pooled data analysis showed that revefenacin 88 µg and 175 µg once-daily nominally reduced COPD exacerbations relative to placebo. Although the sample size was small, nebulised revefenacin 175 µg once-daily reduced the frequency of exacerbations similar to other LAMAs [26]. Afterwards, Dr Donohue mentioned some limitations of this analysis. Firstly, the design of the 12-month trial was open label, so differential withdrawal may have biased the results. Furthermore, some factors must be accounted for when interpreting these positive trends: the absence of selection for exacerbation-prone patients and the small sample sizes, and therefore the lack of statistical power.

No widespread use of macrolide antibiotics

Despite inhalation therapy, 20-50% of patients experience ≥1 exacerbation per year. Acute exacerbations of COPD (AECOPD) are associated with acute worsening of symptoms necessitating medical intervention. 20-25% of exacerbations require hospitalisation, which has a bad prognosis: 6% in-hospital mortality, 12% mortality within 3 months, and 35% risk of readmission. Macrolide antibiotics possess both anti-microbial and anti-inflammatory properties. The role of azithromycin for the prevention of COPD exacerbations was established in 2011 by the publication of a multicentre RCT, showing a 30% reduction of acute exacerbations during a chronic treatment with azithromycin. However, there has not been a widespread use of azithromycin. "That was mainly because of major safety concerns, being cardiac safety (QTc prolongation) and bacterial resistance", explained Prof. Wim Janssens (University Hospital Leuven, Belgium).

Belgian trial with azithromycin

BACE was a Belgian RCT with azithromycin for COPD exacerbations requiring hospitalisation [27]. The hypothesis of the researchers was that the use of azithromycin in the acute setting would be a major step forward to a targeted clinical use. Some potential advantages might be the reduction of time course and dose of treatment; restriction of treatment to the subgroup with the highest need and at the highest risk; and even being able to disrupt the vicious cycle of admission, AECOPD, and readmission. In the BACE trial, patients with an AECOPD were screened for eligibility within 24 hours and randomly received azithromycin or placebo on top of a standardised therapy. Azithromycin was continued for 90 days. The time-to-treatment failure at day 90 (primary endpoint) was not significantly different (HR 0.73; P=0.0526). Prof. Janssens concluded that azithromycin, initiated in the acute setting of a hospitalised patient with

a severe AECOPD and continued for 3 months at low dose, seems to be safe. It is potentially an effective intervention to reduce treatment failure in the highest risk period [27]. The clinically important reduction of step-up in hospital care, i.e. from ward to intensive care unit or readmission after discharge, with significant reduction of total hospital days and days on intensive care, provides an important health-economic potential. Most of the benefits disappear over time if treatment is discontinued after 90 days, opposing against intermittent treatment regimens.

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Current Look on Asthma: from an Archetype Syndrome to Distinct Subsets and Targeted Treatment Options

Written by: Prof. Zuzana Diamant

Skane University Hospital Lund, Sweden and University Medical Center Groningen, the Netherlands

Apart from academic affiliations, Zuzana Diamant acts as Executive Medical and Scientific Director of Respiratory & Allergy at QPS-NL, a CRO that conducts early phase clinical studies for biotech and pharma companies. In the past 3 years, she received honoraria/consultancy fees from ALK, Aquilon, Acucort, AstraZeneca, Boehringer-Ingelheim, Gilead, HAL Allergy, MSD, and Sanofi-Genzyme.

Asthma is a highly prevalent disorder associated with comorbidities, affecting over 350 million people worldwide and imposing a significant health and socio-economic burden [1]. In 2015, as many as 400,000 asthma deaths have been reported [2].

Traditionally, asthma is diagnosed by (a history of) symptoms including wheeze, dyspnoea, chest tightness, and/or cough in combination with variable, often reversible, airway narrowing. Hallmarks of asthma underlying its clinical presentation include chronic airway inflammation, airway hyperresponsiveness, and structural changes within the airways referred to as "airway remodelling". These characteristics are interrelated and have been shown to be more prominently present in uncontrolled disease [1]. Indeed, severe exacerbations reflecting an intense flair-up of the airway inflammation have been found to cause an accelerated decline in lung function in patients with more severe asthma [3, 4]. This underscores the vital importance of reaching optimal asthma control and preventing exacerbations. Despite increased awareness, patient counselling, implementation of comprehensive, evidence-based guidelines, and recent advances in pharmacological treatment options, data from studies and surveys demonstrate that the vast majority of asthma patients are inadequately controlled [5-7]. According to some studies, the percentage of uncontrolled asthmatic patients in Europe amounts up to 45% [8]. Apart from externally contributing factors such as non-adherence to treatments, inadequate inhalation technique, life style, and environmental triggers, some asthma subtypes (especially severe asthma) may be truly difficult to control due to its heterogeneous nature and (relative) unresponsiveness to standard pharmacological treatment [9, 10].

Patients with severe asthma, defined as those requiring treatment with high-dosed inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids (after other causes for lack of control, including adherence, inhalation technique, and comorbidities have been addressed), comprise approximately 5-10% of the entire asthma population but account for >80% of the total healthcare costs of asthma [9]. To aid the development of targeted treatment options, there is an urgent need to identify precipitating factors and inflammatory pathways of distinct subphenotypes of severe asthma.

From clinical, anatomical, pathophysiological, and inflammatory subsets to molecular pathways

Based on growing insights into the underlying mechanisms of asthma during the past 3 decades, our look on asthma has evolved from the archetypic "generalistic" syndrome to distinct disease subsets [10-12]. As in most diseases, the clinical expression (phenotype) of the different asthma subsets results from the combined effect of an individual's genome and exposome (environmental exposures, microbiome, stress, life style, antibiotics) and their interactions [13]. Consequently, asthma should in fact be evaluated and subsequently treated at several levels: i.e. clinical (age of onset, comorbidities, systemic presentations); anatomical (e.g. bronchiectasis, small airways disease/airway remodelling); physiological (e.g. airway narrowing, (non-)reversibility, airway hyperresponsiveness, airway trapping, ventilation, hypoxemia); and immuno-inflammatory (cells, cytokines, mediators, molecular components) (Figure 1).

Patients with adult-onset asthma have usually more severe disease and are less responsive to standard treatment with ICS compared to those with childhood-onset asthma [14]. Clinical predictors of persistence of adult-onset asthma include: older age, comorbidities (especially nasal polyposis and NSAIDs-exacerbated respiratory disease (NERD)), more severe airway hyperresponsiveness, worse asthma control, and a need of more and higher doses of controller medications [15].

The involvement of small airways, characterised by distal lung inflammation and remodelling, is present in a large proportion of patients and is often a hidden cause of more severe asthma associated with a reduced response to standard therapy and a worse control [16-19]. Therefore, active identification (and subsequent treatment) of these 3-D anatomical site-specific phenotypes should be part of the assessment of severe (uncontrolled) asthma.

In the past two decades, non-invasive sampling methods combined with high-tech omics technologies helped to unravel the heterogeneity of severe asthma. Furthermore, unbiased cluster analyses of system biology-acquired data enabled to link distinct clinical phenotypes to underlying inflammatory and molecular pathways and to identify clinically applicable biomarkers [20, 21].

Figure 1 Diagram depicting multiple levels of (severe) asthma

Type2 asthma

At the end of the last century, insights into the effects of a Western lifestyle on the immune system, complemented with animal data, led to the paradigm of asthma as mainly a T-helper type2 (Th2)-driven disease with eosinophils as key players. In the late 1990s/beginning of 2000s, development and validation of non-invasive airway sampling techniques to assess airway inflammation (especially hypertonic saline induced sputum) [22] allowed identification of inflammatory subsets (phenotypes) in asthma: i.e. eosinophilic, neutrophilic, mixed, and pauci-granulocytic phenotypes [23]. Several "early" studies in (more) severe asthma pointed towards the clinical value to discriminate between non-eosinophilic asthma and eosinophilic asthma, the latter being more frequently associated with more severe exacerbations and accelerated lung function decline [24-26]. As eosinophilic inflammation is generally well-responding to corticosteroids, an RCT showed that guiding (ICS) treatment by levels of sputum eosinophils in moderate-to-severe asthma patients resulted in fewer exacerbations as compared to a standard (British Thoracic Society) treatment regimen based on clinical symptoms and signs [27].

More recently, in a study of patients with mild-to-moderate asthma, gene expression analyses provided insight into the underlying molecular pathways and revealed two distinct profiles, i.e. a Th2-high and a Th2-low profile based on the expression

of IL-13-inducible genes. In contrast to Th2-low patients, those with a Th2-high profile responded well to ICS [28].

