duration of ECMO or MV between patients with and without positive virology.

Conclusion In a single regional intensive care unit we demonstrate that requirement for ECMO due to acute asthma is associated with female gender, younger age and positive virology on admission. To our knowledge, this is the first case series analysing factors relating to ECMO use in asthma in the United Kingdom. It highlights the role of respiratory viruses in near-fatal exacerbations and the need for novel anti-viral approaches to reduce morbidity and mortality. Further research is needed in this population to identify whether differences in underlying inflammatory mechanisms exist that may explain the development of such severe events.

P133 SAFETY AND EFFECTIVENESS OF INFLUENZA VACCINES IN PEOPLE WITH ASTHMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction and objectives Influenza vaccination is offered annually in the UK to high-risk individuals such as those with asthma as a preventive measure against influenza infection and influenza-related complications. However, the effectiveness and safety of influenza vaccination in people with asthma is not well established.[1]

Methods We conducted a systematic review and meta-analysis assessing the overall quality of evidence using the GRADE methodology. Published literature was searched through 13 electronic databases from Jan 1970 to Jan 2016 for clinical trials and epidemiological studies. Unpublished or ongoing literature was searched through references and citations of key publications, and by contacting influenza vaccine manufacturers. The screening for eligible studies, data extraction and quality appraisal was conducted by two reviewers independently. Separate meta-analyses were undertaken for observational and experimental evidence using random-effects models.

Results We identified 35 eligible studies, and four contributed to the meta-analyses. Risk of bias was high for one randomised controlled trial (RCT), unclear for 11 RCTs, and low for eight RCTs. The quality of five non-RCTs, four cohorts, and two case-control studies was strong. Moderate quality was found for one non-RCT, and three cohort studies. In people with asthma, pooled vaccine effectiveness (VE) was 45% (OR: 0.55; 95% CI: 0.44 to 0.69; I2 = 0%) for laboratory confirmed influenza. Pooled effectiveness of live vaccines was 81% (RR: 0.19; 95% CI: 0.06 to 0.67; I2 = 0%) for influenza infection (confirmed by cell culture or rise in antibody titre) and 72% (RR: 0.28; 95%: 0.10 to 0.80; I2 = 0%) for influenza-like illness. VE was also observed against asthma attacks. No increased risk of vaccine-induced asthma symptoms and attacks was identified. The quality of the body of evidence was considered very low for all outcomes.

Conclusions Evidence on VE in people with asthma against influenza, asthma exacerbations, and other clinical outcomes is limited and of very low quality. Thus, better quality evidence is required, especially in adults with asthma. Vaccination with inactivated or live vaccines was found to be safe and well tolerated in patients with asthma.

REFERENCE

1 Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Sys Rev* 2013;**2**:Cd000364.

P134 METHACHOLINE CHALLENGE TO DEMONSTRATE THERAPEUTIC EQUIVALENCE OF TERBUTALINE VIA DIFFERENT TURBUHALER DEVICES IN PATIENTS WITH MILD TO MODERATE ASTHMA: APPRAISAL OF A PHASE III, FOUR-WAY CROSSOVER DESIGN

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Background/objective To demonstrate therapeutic equivalence of terbutaline via two different Turbuhaler® devices by evaluating its protective effect against methacholine-induced bronchoconstriction in patients with stable asthma.

Methods In this double-blind, double-dummy, multicentre, single-dose, 4-way crossover study, patients with stable, mild-to-moderate asthma (FEV1 $\geq$ 80% predicted normal) were randomised to 0.5 or 1.5 mg terbutaline via either Turbuhaler® M3 or M2 followed by a methacholine challenge test. Primary outcome variable: concentration of methacholine causing a 20% drop in FEV1 (PC20). Patients had to have a PC20 methacholine < 8 mg/mL, reproducible after 2 weeks, and a stable baseline FEV1 at all visits (90–110% of enrolment value).

Results 60 patients were randomised to treatment and completed the study. There was a clear dose–response for both devices. The within-device ratios (1.5 mg: 0.5 mg) were 1.79 and 1.87 for Turbuhaler M3 and M2, respectively (both p < 0.001). The between-devices ratio (M3:M2) was 0.92 (95% CI: 0.75–1.13) for 0.5mg and 0.88 (95% CI 0.72–1.08) for 1.5 mg. Both CIs lie inside the interval (0.67–1.50), which was the pre-specified condition for equivalent effect.

Conclusions Bronchoprotection with PC20 as the outcome measure in a standardised methacholine challenge model proved to be a useful design to show therapeutic equivalence between devices in patients with mild to moderate asthma. This model provides robust reproducible data, involves smaller patient numbers with fewer dropouts resulting in reduced costs versus a conventional efficacy study.

Disease Progression and Burden in Obstructive Lung Disease

P135 TREATMENT OF LUNG DISEASE IN ALPHA-1 ANTITRYPSIN DEFICIENCY: A SYSTEMATIC REVIEW

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Introduction Alpha-1 Antitrypsin Deficiency (AATD) is a rare genetic condition predisposing individuals to COPD. The

majority of treatment for AATD is similar to non-AATD related COPD; intravenous augmentation of Alpha-1 Antitrypsin is a specific treatment but is inequitably used across Europe and not used in the UK. There is a pressing need to systematically investigate efficacy since the publication of a new placebo controlled RCT and to identify patient centred, clinically meaningful outcomes.[1]

Methods A systematic review was conducted using standard review methodology with meta-analysis and narrative synthesis (registered with PROSPERO-CRD42015019354). Eligible studies were those of any treatment used in severe AATD. RCT's were the primary focus however case series and uncontrolled studies (n > 10 patients receiving treatment or usual care, with baseline and follow-up data >3 months), were eligible for inclusion to ensure natural history of disease outside RCT's could be determined.

