Real world effects of COPD medications: a cohort study with validation against results from randomised controlled trials

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In COPD patients selected from real-world data based on similarity to participants of the TORCH RCT, non-interventional methods generated comparable results to the TORCH analysis of LABA-ICS versus LABA in relation to exacerbations, mortality and pneumonia https://bit.ly/33ky5D0

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ABSTRACT Real-world data provide the potential for generating evidence on drug treatment effects in groups excluded from trials, but rigorous, validated methodology for doing so is lacking. We investigated whether non-interventional methods applied to real-world data could reproduce results from the landmark TORCH COPD trial.

We performed a historical cohort study (2000–2017) of COPD drug treatment effects in the UK Clinical Practice Research Datalink (CPRD). Two control groups were selected from CPRD by applying TORCH inclusion/exclusion criteria and 1:1 matching to TORCH participants, as follows. Control group 1: people with COPD not prescribed fluticasone propionate (FP)-salmeterol (SAL); control group 2: people with COPD prescribed SAL only. FP-SAL exposed groups were then selected from CPRD by propensity score matching to each control group. Outcomes studied were COPD exacerbations, death from any cause and pneumonia.

2652 FP-SAL exposed people were propensity score matched to 2652 FP-SAL unexposed people while 991 FP-SAL exposed people were propensity score matched to 991 SAL exposed people. Exacerbation rate ratio was comparable to TORCH for FP-SAL versus SAL (0.85, 95% CI 0.74–0.97 versus 0.88, 0.81–0.95) but not for FP-SAL versus no FP-SAL (1.30, 1.19–1.42 versus 0.75, 0.69–0.81). In addition, active comparator results were consistent with TORCH for mortality (hazard ratio 0.93, 0.65–1.32 versus 0.93, 0.77–1.13) and pneumonia (risk ratio 1.39, 1.04–1.87 versus 1.47, 1.25–1.73).

We obtained very similar results to the TORCH trial for active comparator analyses, but were unable to reproduce placebo-controlled results. Application of these validated methods for active comparator analyses to groups excluded from randomised controlled trials provides a practical way for contributing to the evidence base and supporting COPD treatment decisions.
Introduction
The long-acting β₂-agonist (LABA)–inhaled corticosteroid (ICS) combination product fluticasone propionate (FP) + salmeterol (SAL) is one of the most widely used COPD treatments. It was studied in large randomised trials (such as the landmark TORCH study [1]), but the effects of treatment in important patient groups who were either not included or underrepresented in trials are unknown. While real-world observational data has the potential to be used to carry out non-interventional studies of COPD drug treatment effects in groups excluded from trials, the use of these data for estimating treatment effectiveness is in its infancy. Demonstrating that non-interventional methods can account for the absence of treatment randomisation in real-world settings is a particular challenge. Rigorous, validated methodology is needed to translate these complex data into reliable evidence [2].

One approach is to analyse “randomised controlled trial (RCT)-analogous” cohorts from non-interventional data sources; if results are comparable to those generated by the reference RCT, this should increase confidence in the validity of the results, and in the non-interventional methods used to obtain them. The validated non-interventional methodology could then go on to be used for the analysis of treatment effects within people prescribed drugs in clinical practice who would have been excluded from (or were underrepresented in) RCTs [2].

In this study, we 1) applied trial inclusion and exclusion criteria to detect trial “eligible” participants from real-world data; 2) selected from these “eligible” participants to obtain a group who were as similar to the TORCH participants as possible by individual matching using TORCH data; and 3) applied standard observational methods to account for confounding [1].

We then assessed whether treatment effects in this real-world cohort were comparable to those measured by the TORCH trial in terms of the effect of the FP-SAL fixed combination product on 1) exacerbations; 2) mortality; and 3) pneumonia.

Materials and methods
Study design
A historical cohort study, with validation against RCT results.

Setting/data sources
This study uses individual trial data from the TORCH RCT (obtained via www.clinicalstudydatarequest.com), and non-interventional data from the UK Clinical Practice Research Datalink (CPRD) linked to Hospital Episodes Statistics (HES) data. We have described the use of CPRD in this study and the characteristics of TORCH in a previous publication (replicated in appendix 1) [2].

Diagnostic and therapeutic codelist
All diagnostic and therapeutic codelist files are available for download (https://datacompass.lshtm.ac.uk/1655/).

Selection of participants: FP-SAL exposed versus unexposed
Step 1: selection of all potentially eligible patients
An initial cohort was selected from all HES-linked patients actively registered in the CPRD between January 1, 2004 and January 1, 2017, who fulfilled the TORCH inclusion criteria (supplementary table A1-1) [1]. The date that an individual met all inclusion criteria with \( \geq 12 \) months prior registration in the CPRD was the “eligible for TORCH inclusion” date.

Step 2: selection of pool of unexposed patients
Time periods during which patients were unexposed to FP-SAL that occurred on or after the eligible for TORCH inclusion date and which did not meet any of the TORCH drug exposure exclusion criteria (supplementary table A1-1) were selected (supplementary figure A1-1) [1]. The start of follow-up date (index date) for the unexposed time period was selected as a random date between the start and end of the unexposed period (supplementary figure A1-1). Individuals in CPRD were able to contribute more than one such unexposed time period to the total pool of unexposed time periods (supplementary figure A1-1). Unexposed time periods were then removed from the cohort if the patient met any of the remaining TORCH study exclusion criteria prior to the index date [1].