In the past decade, emerging evidence pointed towards a key role of the innate immune system in the pathophysiology of type2 asthma [29]. The epithelial cytokines (so-called alarmins) IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are considered to initiate the type2 immune response by activating the innate lymphoid cells (ILCs: ILC1, ILC2, ILC3). Similarly to their "adaptive counterparts", the Th2 cells, activated ILC2s contribute to the immune response in asthma by the release of T(h)2 (now termed type2 or T2) cytokines IL-4, IL-5, and IL-13 [30], thus linking innate and adaptive immunity [31]. Furthermore, both cell types can be activated by cysteinyl leukotrienes (CysLTs) and prostaglandin (PG)-D2 through interaction with the respective receptors (CysLT1R and DP2/CRTH2) on their cell surface [32, 33].

Type2 cytokines are key elements in the immunopathology of eosinophilic asthma which is present in approximately 50% of the asthma population [34]. IL-5 is involved in eosinophil maturation, release from the bone marrow and subsequent recruitment into the airway, while IL-4 and IL-13 are mainly involved in, respectively, IgE synthesis, eosinophil chemotaxis, mucus production, airway hyperresponsiveness, airway narrowing, and remodelling (subepithelial fibrosis, airway smooth muscle proliferation) [35].

Recent evidence from *in vitro* studies suggests that corticosteroid subsensitivity in ILC2 can be induced by exposure to TSLP, a dexamethasone-regulated IL-7R alpha ligand [36]. In line with this finding, increased numbers of ILC2s have been found in patients with more severe and often corticosteroid-insensitive or -resistant asthma [37, 38]. These data support why type2 asthma is often associated with corticosteroid subsensitivity, and therefore requires either treatment with oral corticosteroids or targeted therapies with monoclonal antibodies [39]. Additionally, recent evidence showed that IL-13 may desensitise beta2-receptors in human airways, which further underscores the urge of alternative treatments in type2 asthma [40].

Non-type2 asthma

It has been suggested that non-T2 or T2-low asthma is present in approximately 50% of (adult) patients, has usually a less severe nature, and consists of several different phenotypes and endotypes (a disease subtype defined by a distinct molecular mechanism). Triggers include infections, occupational irritants, and oxidative stress. The mechanisms of non-type2 asthma are not well understood, but may comprise neutrophilic inflammation, Th17 pathway, neurogenic inflammation, barrier defects, airway smooth muscle abnormalities, etc. [35]. Therefore, these asthma subsets usually show a modest or no response to corticosteroids or T2-targeted therapies, while biomarkers and targeted treatment are presently unavailable and, hence, an unmet need.

Airway neutrophilia, often reflecting an underlying respiratory tract infection, can be treated with macrolides, while predominant airway hyperresponsiveness or airway narrowing without a clear inflammatory component can be addressed with bronchodilators or bronchial thermoplasty [41].

However, changes in clinical presentation within individual patients over time are consistent with observations that the underlying immune/inflammatory responses may vary over time and that different inflammatory phenotypes can co-exist in one patient [42]. Hence, regular re-evaluation of an individual's disease status remains important.

Treatments targeting type2-inflammation

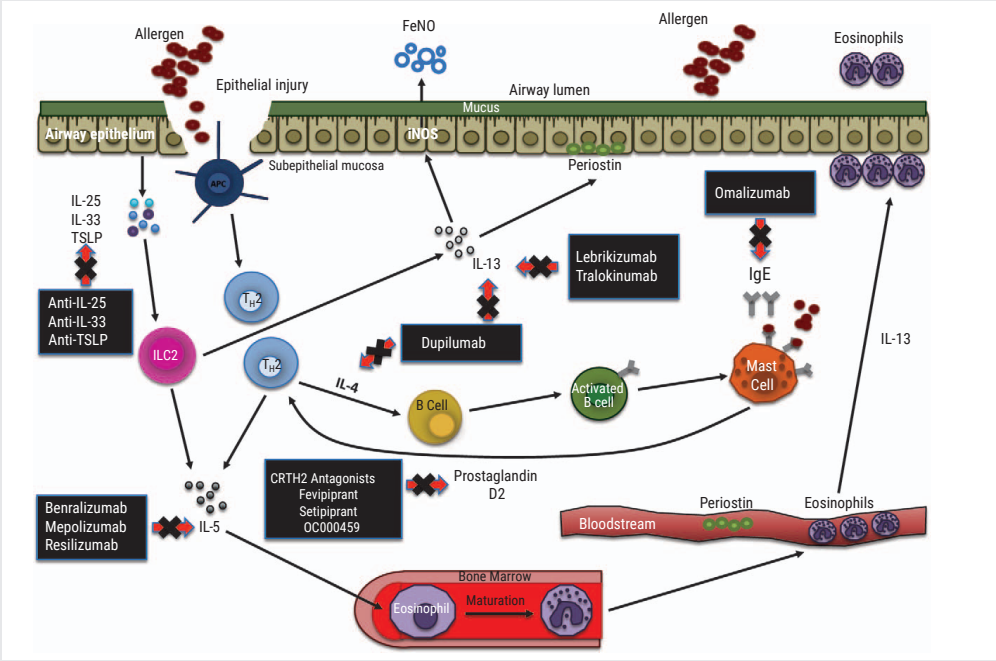
Asthma management has gradually evolved from a "one-size-fits-all" concept into a more personalised approach [1]. While the majority of patients with mild-to-moderate and uncomplicated asthma reach optimal control with ICS-containing therapy, a significant minority with more severe disease fails to reach (optimal) control with ICS as a result of the underlying immuno-patho(physio)logy requiring a personalised approach with targeted therapy guided by biomarkers [39, 43, 44].

Interestingly, guidelines for severe asthma management do not yet insist on standard evaluation of the airway inflammatory components to guide treatment, although the nature of the airway inflammation clearly drives the choice of targeted therapy [1].

For type2 asthma, several add-on treatments targeting different inflammatory pathways are currently available, while several new drugs are in different stages of clinical development (Figure 2) [44]. For patients with a strong allergic component (history and serum IgE ≥30 IU/mL), apart from environmental or life style adjustments, add-on therapy with anti-IgE monoclonal antibodies is recommended for managing asthma (omalizumab is currently the only registered anti-IgE therapy), while for distinct patients with uncontrolled disease and house dust mite allergy, specific sublingual therapy may be considered [1].

More recently, anti-IL-5 targeting monoclonal antibodies have been added to the stepwise approach for management of severe eosinophilic asthma [1]. To guide treatment, eosinophilia is preferably confirmed by induced sputum analysis (sputum eosinophils ≥3%) or by blood eosinophils as a surrogate marker. For blood eosinophils, different cut-offs have been applied across different studies and usually start at least ≥150 cells/μL (to over 300 cells/μL) [45]. Currently, there are three anti-IL-5 monoclonal antibodies available to

Figure 2 Inflammatory pathways and biomarkers underlying type2 asthma and targeted therapies (approved and in clinical development) (44)



Reprinted from Parulekar AD, et al. Role of biologics targeting type 2 airway inflammation in asthma: what have we learned so far? Curr Opin Pulm Med. 2018;24(1):50-5. doi:10.1097/MCP.0000000000000343. By permission of Wolters Kluwer Health, Inc.

treat severe adult asthma: mepolizumab, reslizumab, and (more recently) benralizumab. These agents have a slightly different target (IL-5 or its receptor), reflected by a different pharmacological profile, and offer a substantial reduction in asthma exacerbations and oral steroid intake independent of comorbid allergies [46].

Furthermore, various other monoclonal antibodies to treat asthma are currently under investigation. While targeting IL-13 proved less effective in phase 3 studies, blocking the joint IL-4/IL-13 pathway by targeting the IL-4R alpha with dupilumab showed promising effects on several health-related outcomes in type2 diseases including atopic dermatitis, chronic rhinosinusitis with nasal polyps (CRSwNP), and severe asthma, irrespective of eosinophilia [47-49]. Fractionated exhaled nitric oxide (FeNO ≥25 ppb) is the best currently available biomarker to identify patients responding to IL-4/IL-13 targeted therapy [49]. Importantly, as systemic formulations, targeted therapies also showed beneficial effects on other aspects of asthma, such as comorbidities (e.g. CRSwNP, allergic rhinitis, atopic dermatitis) and may potentially also prove effective for small airways disease.

Future type2 asthma treatments targeting alarmins (e.g. TSLP, IL-33), kinases (e.g. JAK, PI3K), and CRTH2/DP2 seem promising in distinct subsets and the results of phase 3 clinical trials are awaited [10].

