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Long-term mortality follow-up of the ISOLDE participants: Causes of death during 13 years after trial completion

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Summary
The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study was a trial that randomised 752 patients with moderate to severe COPD to fluticasone propionate 1000 mcg/day or placebo for three years.

We aimed to examine the causes of death of the ISOLDE participants after the original three up to 13 years post-randomisation. Death certificates were obtained either from the NHS Strategic Tracing Service or from the Office of National statistics. Deaths were classified according to the trial protocol.

In the subsample of 375 participants from the seven ISOLDE original centers where complete extended follow-up was conducted, the factors associated with observed higher mortality ($p < 0.05$) were male gender, older age and more severe COPD. Causes of death were; 107 (52%) respiratory, 38 (18%) cardiac, 29 (14%) lung cancer, 16 (8%) other cancer and 16 (8%) other causes. The percentage of respiratory-related deaths increased during the follow-up period; from 46% within the three-year trial, to 48% after 3–6 years, 57% after 6–9 years, and 60% after 9–13 years of follow-up (p for trend < 0.05).

We conclude that participants' survival is poor (only 44% in the 13 years after the ISOLDE trial), and that respiratory-related illnesses were the most frequent causes of death in patients with moderate to severe COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) represents an important and increasing burden throughout the world. This burden is expected to increase for the foreseeable future.[1]

COPD is currently considered a preventable, treatable disease in international guidelines.[2,3] Efforts to understand the natural history and all events related to COPD, including death, are to be considered as a research priority.[4] This includes initial triggers to last circumstances.

The Global Burden of Disease Study from the World Health Organization (WHO) has been systematically assessing worldwide statistics on specific causes of death and disability since 1990.[5] According to the WHO, at least 2.9 million deaths are due to COPD every year. Their 30-year projections for the global increase in COPD are startling.[6] Of all of the descriptive epidemiological data available for COPD, mortality data are the most readily accessible. However, this data has to be interpreted with caution. As a ballpark figure, mortality rates due to COPD are 50 per 100,000 in males and 20 per 100,000 in females. The striking increase in COPD as a cause of death is projected to occur because of the worldwide prevalence of smoking and changing global demographics. More people in developing countries are living longer and are, therefore, at risk of COPD for longer periods.[7] Although COPD mortality is common and will become even more frequent, there is a relative scarcity of data on the causes and circumstances of death in COPD patients.[8,9]

The Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study[10] was a trial that randomised 752 patients with moderate to severe COPD to fluticasone propionate (FP) 1000 mcg/day or placebo for three years. The first mortality assessment of ISOLDE looked at causes of death in all patients at three years post-randomisation. This showed a marginal survival advantage in the FP group ($p = 0.057$).[11] Four percent of randomised patients had died within the first three years. The aim of this study is to examine the specific causes of death of the ISOLDE participants between 3 and 13 years post-randomisation.

Methods

Summary of ISOLDE methods

It included the group was aged between 40—75 years and had non-asthmatic chronic obstructive pulmonary disease. Seven hundred and fifty two patients with a mean forced expiratory volume in one second (FEV_1) lower than 50% of the predicted normal were recruited from 18 hospitals in the UK. The original aim was to determine the effect of FP on lung function, exacerbations, and health status. After the three years of randomised treatment, subsequent treatment was resumed by the treating physician. As the randomisation code was unbroken for 1—3 years after trial completion, subsequent management was unlikely to have been influenced by treatment taken during the randomised period. We have no complete information on drugs taken or smoking after the first three years.

The original ISOLDE study was approved by 18 independent local ethics committees whose authority had been superseded by multi-center research ethics committees (MREC) before the current mortality study was started. Seven of 18 local ethics committees approved this study; the others required approval from MRECs, who declined as they had not approved the original protocol. The current study reports all ISOLDE patients up to three years post-randomisation and patients from the seven ISOLDE centers with ethics approval up to 13 years post-randomisation.

Ascertainment of death

Life status was confirmed by the NHS Strategic Tracing Service. Data on known deaths were checked against the NHS central registers to assess accuracy. Death certificates were obtained from the Office of National Statistics. Two investigators independently reviewed all death certificates and grouped the primary (underlying) cause of death into five categories: respiratory, cardiac, lung cancer, other cancer and all other causes. Both assessors were blinded to treatment allocated during the trial.