Step 3: selection of unexposed to FP-SAL people by 1:1 matching FP-SAL time periods to TORCH participants
Each individual TORCH participant from the TORCH RCT (obtained via www.clinicalstudydatarequest.com, as described earlier) was matched 1:1 with the closest available unexposed to FP-SAL time period on the following TORCH baseline characteristics: age, sex, body mass index (BMI), 1-year history of...
exacerbations requiring hospitalisation, history of cardiovascular disease and lung function (forced expiratory volume in 1 s (FEV1)) (appendix 1). An individual could only contribute one unexposed period to the final TORCH-matched unexposed cohort (supplementary figure A1-1); therefore, the output of this step was a cohort of unexposed to FP-SAL people.

**Step 4: selection of exposed to FP-SAL time periods and application of TORCH exclusion criteria**

All prescriptions for FP-SAL that started 1) on or after the initial eligible for TORCH inclusion date specified in Step 1 and 2) ≥4 weeks after the end of a prescription for any of the TORCH study drugs were identified. FP-SAL exposed time periods were created with the index date assigned as the start of an FP-SAL prescription. The same exclusion criteria applied to the unexposed FP-SAL time periods (Step 3) were applied. If an individual contributed time periods to both the unexposed (Step 2) and exposed (Step 4) cohorts, they were contributing different periods of their person-time to each cohort (pre-FP-SAL treatment for Step 2 versus post-FP-SAL treatment for Step 4) (supplementary figure A1-1).

**Step 5: selection of comparable FP-SAL exposed participants by matching FP-SAL exposed time periods to FP-SAL unexposed people**

Using the index date baseline characteristics, propensity scores for receiving FP-SAL were calculated for the (TORCH-matched) FP-SAL unexposed people selected in Step 3 and the FP-SAL exposed time periods selected in Step 4. Each FP-SAL unexposed (TORCH-matched) person selected in Step 3 was matched 1:1 with the FP-SAL exposed time period from Step 4 with the closest propensity score. An individual could only appear once as an exposed participant in the final propensity score matched cohort, meaning that this step selected FP-SAL exposed participants from the initial pool of FP-SAL exposed time periods. It was possible for the same person to be included in the FP-SAL unexposed and FP-SAL exposed cohorts, with different start of follow-up dates in each cohort.

Note that we did not apply matching to the TORCH trial in order to select our FP-SAL exposed group, because we wanted to develop propensity score methodology for obtaining balanced groups that could then be applied to the study of groups of patients who were not included in the trial at all.

**Selection of participants: FP-SAL exposed versus SAL exposed**

The participant selection approach was analogous to the FP-SAL exposed versus FP-SAL unexposed participant selection, except the comparator group was those exposed to SAL, and the study period was 2000–2017 (to obtain sufficient SAL-exposed numbers). The other differences in participant selection are detailed in appendix 1.

**Exposures, outcomes and covariates**

**Exposures**

Exposure status was determined using CPRD prescribing records. Being prescribed FP-SAL was the primary exposure of interest and the comparison exposure groups were 1) people not being prescribed FP-SAL and 2) people being prescribed SAL only. Refer to appendix 1 for further details.

**Outcomes**

Outcomes were COPD exacerbation, all-cause mortality, pneumonia and time to treatment discontinuation (refer to appendix 1: Outcomes – further details on outcome definitions).

**Covariates**

Covariates available for inclusion in the propensity score models have been detailed previously and are listed in appendix 1 [2].

**Statistical analysis**

**Propensity score for addressing confounding**

A pool of initial variables were selected based upon a priori knowledge/clinical expertise. Those variables not associated with outcome in crude analysis were then removed, before applying multivariable logistic regression (on drug exposure status) to generate propensity scores [2]. Variables were selected for inclusion in the final propensity score multivariable logistic regression model using likelihood ratio tests for goodness of fit. Starting from an initial fully adjusted model that included all initial variables found to be associated with outcome, goodness of fit was tested after removing variables sequentially from the logistic regression model (starting with the variable most weakly associated with exposure in the fully adjusted model). Variables with likelihood ratio test p-value >0.1 were removed from the model. Separate propensity scores were developed in this way for each outcome. Standardised differences were used to assess any residual imbalances after matching (with SD >0.1 indicating substantial/important imbalance) [3].
**Methods of analysis**

Comparisons were made for each outcome over 3 years between 1) people exposed to FP-SAL versus people unexposed to FP-SAL (matched on propensity score) and 2) people exposed to FP-SAL versus people exposed to SAL (matched on propensity score). All analyses were performed according to the intention-to-treat principle (appendix 1), estimating the same effect measures as TORCH. The number of exacerbations was modelled using a negative binomial model with the log of treated time as an offset variable. Time to mortality and treatment discontinuation were analysed using Cox proportional hazards regression, and pneumonia risk was analysed using Poisson regression.