Summary

- Chronic airway inflammation is a key feature of asthma and a risk factor of (severe) asthma exacerbations with subsequent accelerated lung function decline.
- Asthma comprises abnormalities at several different levels (including comorbidities and small airways) which should be explored, evaluated, and adequately treated to achieve optimal control.
- Severe asthma (5-10% of asthma population), is difficult to control and accounts for >80% of the total healthcare costs.
- Severe asthma is a heterogeneous disease, roughly consisting of non-eosinophilic and eosinophilic inflammatory phenotypes – the latter being more frequently associated with more severe exacerbations and accelerated lung function decline.
- Eosinophilic severe asthma can be either "allergic" or "non-allergic" – both being driven by type2 (T2) inflammatory pathways including cytokines IL-5, IL-4, and IL-13.
- Although eosinophilic asthma usually responds well to treatment with inhaled corticosteroids, non-allergy-driven T2 asthma (e.g. with chronic rhinosinusitis with nasal polyposis, NERD) is often corticosteroid-subsensitive.
- Several therapies targeting T2 inflammation have been developed.
- Presently available biomarkers of T2 inflammation comprise: sputum and blood eosinophils, FeNO, IgE, and periostin.
- Non-type2 asthma is less well-defined in terms of underlying mechanisms and biomarkers.

Late-breaking news on biologics

During the ERS 2018, long-term safety and efficacy data were presented from 2 'post-phase 3' extension studies with approved anti-IL-5 biologics. The first study, COSMEX, evaluated the long-term safety and effectiveness of mepolizumab in an open label extension of the previous phase 3 COSMOS trials [50]. In this study, 339 patients with very severe, life-threatening, eosinophilic asthma received mepolizumab (100 mg every 4 weeks) for additionally up to 172 weeks. Overall, 93% of patients reported on-treatment adverse events (AEs), which occurred with a frequency of >10%, similar to the previous shorter-term placebo-controlled trials. The frequency of serious AEs was low. Effectiveness of mepolizumab treatment was sustained with substantial reductions in exacerbation rates and oral corticosteroids use, for up to 4.5 years.

The second study, BORA, reported on the long-term safety and effectiveness of benralizumab during an extension of the previous phase 3 trials SIROCCO and CALIMA [51]. In this study, 793 patients with uncontrolled severe eosinophilic asthma were enrolled and 512 continued benralizumab (30 mg every 4 weeks or every 8 weeks), while 281 continued placebo for another 52 weeks as in their previous study. In the BORA study, benralizumab treatment showed similar safety and tolerability outcomes to those in the previous phase 3 trials. Only very few serious AEs were reported, leading to discontinuation in 2-3% of patients. Long-term effectiveness was also similar and consistent with preceding studies, with approximately 75% of patients on benralizumab remaining exacerbation-free.

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Endoscopic Solutions for Difficult-to-Treat Patients

In the last 15 years, several endoscopic procedures have been developed to offer patients with advanced COPD, emphysema, or asthma further therapeutic options, which are complementary to a medical treatment. In addition to the established valve implantation, new approaches have become available. During the symposium 'Endoscopic solutions for obstructive lung diseases', many interventions for these difficult-to-treat patients were discussed.

Endoscopic treatment of emphysema

The aim of (partial) lung volume reduction in emphysema patients is "to make the lung smaller", stated Prof. Felix Herth (UniversitätsKlinikum Heidelberg, Germany) at the beginning of his lecture. Because of the presence of hyperinflated areas in these patients, volume reduction improves breathing mechanics, exercise capacity, and quality of life, and hopefully decreases mortality. For lung volume reduction, five different techniques are available: endoscopic volume reduction surgery (EVRS), valves, coils, steam, and glue.

Evidence for lung volume reduction

Since 2002, multiple studies about lung volume reduction have been published. The most recent one was the LIBERATE study, evaluating the effectiveness of the Zephyr® Endobronchial Valve (EBV®) vs standard of care. This device provided clinically meaningful benefits in lung function, i.e. change in FEV_1 ≥15% of 47.7% of patients in the EBV group vs 16.8% in the standard of care group (P<0.001; Figure 1). Furthermore, exercise tolerance, dyspnoea, and quality of life improved during the follow-up period of ≥1 year (Table 1).

The safety profile in patients with little or no collateral ventilation in the target lobe was acceptable. Pneumothorax was the most common serious AE in the post-intervention period of 45 days, occurring in 26.6% of EBV subjects [1].

Figure 1 Percentage of patients with FEV_1 change of ≥15% after 12 months in the LIBERATE study (primary endpoint) [1]

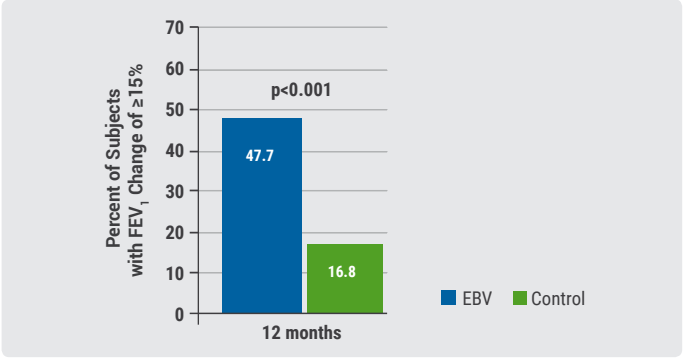

Table 1 Changes in secondary endpoint measures after 12 months in the LIBERATE study [1]

Endpoints	Difference between EBV and standard of care groups	Significance
FEV_1	0.106 L	P<0.001
6MWD	+39.31 metre	P=0.002
SGRQ	7.05 points	P=0.004
Hyperinflation (residual volume)	-522 mL	P<0.001
mMRC	0.8 points	P<0.001
BODE index	-1.2 points	

BODE, Body mass index/airflow Obstruction/Dyspnoea/Exercise capacity; mMRC, modified Medical Research Council dyspnoea scale.

Valves and coils

Multiple studies showed improvements in FEV_1, residual volume (RV), 6-minute walk distance (6MWD), and SGRQ scores after treatment with valves (Table 2) or coils (Table 3) [2-5].

Table 2 Improvement in FEV_1, RV, 6MWD, and SGRQ scores after treatment with valves [2-5]

Trials	Follow-up (months)	FEV_1 (mL)	RV (mL)	6MWD (metre)	SGRQ (points)
STELVIO	6	140	680	74	-14.7
Liberate	12	110	510	38	-7.8
IMPACT	6	120	480	40	-9.6
TRANSFORM	6	140	650	79	-6.5
REACH	6	120	560	42	-14
Emprove	6	100	n.a.	17	-12.3

Table 3 Improvement in FEV_1, 6MWD, and SGRQ scores after coil therapy [6-8]

Trials	Follow-up (months)	FEV_1 (mL)	6MWD (metre)	SGRQ (points)
RESET (n=23)	3	102	64	-8
REVOLENS (n=50)	12	80	21	-11
RENEW (n=158)	12	50	38	-8.1

The RENEW trial is the largest study comparing coils vs standard of care in patients with severe emphysema [8]. "When looking at the patients who responded to the therapy, unfortunately, only 40% had a successful volume reduction", stated Prof. Herth. "However, the improvement in those patients was very strong."

Thermic and chemical procedures

More recently, bronchoscopic thermal vapour ablation (BTVA) and polymeric lung volume reduction (PLVR) have been developed. Both therapies are independent of collateral ventilation and are irreversible. In contrast to valve therapy, BTVA can be used on segmental and PLVR on sub-segmental level. BTVA and PLVR are intended to induce a local inflammation with a following fibrosis and shrinkage, and thus a volume reduction in the treated lung areas. Currently, only patients with predominant upper-lobe emphysema are treated. In some RCTs, both interventions resulted in improvement of lung function, exercise capacity, and quality of life (Table 4). However, the risk profile of PLVR is unfavourable with a high number of adverse respiratory events [9].

Table 4 Improvement in FEV_1, 6MWD and SGRQ scores after BTVA and PLVR [10-12]

Trials	Treatment	Follow-up (months)	FEV_1 (%)	6MWD (metre)	SGRQ (points)
Australian study (n=23)	BVTA	6	17	47	-14
STEP-UP (n=14)	BVTA	12	14.6	10.8	-8.4
Australian study (n=41)	PLVR	6	19	31	-12

Patient selection and team

In order to maximise responder rates, it is essential to have a proper patient selection program. Furthermore, the lung volume reduction procedure and follow-up should be adequate. A multidisciplinary team, consisting of a pulmonologist, thoracic surgeon, and radiologist should meet weekly or every two weeks. In addition, an expert centre is recommended to treat around 1,000 patients per year. In 2017, an expert panel proposed recommendations regarding patient selection and utilisation of these various techniques for the treatment of patients with advanced emphysema [13].

Endoscopic treatment of asthma

The prevalence of asthma is increasing worldwide. However, asthma control is suboptimal in many patients. Worldwide, 250,000 lives are lost annually due to asthma. 80% of costs are driven by 20% of asthma population [14]. The pathogenesis of asthma is characterised by "an inflammatory soup", explained Prof. Pallav Shah (Imperial College London, UK). "We start treatment with inhaled corticosteroids (ICS), but some patients become steroid dependent. We need to find those patients, because they have a high disease burden and account for the majority of costs for asthma care."