Statistical methods

Survival was compared using standard Kaplan—Meier statistics. The following groups were analyzed separately: patients randomised to FP or placebo in the first three years, confirmed non-smokers during randomised treatment, continuing and intermittent smokers, males, females and participants with mild, moderate or severe COPD at randomisation. Comparison of groups was with analysis of variance for continuous variables and Chi square for categorical variables. A p value lower than 0.05 was considered statistically significant.

Results

Baseline characteristics of the 375 participants in the seven centers which completed extended follow-up were similar to the 366 participants of the 11 centers not surveyed (Table 1). The statistical differences in FEV_1 and weight should be considered clinically irrelevant.

Baseline BMI (Table 2) was the only difference in any of the demographic and clinical characteristics considered among the ISOLDE participants who were randomised to FP or placebo and followed up in this study. A total of 209 deaths (56%) were observed out of the 375 participants in these seven centers after 13 years of follow-up. Death certificates were obtained for 206 (98 %) participants. There were no differences in total mortality among the ISOLDE participants randomised to FP or placebo (Fig. 1). Male gender, older age, and more severe COPD at baseline were associated with observed higher mortality ($p < 0.05$), but there were no differences according to baseline smoking status (Fig. 2). Other variables like body mass index and pack-years were not associated with mortality. Regrettably, other potentially important baseline characteristics like cardiovascular comorbidity or socioeconomic status were not collected in a standardised way at baseline.

Table 1 Baseline characteristics of randomised participants from centers in Group 1: without ethics consent; Group 2; with ethics consent

	Group 1 ($n = 366$, 49.4%)	Group 2 ($n = 375$, 50.6%)	p-Value
Age, yrs.	64.5 ± 7.5	64.5 ± 6.7	0.898
Male, n (%)	275 (75.1)	280 (74.7)	0.450
Smoker status, n (%)	168 (45.9)	176 (46.9)	0.915
(ex/mixed/current), n (%)	57 (15.6)	61 (16.3)	
	141 (38.5)	138 (36.8)	
Pack-yrs of smoking	41.9 ± 30.3	45.9 ± 33.2	0.084
FEV_1, l.	1.48 ± 0.5	1.35 ± 0.4	0.000
Weight, kg.	73.4 ± 15.7	69.8 ± 14.4	0.001
Height, cm.	170.3 ± 8.6	169.6 ± 7.9	0.241

Causes of death were distributed as: 107 (52%) respiratory, 38 (18%) cardiac, 29 (14%) lung cancer, 16 (8%) other cancer and 16 (8%) other causes. There were no differences in specific causes of death among the ISOLDE participants randomised to FP or placebo (data not shown).

The percentage of respiratory-related deaths increased with longer follow-up from 46% within the three-year trial, 48% after 3—6 years, 57% after 6—9 years and to 60% after 9—13 years of follow-up (p for trend < 0.05) (Fig. 3).

Death certificates mentioning pneumonia or bronchopneumonia as a cause of death during the three year randomised treatment period were compared between the FP and placebo arms for all centers and participants ($n = 751$). There were three deaths from pneumonia and 10 from bronchopneumonia in the placebo group and one death from pneumonia and four from bronchopneumonia in the FP arm (p not significant). Post-randomisation, there were 10 in placebo and four in FP in the subsample analyzed.

Discussion

By following up ISOLDE participants up to 13 years after randomisation, this study confirms that COPD is associated with high lethality and that respiratory-related illnesses were the most frequent causes of death in these moderate to severe COPD patients. Some limitations are worth considering. As previously stated, there was incomplete access to data from all centers; however, the seven participating centers should have no major bias. There are some limitations when using death certificate data. Since this was a 13-year assessment, there is an absence of information on both smoking after the baseline assessment and of switchers of respiratory medications after trial completion.