**Validation of results against TORCH**

Detailed criteria for considering results to be comparable with TORCH were pre-specified and have been published previously (appendix 1) [2].

**Missing data**

Complete records analysis was applied given the low proportion of missing data (only socioeconomic status, alcohol or BMI had any missing data, and of these variables, none had >5% missing data).

**Analysis of impact of TORCH matching and TORCH criteria (post hoc analysis)**

A post hoc analysis was performed assessing the impact of 1) omitting TORCH matching and 2) omitting both TORCH matching and application of TORCH trial inclusion/exclusion criteria (refer to appendix 1 for details).

**Ethics**

Scientific approval was provided by the London School of Hygiene and Tropical Medicine research ethics committee (ref 11997) and the independent scientific advisory committee of the Medicines and Healthcare Products Regulatory Agency (protocol no. 17_114R). CPRD data are already approved via a national research ethics committee for purely non-interventional research of this type. Approval for use of the TORCH trial data was obtained from the Wellcome Trust, the relevant sponsor (GSK) and an independent review panel.

**Results**

**Participants**

**FP-SAL exposed versus FP-SAL unexposed**

Between January 1, 2004 and January 1, 2017 there were 125 671 people in CPRD with a diagnosis of COPD, 73 889 (59%) of whom were from HES-linked CPRD practices (figure 1). Application of TORCH inclusion criteria reduced this to 18 715 people, contributing 35 746 unexposed to FP-SAL time periods and 26 390 exposed to FP-SAL time periods. After applying TORCH exclusion criteria, dropping records with missing covariate data and matching the unexposed patients to TORCH participants, there were 4196 unexposed patients available for propensity score matching to 10 463 FP-SAL exposed time periods. The final propensity score matched cohorts included 2652 patients in each exposure group for the exacerbations analysis, 2708 for mortality and 2779 for pneumonia.

**FP-SAL exposed versus SAL exposed**

For the FP-SAL versus SAL analysis, there were 154 785 people with a diagnosis of COPD in CPRD between January 1, 2000 and January 1, 2017, 91 733 (59%) of whom were from HES-linked CPRD practices (figure 2). 1146 SAL exposed patients were available for propensity score matching to 11 235 FP-SAL-exposed periods. The final propensity score matched cohorts included 991 (exacerbations), 432 (mortality), 935 (pneumonia) and 996 (treatment discontinuation) patients per exposure group.

**Application of TORCH inclusion/exclusion criteria and matching to TORCH**

Applying the TORCH inclusion/exclusion criteria and matching to TORCH resulted in cohorts that were much more similar to those recruited to the TORCH trial (e.g. FEV₁ for the FP-SAL versus unexposed to FP-SAL analysis was 66.3% predicted in CPRD before applying any criteria or matching, compared to 47.2% pred after these steps, compared to a TORCH placebo group value of 44.2% pred; supplementary table A2-1). The largest residual difference to the TORCH placebo group was for prior cardiovascular disease for both comparisons (supplementary tables A2-1 and A2-2).

**Propensity score matching of CPRD cohorts**

Details of the variables included in the final propensity score models are provided in supplementary table A2-3.
People in CPRD linked to HES with a first diagnosis of COPD recorded in CPRD between January 1, 2004 and January 1, 2017
n=73 889

Did not meet TORCH inclusion criteria due to:
- Age (n=11 990)
- Smoking status (n=5646)
- No lung function records (n=19 198)
- Lung function criteria (n=18 340)
- n=55 174

People in CPRD who meet TORCH inclusion criteria
n=18 715

FP-SAL exposed time periods
n=26 390 (from 9513 people)

Excluded time periods due to TORCH exclusion criteria
n=15 336
Detail:
- Current/previous exposure to COPD drugs (n=1945)
- Asthma (n=11 110)
- Pre-existing lung conditions (n=884)
- Substance abuse (n=386)
- Oxygen therapy (n=107)
- Likely death or study interference (n=578)
- Run-in exacerbation (n=417)

Exposed time periods after applying TORCH exclusion criteria
n=11 054 (from 4513 people)

Missing BMI
n=56

Exposed time periods ready for propensity-score matching
n=10 463 (from 4259 people)

Unmatched
- Exacerbations n=1607
- Mortality n=1551
- Pneumonia n=1480

Unmatched Exacerbations n=1544
- Mortality n=1488
- Pneumonia n=1417

Final analysis cohort for exacerbations
n=2652 per exposure group

Final analysis cohort for mortality
n=2708 per exposure group

Final analysis cohort for pneumonia
n=2779 per exposure group

FP-SAL unexposed time periods
n=35 746 (from 18 242 people)

Excluded time periods due to TORCH exclusion criteria
n=15 336
Detail:
- Current/previous exposure to COPD drugs (n=2931)
- Asthma (n=12 795)
- Pre-existing lung conditions (n=1149)
- Substance abuse (n=386)
- Oxygen therapy (n=107)
- Likely death or study interference (n=827)
- Run-in exacerbation (n=282)

Unexposed time periods after applying TORCH exclusion criteria
n=17 269 (from 10 257 people)

