Supplemental Material

Supplemental Methods

Data source

The NHFA was established in 2007 for hospitals in England-Wales to assess the quality of care and outcomes of hospitalised patients with a HF diagnosis in the first position at death or discharge, identified using ICD-10 codes (**Supplementary Table 1**). Admissions coded in the audit are compared to HF episodes in the Hospital Episode Statistics (HES) in England and the Patient Episode Database of Wales (PEDW) to determine the case ascertainment rate. The number of participating NHS trusts fluctuated from 145 in 2012–13 (97%) to 136 (82%) in 2017/2018. This corresponds to an increase from capturing 60% of national HF admissions in 2012, to 76% at the end of April 2018. Data are entered into the audit by hospital staff, using case ascertainment forms and data are categorised as mandatory (main indicators such as HF treatments, comorbidities, echocardiography) or non-mandatory (i.e., smoking status, pulmonary oedema, ethnicity). Since non-mandatory data elements are not expected to be included, there are considerable proportions of missing data across these variables (**Supplemental Table 2**). Some mandatory variables also have significant amounts of missing data (e.g., more than 70% missing data on BNP measurements, weight, height). The breadth of variables collected varied throughout the history of the audit, to reflect changes in HF guidelines and quality standards, which evolved over time. For example, haemoglobin and serum creatinine were collected routinely only after 2012[1].

Statistical analysis

The analysis for the main outcome was implemented in a stepwise manner. First, an unconditional model including, COPD was considered. In a second step we added asthma. Third, we added an interaction term between COPD and asthma, to assess whether both diagnoses had a significant contribution to the model. In lack of statistical significance these patients were not considered in further analyses. We then evaluated effect modification by EF status (HFrEF/HFpEF) by including separately an interaction term between COPD and EF, then asthma and EF.

Handling of missing data

Sensitivity analysis – missing data imputation

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While the proportions of missing data (see above) were considerable, we deemed necessary to investigate further two important factors: “smoking status” and “Body Mass Index (BMI)”. In particular, we were interested in assessing whether COPD has an independent association with death in patients with HF, when controlling for smoking status, or whether the relationship is influenced by this factor.

We assumed data on smoking and BMI to be missing at random in our cohort, as the distribution in observed cases was similar to other UK cohorts of patients with HF[2 3]. We then used a multi-level approach[4] which takes into consideration the hierarchical data structure, clustered at hospital level. A Gibbs sampling procedure was used to generate 20 imputed data sets after a burn-in of 1000 iterations.

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Table 1. Inclusion criteria for National Heart Failure Audit

ICD-10 code	**Diagnosis**
I11.0	Hypertensive heart disease with (congestive) heart failure
I25.5	Ischaemic cardiomyopathy
I42.0	Dilated cardiomyopathy
I42.9	Cardiomyopathy, unspecified
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
ICD= International Statistical Classification of Diseases and Related Health Problems	

Table 2. Comorbidity definitions, according to NHFA dataset[1], variables recorded from patient history

COPD	History of COPD - chronic bronchitis, emphysema or their cooccurrence. Must be indicated by pulmonary function testing evidence .ie FEV1<75% predicted value or use of beta agonist/steroid inhalers.
Asthma	History of childhood asthma and atopy, or asthma confirmed by respiratory physician for adult onset.
Diabetes	Diagnosis of diabetes prior to admission. This includes a confirmed diagnosis of diabetes and/or the use of an oral hypoglycaemic agent or insulin, and/or a fasting blood glucose >6.7, and/or a random blood glucose >11.
Hypertension	Recorded Blood Pressure >140/90 on at least two occasions prior to admission, or already receiving treatment (drug, dietary or lifestyle) for hypertension
Ischemic heart disease	History of myocardial infarction, angina, ECG evidence of MI, CABG or angiogram documenting coronary artery disease.
Cerebrovascular accident	A past neurological deficit of cerebrovascular cause, including episodes that persist beyond 24 hours and transient ischaemic attacks lasting less than 24 hours.
Atrial fibrillation	An ECG was performed showing atrial fibrillation.
Valve disease	History of clinically diagnosed valve disease, moderate or severe stenosis or regurgitation on imaging, or an operative valve replacement/repair

[1] Available: https://www.nicor.org.uk/national-cardiac-audit-programme/datasets/

Table 3. Model building - association between COPD, asthma (including interaction with ejection fraction group) and in-hospital death in patients hospitalised for heart failure.