Some strengths of the study include near complete availability of death certificates, and consistency with *a priori* knowledge of death by age, gender and COPD severity. These results compare well with some recent extended follow-up studies after trial completion in COPD, mirroring examples in cardiovascular and cancer trials. The Lung Health Study researchers (LHS)[12] reported in 2005, an extension of the initial trial assessment of deaths after a 14-year follow-up.[13] From this original sample of mild COPD participants, 731 patients died: 33% of lung cancer, 22% of cardiovascular disease, 7.8% of respiratory disease other than cancer, and 2.3% of unknown causes. There were differences in mortality in the LHS usual care group compared with the smoking

Table 2 Baseline characteristics of ISOLDE participants who were followed up beyond the three years of the trial duration

($n = 375$)	FP ($n = 185$)	Placebo ($n = 190$)
Age in years, mean (SD)	64.4 (6.4)	64.5 (6.9)
Women, n (%)	42 (22.7)	53 (27.9)
Body mass index in kg/m^2, mean (SD)	23.7 (4.2)[a]	24.6 (4.7)
Smoking pack-years at randomisation, mean (SD)	47.0 (32.0)	44.8 (34.4)
Baseline PBD FEV_1 in ml, mean (SD)	1.35 (0.4)	1.34 (0.4)
% predicted baseline PBD FEV_1, mean (SD)	47.7 (14.0)	48.5 (14.6)
Deaths during 0—3 years	30 dead (16.2%)	34 dead (17.9%)
	155 alive	156 alive
Deaths during 0 —13 years	103 dead (55.7%)	106 dead (55.8%)
	82 alive	84 alive

[a] p-value < 0.05.

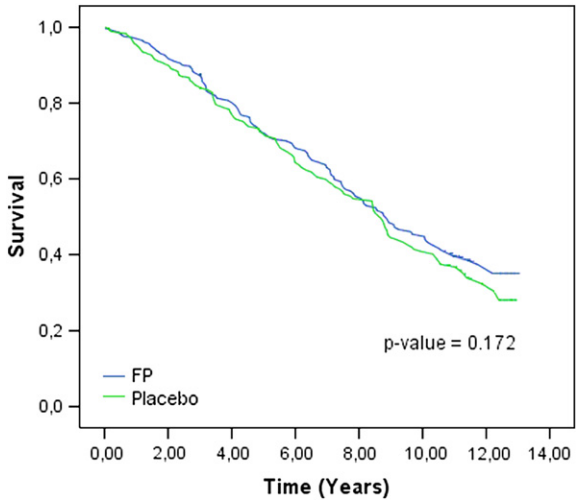

Figure 1 Kaplan—Meier survival curves of individuals with complete long-term follow-up randomised to FP or placebo.

intervention group. Death rates for both lung cancer and cardiovascular disease were greater when rates were analyzed by smoking habit.

Reanalysis of old trial data can generate new hypotheses. For example, investigators from the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP)[14] also recently reported the mortality results of this study, supporting the hypothesis that treatment with inhaled corticos teroids tends to reduce ischaemic cardiac events in patients with mild COPD.[15]

The largest and most comprehensive assessment of COPD deaths completed to date is from the TOwards a Revolution in COPD Health (TORCH) trial.[16] Overall, 911 deaths were reviewed and a final consensus on the specific cause/s of death was reached for each.[17] The TORCH inclusion criteria for COPD severity were very similar to the ISOLDE inclusion criteria The proportions were; respiratory 35%, cardiovascular 27%, cancer 21%, other 10% and unknown 8%. There were, therefore, strong similarities between the ISOLDE study and the TORCH results in which 40% of deaths were definitely or probably related to COPD.[18] Interestingly, there were less reports of pneumonia and bronchopneumonia in the ISOLDE participants randomised to FP than to placebo during the ISOLDE trial, or after trial completion up to 13 years of follow-up.

A methodological issue of potential interest to other researchers when conducting extended follow-ups of completed trials is the variable and inconsistent response from MRCEs. Regrettably, within our study the MRCEs of 11 out of the 18 original ISOLDE participating centers did not grant permission to search for survival/mortality data after trial