Unexposed time periods ready for matching to TORCH participants
n=17 176 (from 10 193 patients)

People not matched to TORCH n=5834

TORCH-analogue unexposed people n=4359

Unexposed time periods ready for propensity-score matching
n=4196

Propensity-score matched to

Unmatched
- Exacerbations n=1544
- Mortality n=1488
- Pneumonia n=1417

Final analysis cohort for exacerbations
n=1544 per exposure group

Final analysis cohort for mortality
n=1488 per exposure group

Final analysis cohort for pneumonia
n=1417 per exposure group

Missing BMI (required for TORCH matching) n=93

Missing alcohol n=528

Missing SES n=7

Missing alcohol n=161

Missing SES n=2

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FP-SAL exposed versus FP-SAL unexposed
Prior to propensity score matching, differences by exposure status were noted for sex, FEV1, BMI, prior exacerbations, coronary heart disease, peripheral vascular disease, cerebrovascular disease, prescriptions for aspirin, COPD medications, number of general practice (GP) consultations and number of distinct medications (table 1). After propensity score matching, only the difference with respect to coronary heart disease, peripheral vascular disease, LABA and consultations persisted (table 1). Plots of propensity score distributions indicated close propensity score matching for exacerbations and all other outcomes under study (supplementary figure A2-1).

FP-SAL exposed versus SAL exposed
For the FP-SAL versus SAL exacerbations analysis, after propensity score matching there were notable imbalances in prior prescriptions for a LABA or an ICS, with smaller imbalances for lung function, BMI, coronary heart disease, statin prescription, aspirin prescription, LAMA and ICS plus LABA (table 2). Plots of propensity score distribution indicated that overall groups were well matched on propensity score for each outcome (supplementary figure A2-1).

Main results
FP-SAL exposed versus FP-SAL unexposed
For the exacerbations analysis, the rate ratio in the propensity score matched groups was 1.30 (95% CI 1.19–1.42) (table 3). According to our pre-specified protocol this (harmful) association was not considered to be consistent with the (protective) TORCH placebo-controlled result for the same outcome (0.75, 0.69–0.81) [2]. Similarly, our result for the mortality outcome (hazard ratio (HR) 1.11, 95% CI 0.95–1.26) was in the opposite direction to the TORCH placebo-controlled result (0.83, 0.68–1.00). For the pneumonia analysis, we found weak evidence for a 14% increased risk associated with FP-SAL (risk ratio 1.14, 0.96–1.34) which was not consistent with the stronger harmful association found by the TORCH placebo-controlled analysis (1.59, 1.35–1.88).

FP-SAL exposed versus SAL exposed
For the exacerbations analysis, we obtained a propensity score matched rate ratio of 0.85 (95% CI 0.74–0.97). According to our pre-specified protocol this (protective) effect was considered to be consistent with the TORCH FP-SAL versus SAL result for the same outcome (0.88, 0.81–0.95) [2]. Similarly, our result for the mortality outcome (HR 0.93, 95% CI 0.65–1.32) was consistent with the TORCH FP-SAL versus SAL result (0.93, 0.77–1.13). For the pneumonia analysis, we found evidence for a 39% increased risk associated with FP-SAL (risk ratio 1.39, 95% CI 1.04–1.87), which was also consistent with the harmful association found by the TORCH FP-SAL versus SAL analysis (1.47, 1.25–1.73). For the time to treatment discontinuation analysis, the effect was apparently much stronger outside of the trial setting (non-interventional HR 0.23, 95% CI 0.20–0.27 versus TORCH 0.89, 0.79–1.09).

Analysis of impact of TORCH matching and TORCH criteria (post hoc analysis)
Repeating the FP-SAL versus SAL analysis omitting the TORCH matching step led to an exacerbations rate ratio of 0.87 (95% CI 0.81–0.94) (table 5), very similar to both the main analysis and TORCH result. In contrast, applying neither the TORCH criteria nor matching led to a completely different effect estimate (1.64, 1.52–1.77).

Discussion
We have demonstrated that methods applied to non-interventional data can generate results comparable to active comparator trials for COPD treatment effects. In contrast, we found that the same methods were unable to replicate placebo-controlled trial results.
People in CPRD linked to HES with a first diagnosis of COPD recorded in CPRD between January 1, 2000 and January 1, 2017
n=91 733

Did not TORCH inclusion criteria due to:
- Age (n=16,683)
- Smoking status (n=10,333)
- No lung function records (n=23,783)
- Lung function criteria (n=20,468)
- n=69,267

People in CPRD who meet TORCH inclusion criteria
n=22,466

FP-SAL exposed time periods
n=33,805
(from 11,879 people)

SAL exposed time periods
n=48,280
(from 34,088 people)

Excluded time periods due to TORCH exclusion criteria
n=21,918
Detail:
- Exposure to TORCH study drugs or OCS (n=33,748)
- Exposure to long-acting bronchodilator (n=1102)
- Asthma (n=6692)
- Pre-existing lung conditions (n=483)
- Substance abuse (n=89)
- Oxygen therapy (n=29)
- Likely death or study interference (n=308)
- Run-in exacerbation (n=133)