Bronchial thermoplasty

Prof. Shah described some endoscopic treatments for severe and/or refractory asthma patients. During bronchial thermoplasty, airway smooth muscle and bronchial epithelial cells are exposed to media (37-70°C) for 10 seconds, to mimic thermoplasty [15]. These interventions have been studied in a spectrum of asthma patients, for example in AIR2 [16] and a couple of years later in PAS2 [17] (Table 5).

Table 5 Bronchial thermoplasty clinical trials [16-20]

Feasibility	n=16	Single arm Safety study Mild to severe asthma	Well tolerated Lung function Symptom-free days ↑ Persistent effect
AIR	n=109	Randomised, controlled Safety and efficacy study Moderate to severe asthma	AQLQ Oral steroids ↓ Exacerbations ↓ Rescue medications ↓ Symptom-free days ↑
RISA	n=32	Randomised, controlled Safety and efficacy study Severe refractory asthma	AQLQ ↑ ACQ Rescue medications ↓ Oral steroids ↓
AIR2	n=297	Randomised, sham controlled Safety and efficacy study Moderate to severe asthma	AQLQ ↑ Severe exacerbations ↓ ER visits ↓ Days lost work/school ↓
PAS2	n=190	Single arm Safety and efficacy study Moderate to severe asthma	Severe exacerbations ↓ ER visits ↓ Hospitalisations ↓ Oral steroids ↓

AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire

Safety of bronchial thermoplasty

An important aspect of these interventions is the short-, medium-, and long-term safety:

- short-term: treatment period of approximately 12-week period;
- medium-term: post treatment period of approximately 46-week period; and
- long-term: post treatment period of approximately 5 years.

With respect to the short-term safety of bronchial thermoplasty, respiratory AEs were transient, typical of airway irritation, and included symptoms of worsening asthma, such as cough, wheeze, increased sputum production, chest pain, and dyspnoea. The median time to onset was 1 day and the median time to resolution was 7 days. All AEs resolved with standard care and no unanticipated device-related AEs occurred. The severity increased with increasing severity of asthma. The medium-term safety is characterised by improvements in Asthma Quality of Life Questionnaire (AQLQ), severe exacerbations, emergency room visits, and days lost from work, school, and/or other activities. During long-term follow-up, respiratory AEs were lower for patients who received bronchial thermoplasty, compared to sham-treated patients. "Everyone wanted to know the long-term safety profile of these interventions", said Prof. Shah. A comparison of the CT scans at baseline versus 1-5 years after bronchial thermoplasty showed no clinically significant findings for any of the CT pairs and no evidence of bronchiectasis, thus supporting long-term safety of the procedure.

Targeted lung denervation and re-surfacing

The parasympathetic nervous system has an important role in the pathogenesis of asthma. In targeted lung denervation, the parasympathetic nerve signalling to and from the lungs is disrupted. The resulting decreased release of acetylcholine provides an 'always-on' effect, leading to relaxation of the basal airway tone and a decreased mucus production. Furthermore, the blunted nerve hyper-responsiveness after the denervation reduces the tendency to exacerbate. The term 'targeted' in this intervention refers to the fact that it is anatomically restricted to the lung, at the depth where the airway nerves are located. Another new technique, which was also discussed by Dr Karin Klooster (University Medical Center Groningen, the Netherlands), is epithelial re-surfacing using a cryospray (RejuvenAir procedure). It utilises a spray of low-pressure liquid nitrogen to quickly freeze the endobronchial tissue at -196°C with a pre-determined dose which ablates the epithelium, hyperplastic goblet cells, and secretory glands, resulting in remodelling/regeneration of neo-mucosa and cilia for more normal mucous production and clearance.

Endoscopic treatment of chronic bronchitis

Compared to COPD patients, chronic bronchitis patients experience greater FEV_1 decline [21], worse health-related quality of life [22], and higher risk of death [23]. Chronic bronchitis has been defined as the presence of productive cough with sputum production for 3 months in 2 successive years. Cough and sputum production in COPD patients may be associated with worse lung function, impaired health status, reduced exercise tolerance, more frequent exacerbations, and increased mortality. Chronic bronchitis may lead to ciliary dysfunction or loss, airflow limitation, and mucus hyper-secretion by overgrowth of goblet cells. These cell types are present to the segmental bronchus level in the airways. Goblet cells and submucosal glands are the end effectors in the pathophysiology of chronic bronchitis.

Endoscopic treatments

For chronic bronchitis patients, the evidence for treatment options is not conclusive or lacking [22]. "So, it is good to look at other opportunities for the treatment of these patients", mentioned Dr Klooster. "There are some new non-pharmacological therapies, but they are still under investigation." Cryotherapy uses nitrogen gas which creates extremely cold temperatures to destroy diseased tissue. The use of a liquid nitrogen metered cryospray is intended to destroy the goblet cells and also the submucosal glands. These cell types are present in the central airways up to the segmental level in the airways. Cryotherapy results in a non-scarring healing effect. In this procedure, the application of liquid nitrogen at -196°C with a pre-determined dose results in rapid endobronchial tissue freezing. The aim is to cryoablate abnormal surface epithelium with overgrown mucin producing goblet cells and adjacent submucosa up to a depth of 0.5 mm. Furthermore, this procedure facilitates normal bronchial epithelium regrowth with ciliated respiratory epithelial cells that will facilitate removal of mucins from the bronchial airways. Finally, the resulting reduction in chronic inflammation leads to increased airway elasticity and diameter. The treatment is well tolerated and is associated with minimal device-related (serious) AEs. The durability of the treatment is not yet known, so "we do not know whether exacerbations will be reduced", added Dr Klooster. "We only know that, in one study, it improved respiratory symptoms and quality of life."

Bronchial rheoplasty

Another treatment which targets the airway epithelium is aimed to restore the goblet cells and submucosal glands and is called bronchial rheoplasty pulsed electric field airway ablation. In this intervention, high frequency short duration energy is delivered to the airway epithelium and submucosal tissue layers, which induces cell death via apoptosis. A pulse electric field is specifically designed to target the end effectors of the goblet cells and submucosal glands. The epithelium regenerates as healthy tissue with fewer goblet cells, hopefully resulting in less mucus production. The Gala Airway Treatment System (RheOx™) was designed to ablate abnormal mucus glands of the epithelium, thereby reducing mucus production and improving symptoms and outcomes in chronic bronchitis patients. The high frequency energy is delivered through the bronchoscope. The FDA gave approval to conduct an early feasibility study in the US, to examine the safety of the RheOx™ system in subjects with chronic bronchitis. Preliminary results showed significant improvement in quality of life.

Lung denervation

The final subject Dr Klooster discussed was targeted lung denervation, which is intended for patients with COPD, so not with chronic bronchitis. It is a single bilateral procedure which takes approximately 1 hour and is performed under general anaesthesia. "We have to use fluoroscopy", she added, "to look at the electrode. Furthermore, an oesophageal balloon is used for real-time localisation of the oesophagus to prevent gastric side-effects." The first-in-human studies showed that targeted lung denervation is safe and feasible.

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PAH: Risk Stratification, Drugs in Development, and the Role of Angioplasty

Multi-parameter risk assessment is essential to determine the prognosis and to define the optimal treatment strategy for all patients. Recent studies have provided strong evidence to support multi-parameter risk assessment in patients with pulmonary arterial hypertension (PAH) at baseline and follow-up. Because a low risk profile is associated with an increased survival, the ultimate goal of treatment should be to achieve a low risk profile at any time.

Risk stratification is fundamental for the determination of optimal treatment strategy in PAH. According to the ESC/ERS guidelines, the choice of the initial PAH therapy is dependent on the risk of the patient (Figure 1) [1]. "For patients with low or intermediate risk (WHO functional class II-III), we have to consider initial monotherapy or initial oral combination therapy", stated Prof. Olivier Sitbon (Hôpitaux Universitaires Paris-Sud, France) with regard to the guideline recommendations. "High risk patients (WHO functional class IV) should be treated with initial combination therapy, including intravenous prostacyclin analogues. We have to reassess the risk on therapy regularly, at least 3-6 months after initiation of the first-line therapy, and regularly during the course of the disease."

A "very famous" table of the 2015 ESC/ERS guidelines divided patients into 3 risk groups based on some clinical variables, imaging, functional tests, and biomarkers (Table 1). "So, functional class is not enough to stratify patients. We have to do a multi-parameter assessment. This table is based mainly on expert opinions, because we don't have large studies."

Table 1 Risk assessment (1-year mortality risk) in PAH according to the 2015 ESC/ERS guidelines [1]

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44,9	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0-2.4 L/min/m^2 SvO_2 60-65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <65%

BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen consumption.
[a] Most of the proposed variables and cut-off values are based on expert opinion.
[b] Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.
[c] Repeated episodes of syncope, even with little or regular physical activity.