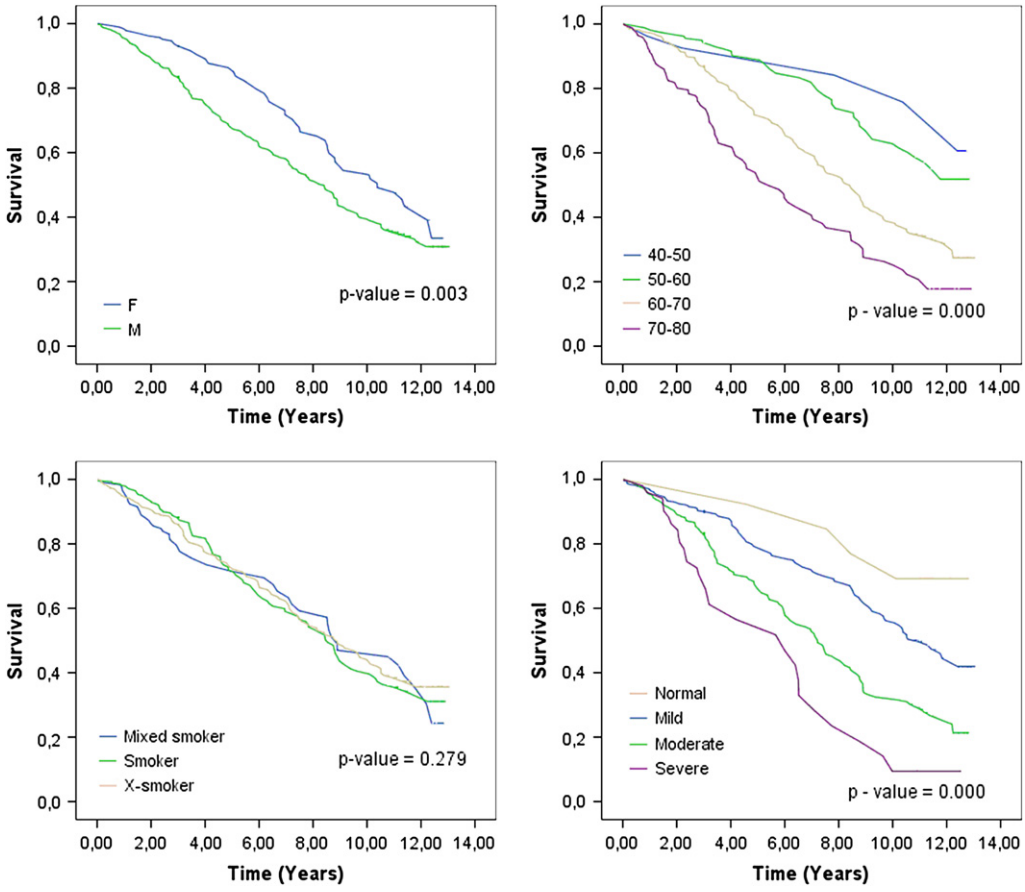

Figure 2 Kaplan—Meier survival curves of ISOLDE participants with complete long-term follow-up (clockwise from top left) according to gender, age *[10-year bands]*, smoking, and severity of COPD (composite).

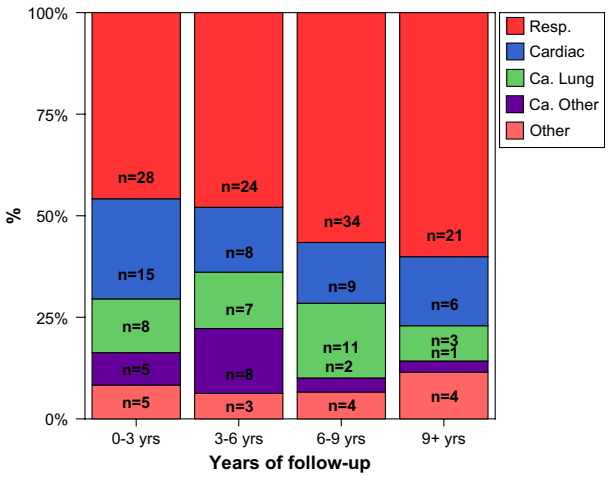

Figure 3 Cause of death by year interval of ISOLDE participants with complete long-term follow-up.

completion. This limitation has been identified by others elsewhere.[19,20] A fine balance between protection of participants and community knowledge should be searched when assessing each study proposal by MRCEs.

We conclude that survival of ISOLDE participants is poor (44%) 13 years after the trial completion, and that respiratory-related deaths were the most frequent causes of death in these moderate to severe COPD patients.

Conflict of interest

The authors have no conflict of interest.

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