FP-SAL exposed time periods after applying TORCH exclusion criteria
n=11,887 (from 4798 people)

SAL exposed time periods after applying TORCH exclusion criteria
n=56,771 (from 1292 people)

Missing BMI
n=69

Missing BMI (required for TORCH matching)
n=25

FP-SAL exposed people ready for propensity-score matching
n=11,235 (from 4523 people)

SAL exposed people ready for propensity-score matching
n=11,446

Unmatched Exacerbations n=3580
Mortality n=3445
Pneumonia n=3588
Treatment discontinued n=476

Unmatched Exacerbations n=155
Mortality n=714
Pneumonia n=211
Treatment discontinued n=150

Final analysis cohort for exacerbations
n=991 per exposure group

Final analysis cohort for mortality
n=432 per exposure group

Final analysis cohort for pneumonia
n=935 per exposure group

Final analysis cohort for treatment discontinuation
n=935 per exposure group

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TABLE 1 Characteristics of the fluticasone propionate (FP)-salmeterol (SAL) versus unexposed to FP-SAL cohort before and after propensity score matching for the exacerbations analysis

|                   | Before propensity score matching | After propensity score matching |
|-------------------|---------------------------------|---------------------------------|
|                   | Unexposed to FP-SAL*            | Exposed to FP-SAL*              | Standardised difference |
|                   | Unexposed to FP-SAL*            | Exposed to FP-SAL*              | Unexposed to FP-SAL*    | Exposed to FP-SAL*    | Standardised difference |
| Subjects          | 4196                            | 10,463                         | 0.103                      | 2652               | 2652                      | 0.083                      |
| Age, years        | 67 (61–73)                      | 68 (62–74)                     | 0.116                      | 68 (61–73)         | 68 (62–74)                | 0.015                      |
| Male              | 3175 (76)                       | 6515 (62)                      | 0.293                      | 1868 (70)          | 1850 (70)                 | 0.010                      |
| Lung function     | FEV1 % pred                     | 53 (44–61)                     | 0.297                      | 49 (39–57)         | 48 (38–56)                | 0.024                      |
|                   | FEV1/FVC %                      | 53 (44–63)                     | 0.073                      | 53 (44–62)         | 52 (43–61)                | 0.045                      |
|                   | BMI*                           | 26 (22–29)                     | 0.191                      | 26 (23–30)         | 26 (22–30)                | 0.024                      |
| Prior exacerbations | 47 (38–56)                     | 47 (38–56)                     | 0.191                      | 47 (38–56)         | 47 (38–56)                | 0.024                      |
| Cardiovascular disease | 526 (13)                     | 1496 (14)                      | 0.103                      | 2652               | 2652                      | 0.060                      |
| Coronary heart disease | 1114 (27)                     | 1783 (17)                      | 0.232                      | 720 (27)           | 441 (17)                  | 0.257                      |
| Peripheral vascular disease | 390 (9)                      | 648 (6)                        | 0.116                      | 253 (10)           | 166 (6)                   | 0.122                      |
| Cerebrovascular disease | 434 (10)                     | 714 (7)                        | 0.126                      | 212 (8)            | 222 (8)                   | 0.014                      |
| Other atherosclerosis | 11 (0)                        | 20 (0)                         | 0.015                      | 7 (0)              | 7 (0)                     | 0.008                      |
| Statin prescription | 2066 (49)                     | 4614 (44)                      | 0.103                      | 1227 (46)          | 1238 (47)                 | 0.008                      |
| Aspirin prescription | 1563 (37)                     | 3129 (30)                      | 0.156                      | 954 (36)           | 828 (31)                  | 0.101                      |
| Other COPD medication prescriptions | 295 (7)                     | 333 (3)                        | 0.175                      | 197 (7)            | 106 (4)                   | 0.148                      |
| LABA**            | 530 (13)                        | 842 (8)                        | 0.151                      | 230 (11)           | 333 (13)                  | 0.063                      |
| LAMA**            | 1450 (35)                       | 6284 (60)                      | 0.528                      | 1166 (44)          | 1177 (44)                 | 0.008                      |
| Type 2 diabetes   | 543 (13)                        | 1496 (14)                      | 0.040                      | 373 (14)           | 337 (13)                  | 0.04                      |
| History of cancer | 696 (17)                        | 2105 (20)                      | 0.091                      | 486 (18)           | 451 (17)                  | 0.035                      |
| Chronic kidney disease | 540 (13)                     | 1477 (14)                      | 0.037                      | 389 (15)           | 333 (13)                  | 0.062                      |
| Healthcare utilisation | 21 (15–29)                    | 16 (10–26)                     | 0.409                      | 18 (14–29)         | 16 (10–26)                | 0.143                      |
| GP consultations | 4 (2–7)                         | 5 (3–8)                        | 0.180                      | 4 (2–7)            | 5 (3–8)                   | 0.073                      |
| Distinct medications | 0 (0–1)                       | 0 (0–1)                        | 0.008                      | 0 (0–1)            | 0 (0–1)                   | 0.007                      |
| Hospitalisations | 0 (0–0)                         | 0 (0–1)                        | 0.022                      | 0 (0–0)            | 0 (0–0)                   | 0.011                      |