Figure 1 Risk stratification according to the ESC/ERS guidelines about PAH [1]

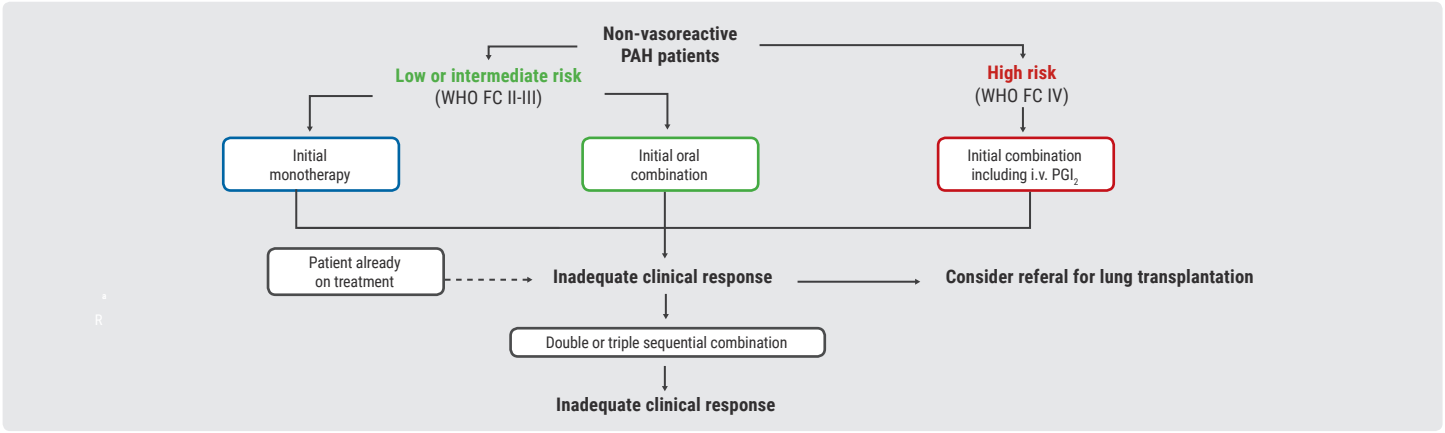
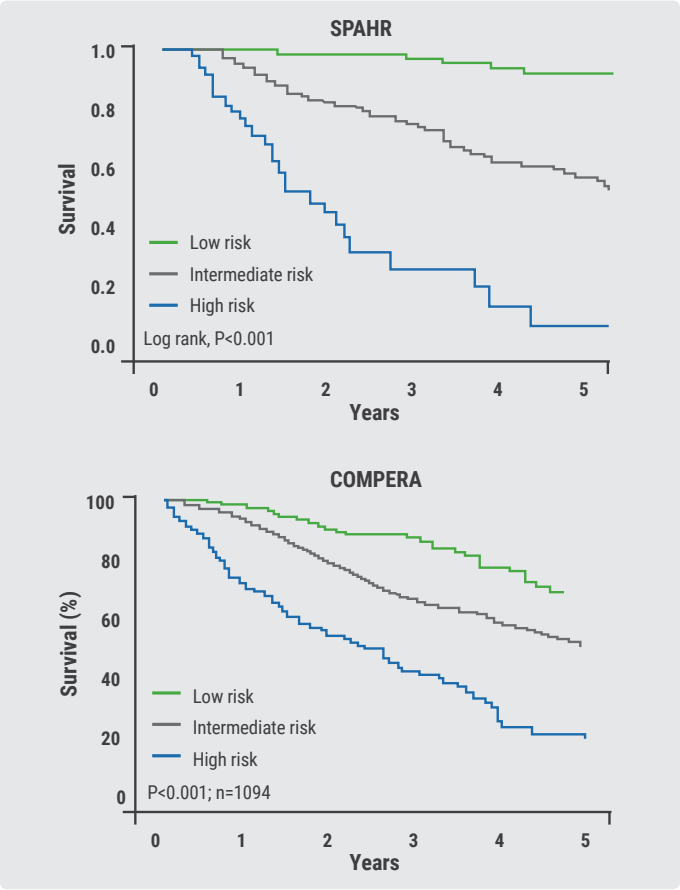


Figure 2 Relationship between risk profile at follow-up and long-term survival rates in the SPAHR and COMPERA registries [2, 3]



Obtain a low risk status!

According to the ESC/ERS guidelines, the goal of treatment in all PAH patients is to achieve a lower risk status during the course of the disease [1]. "The class of this recommendation is very good, class I, but the level of evidence is quite weak, only C, because we don't have prospective studies to demonstrate this." Findings of Swedish [2] and pan-European PAH registries [3] suggest that comprehensive risk assessments and the aim of reaching a low risk profile are valid in PAH.

Obtaining a low risk status at 1 year is associated with a good prognosis, irrespective of the risk status at baseline [2]. "So, this methodology works to determine the risk status at baseline and at follow-up. Importantly, by lowering the risk it is possible to improve the prognosis of the patient." However, in the two registries it was found that around 75% of PAH patients did not achieve a low risk profile at follow-up [2, 3]. "This could be due to the age of these patients," suggested Prof. Sitbon "as the median age in the COMPERA registry was 70 year." A recent publication of two Swedish registries, i.e. SveFPH and the earlier mentioned SPAHR, confirmed the impact of age and comorbidities on risk stratification, showing that most older patients (age >75 years) have an intermediate risk [4]. In addition, a retrospective study from the French pulmonary hypertension registry (n=1,017) found an association between the number of low risk criteria, both at baseline and at follow-up, and survival [5]. The researchers analysed 4 low risk criteria: WHO/NYHA functional class I or II, 6-minute walk distance (6MWD) >440 metres, right atrial pressure <8 mmHg, and cardiac index ≥2.5L/min/m^2.

Improved long-term outcomes

The study by Boucly et al. showed that achievement of multiple low risk criteria is associated with improved long-term outcomes [5]. This effect was more evident at follow-up. The number of non-invasive low risk criteria at follow-up was also associated with prognosis [5].

In another analysis, published in *Circulation*, the French researchers found that the stroke volume index (SVI) and right atrial pressure were the haemodynamic variables that were independently associated with death or lung transplantation [6]. Finally, Prof. Sitbon mentioned another approach to estimate survival at 1 year in PAH patients: the REVEAL score. In this score, next to the 4 low risk parameters, also the subtype of PAH and some comorbidities are included. This score has shown a quite good discrimination with respect to the survival at 1 year [7, 8]. REVEAL identifies 3 good prognostic factors: improvement in BNP level, improvement of 6MWD and improvement in WHO/NYHA functional class."

New therapeutic targets: moving form preclinical data to phase 2 studies

In the pathogenesis of PAH, i.e. the development of vasoconstriction and excessive proliferation, 3 pathways have a central role: endothelin, nitric oxide, and prostacyclin. These pathways provide validated targets for PAH drugs [9]. "Despite the success of these drugs in improving the wellbeing of our patients, we feel that we can do better", said Prof. Martin Wilkins (Imperial College London, UK) at the beginning of his lecture. "The ultimate goal is to stop disease progression and, if possible, reverse the remodelling that characterises PAH. The problem is that we lack knowledge about the interplay between these pathways in the remodelling process. The good news is that we have a number of druggable targets in each of these pathogenic mechanisms (Table 2). The real challenge is to prioritise and identify which of these candidate drugs might offer the most rapid progress." Many of these drugs have entered clinical trials. However, only prostacyclin analogues have reached the phase 3 stadium.

Table 2 Overview of several drug targets in PAH

Mechanism	Target	Drug
Genetic	BMRP2 TGFb (ligand trap)	Tacrolimus Sotatercept
Inflammation	CD20 IL6 receptors	Rituximab Tocilizumab
Metabolic	AMPK Nf2 and NFkB	Metformin Bardoxolone
Oestrogen signalling	Aromatase	Anastrozole
Humoral	ACE2 Mineralocorticoid receptor	Recombinant ACE2 Spironolactone
DNA repair	PARP1	Olaparib

Five key aspects

In selecting the optimal therapy 5 aspects are important according to Prof. Wilkins: the right target, the right tissue, the right safety, the right patient, and the right commercial potential.

"We cannot overemphasise the importance of a valid target. Selecting the right target remains the most important of the 5 aspects and the most important decision we make in drug development."

Balloon pulmonary angioplasty for CTEPH

Pulmonary endarterectomy (PEA) is the recommended treatment for operable patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, up to 40% of them are judged as non-operable due to distal lesions or presence of comorbidities. The management of non-operable CTEPH has recently changed with the availability of effective medical therapies and balloon pulmonary angioplasty (BPA). Most of the leading CTEPH centres worldwide have currently added BPA to their therapeutic options. The current ESC/ERS guidelines state that BPA may be considered in patients with technically non-operable CTEPH [1]. However, there is no consensus about the treatment goals of BPA.