Results 7296 unique records were reviewed with 51 trials analysed on 5632 participants: 26 AAT-augmentation (3 for meta-analysis); 17 surgical intervention (5 Lung volume reduction (LVR) surgery, 1 Bronchoscopic valve LVR and 11 Lung transplantation); 3 medical interventions and 3 trials completed but not published.

Meta-analysis of AAT-Augmentation demonstrated slower lung CT density decline, difference 0.79 g/l/year (95% CI: 0.29–1.29; p = 0.002), and a small increase in annual exacerbations 0.29/year (95% CI: 0.04–0.54; p = 0.02) compared to placebo (Figure 1).

Survival benefit of transplant was observed in one study (p = 0.006) but not in a second with more stringent matching for groups; however significant improvements in health status, total SGRQ and all domain scores, at one year (p < 0.01) were observed. Mortality post lung transplant was comparable between AATD and non-AATD related COPD cohorts. Surgical lung volume reduction demonstrated inferior outcomes when compared to non-AATD related emphysema.

Conclusion CT density, FEV1, DLCO, health status and exacerbation rates were frequently used as outcomes in AATD related treatment trials. AAT-Augmentation is able to slow the progression of severity of emphysema when measured by CT density change compared to placebo. This systematic review will help assist in the improved monitoring and management of patients with AATD.

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P136 RELATIONSHIP BETWEEN PROGRESSION OF LUNG DISEASE IN ALPHA-1 ANTITRYPSIN DEFICIENCY AND CARDIOVASCULAR RISK

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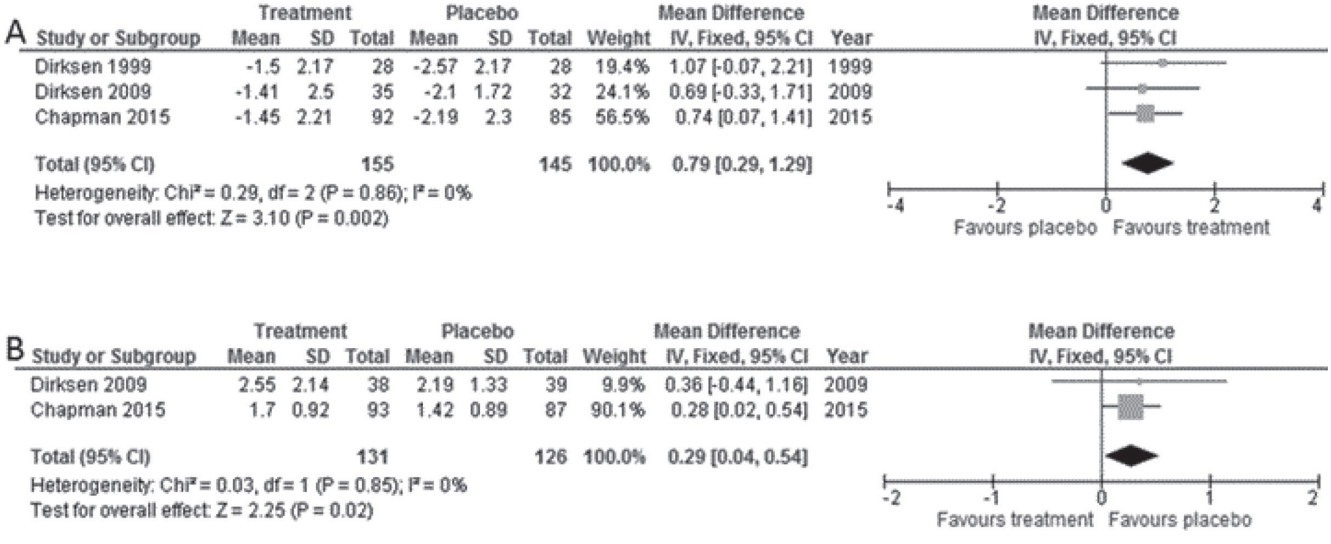
Introduction Patients with alpha-1 antitrypsin deficiency (AATD) who are homozygous for the mutated Z allele (PiZZ) typically present with emphysema and liver cirrhosis, caused by the uncontrolled action of neutrophil elastase in the lungs and toxic gain-of-function AAT polymer aggregates in the ER of hepatocytes. The link between cardiovascular disease and COPD is widely accepted, but is less well understood in AATD. This study aimed to investigate how markers of lung function severity and the rate of disease progression are associated with cardiovascular risk in a cohort of PiZ patients.

Methods Cardiovascular (CV) risk was determined by the degree of arterial stiffness, measured using aortic pulse wave velocity (aPWV). This was recorded with the Vicorder device which uses the transcutaneous distance between the common carotid and femoral arteries, and the time delay between the feet of the 2 diastolic pulse waveforms to calculate the pulse velocity. Cardiovascular risk was additionally assessed using the QRISK2 algorithm. Pulmonary function was evaluated using FEV1, KCO and RV% TLC, and the degree of AATD disease progression used previous pulmonary function test (PFT) data to determine the rate of lung function decline.

Results We enrolled 48 PiZZ AATD patients (mean (SD) age 52.9 (15.9) years, 19 male) and found significant relationships (denoted by: **p < 0.01 and *p < 0.05) between both aPWV



Abstract P135 Figure 1 Forest Plots : A) Annual CT Lung Density Change (g/L per year)in 300 patients across three placebo controlled RCT's. B) Annual patient reported exacerbation episode in 257 patients across two placebo controlled RCT's.