Data are presented as n, median [interquartile range], n (%) or mean±SD, unless otherwise stated. CPRD: Clinical Practice Research Datalink; FEV1; forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; LABA: long-acting β-agonist; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonist; GP: general practitioner. #: variables in this table that were included in the propensity score (see supplementary table A2-3 for list of variables included in final exacerbations propensity score model); †: TORCH inclusion/exclusion criteria applied and matched to TORCH individual patient data; ‡: TORCH inclusion/exclusion criteria applied; §: closest record prior to index date; ‡: all counted within the year prior to index, includes exacerbations recorded in primary or secondary care; ¶: any diagnosis for condition prior to index date; ¶¶: number who had at least one prescription within the previous year; ++: single product only; §§: combination product.
FRALICK et al. [15] applied trial criteria and utilised propensity score matching to replicate cardiovascular results from the ONTARGET trial (comparing telmisartan to ramipril).

Previous studies of COPD drug treatment effects

Results of five (LABA/ICS versus LABA) interventional studies (including TORCH) were summarised in a Cochrane review (rate ratio 0.76, 95% CI 0.68–0.84) [16]. Three out of these five studies estimated effect sizes considerably greater than TORCH; as we mirrored TORCH, our results aligned most closely to TORCH.

A number of studies have found strong survival benefits of ICS therapy after hospital discharge [17, 18]. After accounting for likely time-related biases impacting these studies, a null effect was obtained (rate ratio 0.94, 95% CI 0.81–1.09) [19]. The methodology we applied obtained a mortality effect estimate comparable to the analysis designed to account for time-related biases (0.93, 95% CI 0.65–1.32).

In line with TORCH, previous studies have found an increased risk of pneumonia associated with ICS-containing treatments for COPD [20, 21, 16]. Our result (risk ratio 1.39, 95% CI 1.04–1.87) was consistent with results of a meta-analysis of trials comparing LABA/ICS to LABA formulations.

### TABLE 2 Characteristics of the fluticasone propionate (FP)-salmeterol (SAL) versus SAL cohort before and after propensity score matching for the exacerbations analysis

| Variable                        | Before propensity score matching | After propensity score matching |
|---------------------------------|----------------------------------|---------------------------------|
|                                 | SAL                                | FP-SAL                          |
|                                 | Standardised difference          | Standardised difference        |
| Subjects                        | 1146                              | 11,235 exposed time periods     |
|                                 | from 4,523 people                 |                                 |
| Age years                       | 68 (62–73)                        | 68 (62–74)                      |
| Male#                           | 728 [64]                          | 6960 [62]                       |
| Lung function§                  | FEV₁, % pred                      | 49 (41–57)                      |
|                                 | FEV₁/FVC %                        | 53 (44–61)                      |
|                                 | BMI                               | 26 (23–30)                      |
| Prior exacerbations§            | 0.63±1.02                         | 0.61±1.07                       |
| Cardiovascular disease##        | Coronary heart disease            | 207 (18)                        |
|                                 | Peripheral vascular disease       | 71 (6)                          |
|                                 | Cerebrovascular disease           | 87 (8)                          |
|                                 | Other atherosclerosis             | 1 [0]                           |
| Statin prescription¶¶           | 462 (40)                          | 4906 (44)                       |
| Aspirin prescription¶¶          | 333 (29)                          | 3376 [30]                       |
| Other COPD medication prescriptions¶¶  |                                  |                                 |
| LABA++                          | 793 [69]                          | 98 [1]                          |
| ICS#,++                         | 419 [37]                          | 862 [8]                         |
| LAMA**                          | 477 [42]                          | 6598 [59]                       |
| ICS plus LABA§§                 | 28 [2]                            | 537 [5]                         |
| Type 2 diabetes##               | 116 [10]                          | 1549 [14]                       |
| History of cancer##             | 200 [17]                          | 2252 [20]                       |
| Chronic kidney disease####      | 104 [9]                           | 1535 [14]                       |
| Healthcare utilisation§         | GP consultations n               | 15 [9–23]                       |
|                                 | Distinct medications n            | 5 [3–8]                         |
|                                 | Hospitalisations n                | 0 [0–1]                         |
|                                 | Hospital procedures n             | 0 [0–0]                         |
| Data are presented as n, median (interquartile range), n (%) or mean±SD, unless otherwise stated. CPRD: Clinical Practice Research Datalink; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; LABA: long-acting β-agonist; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonist; GP: general practitioner. #: variables in this table that were included in the propensity score (see supplementary table A2-3 for list of variables included in final exacerbations propensity score model); ¶: TORCH inclusion/exclusion criteria applied and matched to individual TORCH patients; #: TORCH inclusion/exclusion criteria applied; §: closest record prior to index date; ¦: all counted within the year prior to index; ##: any diagnosis for condition prior to index date; §§: number who had at least one prescription within the previous year; ††: single product only; ¤: combination product.

**Fraileck et al.** [15] applied trial criteria and utilised propensity score matching to replicate cardiovascular results from the ONTARGET trial (comparing telmisartan to ramipril).