Evidence for BPA

Multiple studies performed in the last six years have shown that BPA improves clinical status and haemodynamics of non-operable CTEPH patients and is associated with a low mortality rate. Based on these findings, Dr Xavier Jaïs (Hôpitaux Universitaires Paris-Sud, France) mentioned that a refined BPA procedure could be considered as a therapeutic approach for this patient population [10-12]. In a French cohort study, which was presented during the ERS meeting, Dr Jaïs and colleagues reported that the outcomes of BPA procedures were better if the surgeons had performed more interventions in the past, providing evidence for a learning curve with respect to the efficacy and safety of this intervention. These and other aspects of BPA are discussed in more detail in a recent review article [13].

BPA-related complications

During the procedure, the main BPA-related complication is vascular injury, which can be associated with or without haemoptysis. The causes of vascular injury include wire perforation, balloon over-dilatation, and high-pressure contrast injection. Signs and symptoms of vascular injury are extravasation of contrast, hypoxaemia, cough, tachycardia, and increased pulmonary artery pressure (PAP). Another major periprocedural complication is pulmonary artery dissection. After the procedure, lung injury can develop due to vascular injury or reperfusion. It is characterised by radiographic opacity with or without haemoptysis and with or without hypoxaemia. The treatment of BPA-related lung injury depends on the severity: in case of mild lung injury, no treatment is needed; for moderate injury, supplemental oxygen; and for severe injury, ventilation is recommended. These topics were discussed during the sixth World Symposium on Pulmonary Hypertension (WSPH), which took place in February/March 2018 in Nice, France.

Outstanding issues about BPA

There are some main outstanding issues in non-operable CTEPH patients. First, there has not been an RCT comparing the safety and efficacy of medical therapy and BPA in newly diagnosed patients with non-operable CTEPH. The currently ongoing RACE study will compare riociguat and BPA in patients with non-operable CTEPH. Furthermore, it is unclear which impact medical therapy prior to BPA has on the safety and efficacy of BPA. Finally, the complementary actions and improvement in pulmonary haemodynamics and decreased risk of BPA-associated complications are unclear.

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IPF: After Decades of Darkness, the Dawn of a New Therapeutic Era

Idiopathic pulmonary fibrosis (IPF) is a rare, but progressive, and ultimately fatal disease. After decades of clinical trials which failed to identify an efficacious treatment regimen, two phase 3 trials with positive results were published in 2011 [1, 2]. The introduction of these two drugs, nintedanib and pirfenidone, meant that for the first time IPF patients had two treatment options that could reduce disease progression. During the ERS meeting [3] and in a quite recent review article [4], Prof. Ganesh Raghu (University of Washington, USA) summarised the key lessons to be obtained from the clinical trials that led to the current international clinical practice guidelines for the treatment of IPF [5].

"Recent trials have focused on targeting a molecule or pathway, based on the pathological plausibility of that strategy", said Prof. Raghu at the beginning of his lecture. The pathogenesis of IPF is characterised by fibrosis due to chronic injury and aberrant wound healing. It includes the following mechanisms: innate immune activation and polarisation, fibroblast accumulation and myofibroblast differentiation, or extracellular matrix deposition and stiffening. These aspects include putative targets of recently developed and studied drugs for the treatment of IPF [6, 7]. In the past 25 years, many trials have been performed using pharmacologic interventions based on biologic plausibility. Notable inclusions were interferons, etanercept, prednisone/azathioprine/N-acetyl cysteine (NAC), monotherapy with NAC, endothelin receptor antagonists, simtuzumab, and monoclonal antibodies (e.g. anti-IL-4/-13). Unfortunately, most of them failed.

Pentraxin-2 stabilises walking distance

Prof. Raghu mentioned some recent RCTs with positive results, beginning with a trial evaluating the effect of recombinant human pentraxin-2 (rhPTX-2) infusions every 4 weeks vs placebo in patients with IPF. Pentraxin-2 (PTX-2) is an innated immune regulatory plasma protein and member of the short pentraxin family of proteins. It binds so-called danger-associated molecular patterns (DAMPs), which have specificity for damaged tissue, and acts upstream in the fibrosis pathway. The PTX-2-DAMP complex binds to the receptor for the Fc portion of IgG (FcγR) on monocytes and macrophages, blocks fibrocyte and profibrotic/proinflammatory macrophage production, and modulates the fibrotic microenvironment. A recently published phase 2, double-blind, placebo-controlled RCT evaluated the effect of rhPTX-2 vs placebo on change in forced vital capacity (FVC) in patients with IPF [8]. Of 117 randomised patients, 116 received at least 1 dose of study drug (mean age 68.6 years; 81.0% men; mean time since IPF diagnosis 3.8 years), and 111 (95.7%) completed the study. The least-squares mean change in FVC percentage of predicted value from baseline to week 28 (primary endpoint) in patients treated with rhPTX-2 was significantly less for those in the placebo group (-2.5 vs -4.8; P=0.001). In contrast, no significant treatment differences were observed in secondary endpoints, including:

- total lung volume (difference 93.5 mL);
- quantitative parenchymal features on high-resolution CT (normal lung volume difference -1.2%);
- interstitial lung abnormalities difference 1.1%; and
- measurement of diffusing capacity for carbon monoxide (DLCO; difference -0.4).

Patients treated with pentraxin had a more or less stable walking distance compared to baseline. Specifically, at week 28 the change in 6-minute walk distance (6MWD) was -0.5 metre for patients treated with rhPTX-2 vs -31.8 metre for those in the placebo group (P<0.001). "This is to my awareness the first clinical trial over the last 25 years to show stabilisation in the 6MWD as a result of IPF treatment", said Prof. Raghu. RhPTX-2 was well tolerated, with no notable difference in AE rate between the two treatment groups [8]. The most common AEs in the rhPTX-2 vs placebo group were:

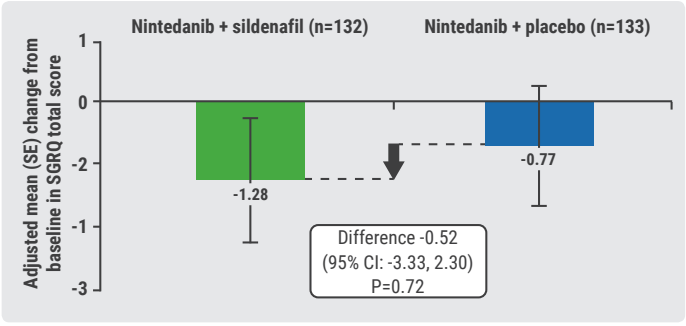
- cough (18% vs 5%);
- fatigue (17% vs 10%); and
- nasopharyngitis (16% vs 23%).

This trial supports further evaluation of the efficacy and safety of pentraxin in patients with IPF.

Combination therapy nintedanib and sildenafil

After studying (new) drugs as monotherapy, in the last years multiple trials with combination therapy have been performed. Firstly, Prof. Raghu mentioned a trial comparing nintedanib with or without sildenafil in IPF patients, published on September 15th in the *NEJM* [9]. Sildenafil, a phosphodiesterase-5 inhibitor, causes predominantly pulmonary vasodilation. It also reduces endothelial cell apoptosis and vascular smooth muscle cell hypertrophy. In the STEP-IPF trial, published in 2010, in patients with IPF and DLCO <35% predicted, there was no significant difference between sildenafil and placebo on the primary endpoint, i.e. proportion of patients with improvement in 6MWD of ≥20% at week 12. Secondary endpoints of change in DLCO, dyspnoea, and SGRQ score were in favour of sildenafil [10]. The INSTAGE trial recently showed no significant difference in the adjusted mean change from baseline in the SGRQ (primary endpoint) total score at week 12 between the nintedanib plus sildenafil group and the nintedanib group (−1.28 points vs −0.77 points, respectively; P=0.72; Figure 1). Also, no benefit from sildenafil treatment was observed with regard to dyspnoea, measured with the use of the Shortness of Breath Questionnaire. Decline in FVC was numerically lower in patients treated with nintedanib plus sildenafil vs nintedanib alone. Nintedanib plus sildenafil was associated with a reduction in risk of an absolute FVC decline of ≥5% predicted or death vs nintedanib alone. The change in FVC from baseline to 12 and 24 weeks in patients treated with nintedanib alone was -25.5 and -58.2 mL, respectively. This is comparable with the changes in FVC observed in the phase 3 INPULSIS trials.

Figure 1 INSTAGE: change from baseline in SGRQ total score at week 12 (primary endpoint) [9]



Diarrhoea was the most frequent AE. Nintedanib plus sildenafil had a manageable safety and tolerability profile, which was consistent with the profiles observed in patients with less advanced disease in the phase 2 TOMORROW trial and the phase 3 INPULSIS trial [11]. In INSTAGE, no new safety signals were identified with either treatment regimen in this very sick patient population. In conclusion, in patients with IPF and a DLCO of ≤35% predicted, ("a very sick patient population", according to Prof. Raghu), nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone [9]. When interpreting these results, it should be taken into account that the participants had a severe impairment in gas exchanges (DLCO ≤35%). This group has largely been excluded from previous trials, and patients were treated for only 24 weeks. The INSTAGE data are important because in patients with severely impaired gas exchange, previously only limited data on the efficacy and safety of IPF treatments, including nintedanib, were available. These results seem to support the use of nintedanib across a range of IPF patients.