Predictors	Model 1	Model 2	Model 3	Model 4	Model 5a	Model 5b	Model 6
Fixed effects [coefficient estimate, SE]							
COPD	0.064 [0.017, p<0.001]	0.0706 [0.0174, p<0.001]	0.060 [0.018, p<0.001]	-0.0445 [0.0256, p=0.081]	0.064 [0.017, p<0.001]	-0.029 [0.0242, p=0232]	0.0468 [0.026, p=0.081]
Asthma	-	-0.263 [0.0255, p<0.001]	-0.287 [0.029, p<0.001]	-0.302 [0.040, p<0.001]	-0.2719 [0.034, p<0.001]	-0.266 [0.0255, p<0.001]	-0.179 [0.028, p<0.001]
COPD*Asthma	-	-	**0.098 [0.0573, p=0.087]**	0.149 [0.076, p=0.051]	-	-	-
EF	-	-	-	-0.208 [0.015, p<0.001]	-0.173 [0.014, p<0.001]	-0.207 [0.0149, p<0.001]	0.0410 [0.017, p<0.05]
COPD *EF	-	-	-	**0.205 [0.036, p<0.001]**	**-**	**0.195 [0.034, p<0.001]**	**0.096 [0.037, p<0.05]**
Asthma*EF	-	-	-	**0.018 [0.058, p=0.753]**	**0.013 [0.05, p=0.797]**	-	-
COPD*Asthma*EF	-	-	-	**-0.093 [0.112, p=0.402]**	-	-	-
Age	-	-	-	-	-	-	0.553 [0.0101, p<0.001]
Female (vs. male)	-	-	-	-	-	-	-0.0922 [0.0150, p<0.001]

Valve disease	-	-	-	-	-	-	0.219 [0.0169, p<0.001]
IHD	-	-	-	-	-	-	0.1204 [0.015, p<0.001]
Hypertension	-	-	-	-	-	-	-0.220 [0.0148, p<0.001]
Diabetes	-	-	-	-	-	-	0.0489 [0.0164, p<0.01]
AF	-	-	-	-	-	-	-0.0056 [0.0147, p=0.703]
NYHA	-	-	-	-	-	-	0.116 [0.018, p<0.001]
Place of care (cardiology vs not cardiology)	-	-	-	-	-	-	-0.363 [0.0168, p<0.001]
Random effects (hospitals, n=219)							
Variance	0.205	0.208	0.208	0.201	0.201	0.201	0.159
SD	0.453	0.456	0.456	0.448	0.449	0.449	0.399
AIC	160533.4	158837.1	158836.2	158652.0	158681.2	158649.7	133038.5

Abbreviations
AIC= Akaike information criterion; AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation; SE= standard error

Results from a 2-level unconditional model that included COPD as fixed-effect and hospital as random effect suggested COPD was associated with an increase in the estimate for in-hospital mortality. The addition of asthma to this model indicated it had an inverse relationship with likelihood of death. A test for the interaction between COPD and asthma was not significant, thus, it was not considered in subsequent analyses. Further, we wanted to assess whether the effects of COPD, respectively asthma on in-hospital death are different with respect to EF status group therefore, we added a three-way interaction between COPD, asthma and EF to the model. We detected a significant interaction between COPD and EF only, suggesting the effect of COPD only, not asthma would

be differential according to the EF status. In the final model, we estimated the association between COPD and mortality in HFrEF and in HFpEF and adjusted for baseline covariates.