### Previous studies of COPD drug treatment effects

Results of five (LABA/ICS versus LABA) interventional studies (including TORCH) were summarised in a Cochrane review (rate ratio 0.76, 95% CI 0.68–0.84) [16]. Three out of these five studies estimated effect sizes considerably greater than TORCH; as we mirrored TORCH, our results aligned most closely to TORCH.

A number of studies have found strong survival benefits of ICS therapy after hospital discharge [17, 18]. After accounting for likely time-related biases impacting these studies, a null effect was obtained (rate ratio 0.94, 95% CI 0.81–1.09) [19]. The methodology we applied obtained a mortality effect estimate comparable to the analysis designed to account for time-related biases (0.93, 95% CI 0.65–1.32).

In line with TORCH, previous studies have found an increased risk of pneumonia associated with ICS-containing treatments for COPD [20, 21, 16]. Our result (risk ratio 1.39, 95% CI 1.04–1.87) was consistent with results of a meta-analysis of trials comparing LABA/ICS to LABA formulations.
Our 3-year probability of treatment discontinuation for FP-SAL (28%) is comparable to non-adherence figures from previous non-interventional real-world data studies (49% [23] and 43% [24]). The probability of discontinuation of salmeterol that we observed (77%) was higher than these two previous non-interventional studies, leading to the discrepancy with TORCH. We hypothesised that during our study period a large proportion of the patients who would have been initially prescribed salmeterol would have been likely to switch to FP-SAL due to prescribing decisions in primary care; a post hoc analysis found that 43% of people prescribed salmeterol switched to FP-SAL during follow-up (compared to only 2% switching from FP-SAL to salmeterol).

Implications and further work
When studying COPD treatment effects, if 1) the analysis is of active comparators; 2) trial exclusion and inclusion criteria are applied; and 3) the propensity score models that we developed for each outcome are applied to balance exposure groups, then the results of studies carried out in routinely collected non-interventional data can be considered robust in the sense that they will be highly comparable to trial results. This now provides a methodological framework for being able to analyse COPD drug treatment effects in real-world data, focusing on groups that were either not included or underrepresented in trials [2].

Our inability to replicate placebo-controlled analyses suggests uncontrolled confounding by indication [25]. One possibility for how this confounding by indication may be manifesting relates to the aspect of our study...
design that allowed people to be included in both the exposed and unexposed cohorts; the result we obtained could be strongly influenced by people initially in the unexposed group who are relatively healthy, but then get sicker over time and require FP-SAL treatment and end up in the exposed group. However, in a post hoc analysis of exacerbations, mortality, pneumonia and time to treatment discontinuation for fluticasone propionate (FP)-salmeterol (SAL) versus SAL (compared to TORCH results)

| TABLE 4 Results for the analysis of exacerbations, mortality, pneumonia and time to treatment discontinuation for fluticasone propionate (FP)-salmeterol (SAL) versus SAL (compared to TORCH results) |
|-----------------------------------------------|
| **CPRD non-interventional population** | **TORCH trial population** |
| SAL | FP-SAL | SAL | FP-SAL |
| Subjects | 1146 | 11235 | 1521 | 1533 |
| **Exacerbations** | | | | |
| Person-years at risk | 2566 | 24062 | 0.88 (0.81–0.95) | 1.64 (1.52–1.77) |
| Events | 1515 | 14034 | 0.73 | 1.06 |
| Rate per person per year | 0.73 | 0.59 | 0.97 | 0.85 |
| Crude rate ratio | 1 | 0.80 (0.72–0.88) | 1 | 0.85 (0.81–0.95) |
| Propensity matched rate ratio | 1 | 0.85 (0.74–0.97) | 1 | 0.85 (0.81–0.95) |
| **Mortality** | | | | |
| Person-years at risk | 2566 | 24062 | 1.12 (0.94–1.34) | 1.47 (1.25–1.73) |
| Events | 138 | 1445 | 16.84 | 13.48 |
| Probability at 3 years§ % | 15.09 | 16.74 | 13.48 | 12.59 |
| Crude hazard ratio | 1 | 1.39 (1.04–1.87) | 1 | 1.47 (1.25–1.73) |
| Propensity matched hazard ratio | 1 | 0.93 (0.65–1.32) | 1 | 0.93 (0.77–1.13) |
| **Pneumonia** | | | | |
| Events | 86 | 1137 | 7.50 | 10.12 |
| % of total patients | 7.50 | 10.12 | 13.29 | 19.60 |
| Crude risk ratio | 1 | 1.35 (1.09–1.66) | 1 | 1.47 (1.25–1.73) |
| Propensity matched risk ratio | 1 | 1.39 (1.04–1.87) | 1 | 1.47 (1.25–1.73) |

Data are presented as n, unless otherwise stated. CPRD: Clinical Practice Research Datalink. §: only results reported in the TORCH trial publication are shown; †: calculated using a Cox proportional-hazards model; #: n=991 in each exposure group after propensity score matching [see supplementary table A2-3 for list of variables contributing to propensity score for exacerbations analysis]; ‡: n=443 in each exposure group after propensity score matching [see supplementary table A2-3 for list of variables contributing to propensity score for mortality analysis]; †: n=996 in each exposure group after propensity score matching [see supplementary table A2-3 for list of variables contributing to propensity score for pneumonia analysis]; ‡: n=935 in each exposure group after propensity score matching [see supplementary table A2-3 for list of variables contributing to propensity score for time to treatment discontinuation analysis].