Long-term safety and tolerability of nintedanib

The efficacy and safety of nintedanib in IPF patients was assessed in two phase 3, placebo-controlled INPULSIS trials (n=807). Patients who completed the 52-week treatment period in an INPULSIS trial could receive open-label nintedanib in the extension trial, INPULSIS-ON (n=734, 91%). In INPULSIS, 59% of patients had received nintedanib and continued nintedanib in INPULSIS-ON. The remaining 41% had received placebo in and initiated nintedanib in INPULSIS-ON. The results from INPULSIS-ON were published in *The Lancet Respiratory Medicine* on September 14th [12]. In the INPULSIS-ON trial, the annual rate of decline in FVC over a median of almost 4 years was -135.1 mL/year. This was consistent with the annual rate of FVC decline in patients treated with nintedanib in the INPULSIS trials (-113.6 mL/year in patients treated with nintedanib). These data suggest that the effect of nintedanib on slowing disease progression of IPF persists beyond 4 years. The incidence rate of acute exacerbations in INPULSIS-ON was similar to that of INPULSIS. The safety profile of nintedanib in INPULSIS-ON was also consistent with that observed in INPULSIS. Diarrhoea was the most frequent AE in INPULSIS-ON, as was the case in the above mentioned INSTAGE trial. In total, 5% of patients who continued nintedanib and 10% of patients who initiated nintedanib permanently discontinued treatment because of diarrhoea. The AE that most frequently led to permanent discontinuation was progression of IPF (12% patients continuing nintedanib and 14% of patients initiating nintedanib) [12].

Relation between gastroesophageal reflux and IPF

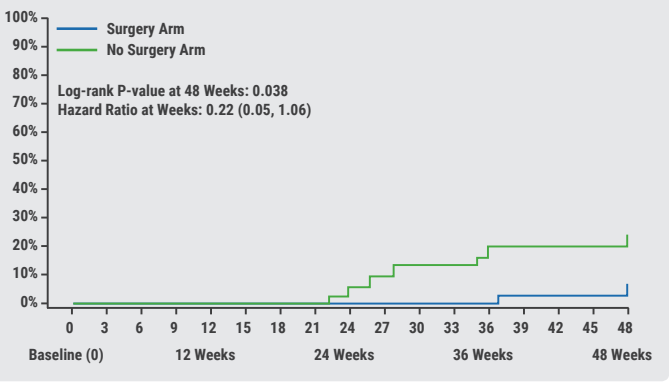
There is a possible relationship between abnormal gastroesophageal reflux (GER) and the development or progression of IPF, and risk of acute exacerbation. The

hypothesis is that, in a genetically predisposed person, recurrent injury to epithelium caused by micro-aspiration of contents of gastric juice (refluxate), leads to alveolar damage and pulmonary fibrosis and ultimately to the manifestation of (pre-existing) IPF. "GER has a high prevalence in this patient population, so we need to prevent micro-aspiration", concluded Prof. Raghu based on this concept. Retrospective data showed that Nissen fundoplication, a laparoscopic surgical procedure to treat gastroesophageal reflux disease (GERD), improves survival. Prof. Raghu and others undertook a multicentre, randomised, controlled phase 2 trial, the WRAP-IPF study. The results were published recently in *The Lancet Respiratory Medicine* [13]. The WRAP-IPF trial determined whether treatment of abnormal acid GER with laparoscopic anti-reflux surgery reduced the rate of disease progression of IPF. Patients with IPF, abnormal acid GER (DeMeester score of ≥14.7), and preserved FVC were recruited from 6 academic centres in the USA. Concomitant therapy with nintedanib and pirfenidone was allowed. Of the 72 originally screened patients, 58 patients randomly received surgery or no surgery. A total of 27 patients in the surgery group and 20 patients in the no surgery group had an FVC measurement at 48 weeks (P=0.041). The primary endpoint was change in FVC from randomisation to week 48. Intention-to-treat analysis (adjusted for baseline anti-fibrotic use) demonstrated an adjusted rate of change in FVC over 48 weeks was:

- -0.05 L (95% CI -0.15 to 0.05) in the surgery group and
- -0.13 L (95% CI -0.23 to -0.02) in the non-surgery group (P=0.28).

Acute exacerbation, respiratory-related hospitalisation, and death was less common in the surgery group, but the difference was not statistically significant. The time to composite endpoint was significantly different (Figure 2).

Figure 2 Kaplan-Meier estimates of time to the composite endpoint of 10% decline in FVC or death in the WRAP-IPF study



In conclusion, the WRAP-IPF study showed that laparoscopic anti-reflux surgery in patients with IPF and abnormal acid GER is safe and well tolerated. Abnormal acid GER was normalised after surgery in all patients. There was no statistically significant impact of laparoscopic anti-reflux surgery on FVC decline. However, according to Prof. Raghu, secondary endpoints are encouraging and warrant a large, well powered, randomised controlled study of anti-reflux surgery in this select population of patients with abnormal acid GER.

Lessons learned & treatment guidelines

Based on the published reports of clinical trials since 1991, Prof. Raghu summed up some lessons learned. "First, we have learned that what works or worked at the bench and is biologically plausible does not necessarily work at the bedside", he stated. "Standard physiological/clinical assessment of disease progression is still the current standard of assessment of treatment response." With respect to the treatment of IPF, he mentioned the following take-away: "Preventive measures might minimise risks for micro-aspiration. Cellular, molecular, and genetic biomarkers are being considered to stratify treatment in new clinical trials. Recent pharmacogenomic data from a subgroup of patients participating in the PANTHER trial is encouraging for the use of NAC in some patients, based on a specific genotype [14]." In the IPF treatment guidelines, there are currently no pharmaceutical treatments with a "strong yes" recommendation (Table 1). "This void needs to be filled in, hopefully based on the finding of new clinical trials."

Table 1 Treatment recommendations in the 2015 international guidelines for the treatment of IPF [5]

Strong yes	Weak yes	Weak no	Strong no
Lung transplant Oxygen	Antacids Nintedanib Pirfenidone	Sildenafil NAC monotherapy IPAH drugs (for IPF-PH)	Warfarin Ambrisentan Azathioprine/presdnisone/NAC Imatinib

'Yes' recommendations mean: The majority of patients would want the intervention, but a significant minority would not. 'No' recommendations mean: The majority of patients would not want the intervention, but a significant minority would.

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Oncology: Rationale of (Targeted) Treatment and Use in Brain Metastases

Our insights in the pathophysiology and the development of new targeted treatment options are going hand in hand in hand. "So, it is not possible to discuss the biology of lung cancer without mentioning treatment", said Dr Céline Mascaux (Aix-Marseille University, France) at the beginning of the first lecture of a state-of-the-art session about thoracic oncology. During the other lectures of this session, the treatment of brain metastases and comorbid interstitial lung diseases (ILD) were also discussed.

Up to approximately 2010, there were only a few therapeutic options for patients with (non-)small-cell lung cancer (SCLC and NSCLC), i.e. surgery, radiotherapy, and chemotherapy. "Since then, two therapeutic revolutions based on our understanding of the tumour biology occurred", added Dr Mascaux. "The first one is the development of targeted therapies against different oncogenic drivers." This coincided with a paradigm shift: from a 'one size fits all' strategy to a personalised strategy, in which the targeted drug was chosen based on the characteristics of the tumour cells, such as genetic alterations.

EGFR-targeted treatments

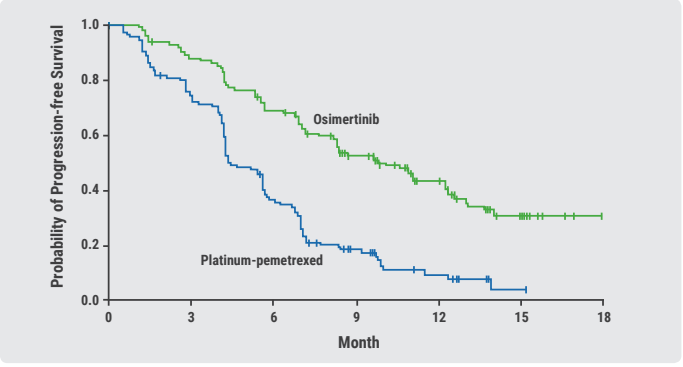
The development of targeted treatment for (N)SCLC started with the inhibition of the epidermal growth factor receptor (EGFR) [1]. Activation of EGFR induces the activation of various metabolic pathways, leading to survival of the tumour cells, increased proliferation, and less apoptosis (programmed cell death). In 2004, several *EGFR* mutations were discovered. These mutations could confer a higher sensitivity for treatment with EGFR-directed tyrosine kinase inhibitors (EGFR-TKIs). Furthermore, it was discovered that these mutations are associated with several clinical characteristics. They were more frequently detected in females, patients with adenocarcinoma, Asian people, and non-smokers. However, still only 60% of patients with these characteristics will have an *EGFR* mutation, and patients with other characteristics can also have an *EGFR* mutation-positive tumour. During the development of an increasingly personalised treatment of lung cancer patients, IPASS was the first trial showing that the best treatment for patients could be chosen by using a biomarker.

In the IPASS trial, it was found that the progression-free survival (PFS) in *EGFR* mutation-positive and -negative patients was significantly different (P<0.0001) [2]. Based on these findings, Dr Mascaux advised to give an EGFR-TKI instead of chemotherapy in the first-line setting in case of an *EGFR* mutation-positive NSCLC. "In contrast, if this mutation is not present, you should better give chemotherapy and not an EGFR-TKI." These data have meanwhile been confirmed in clinical trials studying other EGFR-TKIs.

Resistance

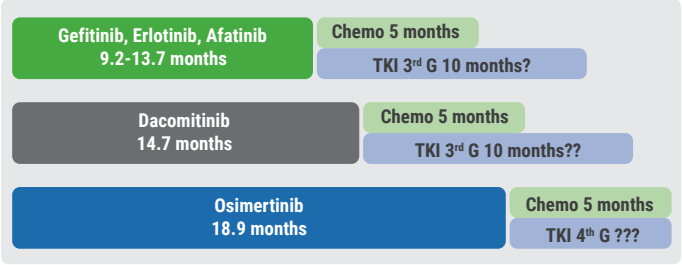
There are different types of *EGFR* mutations. Some are associated with sensitivity for certain drugs, such as a deletion in exon 19 and 21, while other mutations are associated with resistance. The most frequently detected resistance-associated mutation is T790M, located in exon 20, which leads to secondary resistance after first- or second-line treatment with an EGFR-TKI. In clinical studies, third generation EGFR-TKIs were found to inhibit T790M-mutated tumours with a very high sensitivity. The first trial showing this effect, was AURA3. After a median follow-up period of 8.3 months, PFS was significantly longer in the osimertinib group than in the platinum–pemetrexed group (median 10.1 months vs 4.4 months; HR after adjustment for Asian or non-Asian race, 0.30; P<0.001) (Figure 1) [3]. "The combination of different lines of EGFR-TKI therapy has a more than additive effect", mentioned Dr Mascaux. "The PFS would not increase to 10 plus 10 months, but the patient can reach a PFS of 50 months."

Figure 1 PFS in the intention-to-treat population of the AURA3 study (primary endpoint) [3]



Subsequently, osimertinib has been tested in the first-line setting. In the FLAURA study, osimertinib was compared with a standard of care EGFR-TKI, either gefitinib or erlotinib, as first-line treatment in patients *EGFR*-mutated advanced NSCLC. The median PFS was 18.9 months for osimertinib vs 10.2 months for standard of care (HR 0.46; P<0.0001) [4]. The PFS has progressively increased using first-, second- and third-generation EGFR-TKIs (Figure 2). Fourth-generation TKIs are still under development, and while they may already be efficacious they are not yet used in the clinical setting."

Figure 2 PFS using first-, second-, and third-generation EGFR-TKIs



Loss of T790M does not indicate re-sensitisation to a first-generation EGFR-TKI, but often indicates overgrowth of a competing resistance mutation. Dr Mascaux advised to look out for a range of rare genetic resistance mechanisms, such as KRAS mutations, RET fusions, and FGFR fusions.

ALK inhibition, guidelines, and liquid biopsies

The development of ALK inhibition went faster than EGFR inhibition. Currently, there are several options for the first-line treatment of *ALK*-positive NSCLC: first crizotinib [5], then ceritinib [6], and finally alectinib, which was studied in two patient populations: in Japan [7] and in Europe and the United States [8]. The guidelines of the National Comprehensive Cancer Network (NCCN) advise first to establish the histological subtype of the tumour with adequate tissue for molecular testing and to consider re-biopsy if appropriate. The recommended molecular tests depend on the tumour type (Table 1) [9].

Table 1. NCCN guidelines recommendations [9]

In case of …	Molecular testing
Adenocarcinoma Large cell NSCLC not otherwise specified	*EGFR* mutation testing (category 1) *ALK* testing (category 1) *BRAF* and *ROS* testing Testing should be conducted as part of broad molecular profiling
Squamous cell carcinoma	Consider *EGFR* mutation and *ALK* testing in never smokers or small biopsy specimens, or mixed histology Consider *BRAF* and *ROS1* testing Testing should be conducted as part of broad molecular profiling

Another subject Dr Mascaux discussed was the development of liquid biopsies, which determines the presence of circulating tumour cells in the blood [10]. This diagnostic tool is easy for both patient and doctor. In the AURA3 and FLAURA studies with osimertinib, tumour cells in the blood and in the tissue showed a high concordance with respect to their molecular biology. "However, a negative blood test could be false negative, so a tissue sample should still be analysed."

Immunotherapy

Next to targeted therapies, another important development in the treatment of lung cancer, is that of immunotherapy. These drugs are directed either against PD-L1 which is expressed on T-cells, or PD-1 on tumour cells [11]. "In some patients, immunotherapy results in a durable response which can endure years after stopping the drug", stated Dr Mascaux. "The more mutations are present in the tumour (i.e. higher mutational load), the better the response to immunotherapy. We need better biomarkers to predict the sensitivity for immunotherapy. Furthermore, combination therapy is needed to combat the heterogeneity of the tumour."

Pathogenesis of brain metastases

According to Dr Torsten Blum (Helios Klinikum, Berlin-Zehlendorf, Germany), brain metastases can be present already at diagnosis of lung cancer. A population-based study from the USA showed that patients with lung cancer had the highest proportion of brain metastases at time of primary cancer diagnosis (10.8%) among the evaluated cancer types [12]. Of the brain metastases, approximately 10-20% are synchronous [13] and 40-50% metachronous [14]. Brain metastases are most frequently located in the cerebrum (80%), followed by the cerebellum (15%) and brain stem (5%) [15]. "With respect to the pathogenesis of brain metastases, we should be aware of the blood-brain barrier [16]. In its function as security control, blocking potentially toxic substances from entering the brain, it puts a limitation on which drugs can be used." The formation of brain metastases is based on the 'seed and soil' concept, so an interaction between the brain tissue and tumour cells. Multiple pathways are involved in this process. The ALK, EGFR, and VEGF pathways stimulate the proliferation, cell invasion, and angiogenesis of tumour cells, respectively [17].

Multimodal management of brain metastases

The possibility of surgical resection of brain metastases was studied in the early nineties of the previous century.

"Some publications showed that surgical resection in addition to whole brain radiotherapy could improve survival", stated Dr Blum. "Later on, it was shown that surgical resection alone led to a higher recurrence rate." In 2016, the results of the QUARTZ trial, evaluating dexamethasone plus best supportive care with or without whole brain radiotherapy, showed a similar median overall survival between both groups (overall survival 9.2 vs 8.5 weeks, respectively; HR 1.06; P=0.8084). The same was true for the quality of life outcomes [18]. "But, a frequently suggested point of critique about this trial is that it included very sick patients with advanced disease who were unsuitable for stereotactic radiotherapy." Finally, Dr Blum mentioned the developments in the field of systemic treatment of brain metastases. "What is really thrilling nowadays, are the targeted therapies. We currently have some data with respect to the effect on brain metastases, although in small patient groups. EGFR-targeted treatments showed quite high response rates [19] and an improved PFS and overall survival [20]. "We are all awaiting the data of osimertinib in the treatment of brain metastases. And for ALK-targeted treatments, we have comparable promising figures" [21].

Lung cancer and interstitial lung disease

Prof. Jacques Cadranel (Constitutive Center on Rare Pulmonary Diseases, Paris, France) stated that there is an association between different forms of interstitial lung disease (ILD) [23], especially interstitial lung fibrosis (IPF), and the risk of lung cancer. Both conditions have common risk factors, such as higher age and smoking [24]. Lung cancer in IPF patients mainly presents in the lower lobe, usually in a lobe with fibrosis. The volume double time of a lung cancer nodule is usually ≤90 days [25]. The treatment of locally advanced NSCLC should be a combination of radiation therapy and chemotherapy. However, there are very few studies evaluating the efficacy and toxicity of conventional radiation therapy in patients with ILD-associated lung cancer. In total, 27-31% of radiation pneumonitis in IPF and 54% of fatal radiation pneumonitis were from patients with pre-treatment ILD [26]. According to Prof. Cadranel, conventional radiation therapy should not be used in lung cancer patients with IPF [27].

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