TABLE 5 Impact of choice of selection methods on ability to replicate trial results for the analysis of exacerbations, in people exposed to fluticasone propionate (FP)-salmeterol (SAL) versus people exposed to SAL

| Rate ratio | Subjects per exposure group n |
|-----------|-------------------------------|
| **TORCH trial** | | |
| SAL | FP-SAL | SAL | FP-SAL |
| Subjects | 1524 | 1533 | 1521 | 1533 |
| **CPRD non-interventional selection method** | | | |
| TORCH inclusion and exclusion criteria and matched to TORCH§ | 1 | 0.85 (0.74–0.97) | 1 | 0.85 (0.74–0.97) |
| TORCH inclusion and exclusion criteria only | 1 | 0.87 (0.81–0.94) | 1 | 0.87 (0.81–0.94) |
| No TORCH criteria or matching | 1 | 1.64 (1.52–1.77) | 1 | 1.64 (1.52–1.77) |

CPRD: Clinical Practice Research Datalink. §: SAL and FP-SAL groups were propensity score matched for all selection methods; †: as per the main analysis and presented in table 4.
One point of note relates to the large difference in incidence rate between the TORCH placebo group (1.13 exacerbations per person per year) and our FP-SAL unexposed group (0.53 exacerbations per person per year). In order to investigate underlying reasons for this discrepancy, we performed a post hoc analysis where we compared the characteristics of the 1753 people from TORCH who were not able to be matched to our unexposed to FP-SAL population in Step 3 with those who were successfully matched. We found that those not matched were younger (mean age 60.7 years versus 65.8 years), sicker (e.g. history of cardiovascular disease 93% versus 46%), had worse lung function (e.g. FEV₁ 34.9% pred versus 45.9% pred), and included a higher proportion recruited from Eastern European trial sites (27% versus 17%). People with these characteristics may have been highly suitable for recruitment to clinical trials, but are very difficult to find in UK primary care, and illustrate why it is likely to be challenging to obtain comparable absolute rates in emulated cohorts within a single country based on historical international trials.

Previous authors have recommended that when trying to emulate trial results, it is important to choose an active comparator trial [15]. However, there are examples where placebo-controlled analyses have been successfully replicated [13, 14]. One possibility is that replication of placebo-controlled results works better when the drug studied is 1) preventative and 2) used in a generally healthy cohort (for example, the cited studies were of statins and of post-menopausal hormone therapy both prescribed in some instances to people without a specific underlying chronic disease, in contrast to the patients with COPD who received therapy in our study). We consider that further avenues of research could be followed to understand if there remains a possibility of replicating placebo-controlled studies within a non-interventional setting for COPD therapies. These could include application of high-dimensional propensity scores or the use of instrumental variables. In addition, our work suggests that treatment discontinuation in the setting of non-interventional data may be driven by very different factors to those seen in trials and, at least in the setting of COPD, may not be a useful outcome to study. For example, it is difficult to establish from routinely collected data whether a patient has truly stopped taking their medicine, or is just taking the medicine differently than prescribed (e.g. is taking less than has been prescribed over a longer period).

Finally, in our post hoc analysis we found that the application of the trial-matching step did not confer any advantage over application of trial criteria alone in this setting. This suggests that treatment-covariate interactions are not as critical as we initially thought in this therapeutic area.

Limitations

Some of the TORCH inclusion criteria were not fully assessable using CPRD data, meaning that the inclusion/exclusion criteria are analogous with TORCH criteria, but we acknowledge they are not identical. We originally planned to apply frequency of COPD therapy prescriptions in the previous year as a matching character/criteria. In practice, this was not feasible. However, it appears that matching at this level of detail was not required to be able to replicate trial results for active comparator analysis. Finally, within TORCH, the dose of the fixed combination product FP-SAL was specified as 500 µg of FP and 50 µg of SAL (500/50), and the dose of SAL alone as 50 µg, whereas in our study we did not limit to a specific dose. The reason for this is that dosage information is incompletely captured in CPRD, but as these are the only approved doses of FP-SAL and of SAL for COPD in the UK, we consider the doses that people were prescribed in our study would have been generally similar to that administered in the TORCH trial.

Conclusions

By replicating the COPD TORCH trial selection procedures and inclusion/exclusion criteria in real-world data and developing propensity score models to account for any remaining differences between groups, we were able to obtain highly comparable relative effect estimates to the TORCH RCT active comparator analysis for exacerbations, mortality and pneumonia. Replication of placebo-controlled analyses was not possible, and further work to investigate whether likely residual confounding by indication can ever be accounted for in this therapeutic area is warranted. Application of the same selection procedures and propensity score models developed here to active comparator analyses of COPD drug treatment effects in groups underrepresented or excluded from trials provides a practical way for key evidence gaps to be filled.

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