Table 4. Association between COPD, asthma and in-hospital death

Predictors	**COPD only (95% CI)**	**COPD + asthma**	**Fully adjusted model**	**Model with COPD and EF interaction, fully adjusted OR (95% CI)**
Fixed effects (95% CI)				P-value for interaction =0.01
COPD	**1.07 (1.03 – 1.10)**	**1.07 (1.04-1.11)**	**1.10 (1.06 – 1.14)**	1.04 (0.99-1.10)
Asthma	**-**	**0.77 (0.73 – 0.80)**	**0.84 (0.79, 0.88)**	0.83 (0.79-0.88)
COPD (Yes vs. No): HFpEF	-	-	**-**	**1.05 (0.99 – 1.10)**
COPD (Yes vs. No): HFrEF	-	-	**-**	**1.15 (1.09 – 1.21)**
Age	-		1.74 (1.71 -1.78)	1.74 (1.71-1.77)
Female (vs. male)	-		0.91 (0.89-0.94)	0.91 (0.89-0.94)
Valve disease	-		1.25 (1.20-1.29)	1.25 (1.20-1.29)
IHD	-		1.12 (1.10-1.16)	1.13 (1.10-1.16)
Hypertension	-		0.8 (0.78-0.83)	0.80 (0.78-0.83)
Diabetes	-		1.05 (1.02-1.08)	1.05 (1.02-1.08)
AF	-		0.99 (0.97-1.02)	0.99 (0.96-1.02)
NYHA (III/IV vs. I/II)	-		1.12 (1.08-1.17)	1.12 (1.08-1.17)
Place of care (cardiology vs. not cardiology ward)	-		0.69 (0.67-0.72)	0.69 (0.67-0.71)
Random effects (Variance)				
LR test p-value	P<0.001	P<0.001	P<0.001	P<0.001
Likelihood ratio test comparing fixed to random effects for hospital model fit, significant indicates random effects model performed better than fixed effects model Abbreviations				

AF= atrial fibrillation; COPD= chronic obstructive pulmonary disease; CI=confidence intervals; EF= ejection fraction; LR= Likelihood ratio test; NYHA= New York Heart Association; IHD= ischemic heart disease; SD= standard deviation.

Table 5. Association between COPD and in-hospital mortality in patients hospitalised with heart failure. Results from 20 models using imputed smoking status and BMI (estimates combined using Rubin's rule).

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.12 (1.07 – 1.17)
Asthma	0.84 (0.80 – 0.90)
Age	1.67 (1.62 – 1.71)
Female (vs. male)	0.89 (0.86 – 0.92)
Valve disease	1.22 (1.18 – 1.26)
IHD	1.13 (1.10 – 1.17)
Hypertension	0.82 (0.89 – 0.85)
Diabetes	1.12 (1.08 – 1.15)
AF	1.01 (0.98 – 1.04)
NYHA (III/IV vs. I/II)	1.15 (1.10 – 1.20)
Place of care (cardiology vs. no cardiology ward)	0.70 (0.69 – 0.73)
EF	1.03 (0.99 – 1.06)
Smoking status (ref: Current smoker)	
Ex-smoker	0.90 (0.77 – 1.06)
Never	1 (0.84 – 1.19)
BMI (ref: normal weight)	
Underweight	1.31 (1.21 – 1.43)
Overweight	0.86 (0.81 – 0.91)
Obese	0.77 (0.73 – 0.81)
Random effects (Variance)	
LR test p-value	P<0.001

Abbreviations
AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; NYHA= New York Heart Association; OR= Odds ratio; ref= reference

Table 6. Association between COPD and in-hospital mortality in patients hospitalised with a confirmed diagnosis of HF.

	Fully adjusted model, OR (95% CI)
Fixed effects (95% CI)	
COPD	1.11 (1.07 - 1.16)
Asthma	0.84 (0.79 - 0.89)
Age	1.04 (1.04 - 1.05)
Female (vs. male)	0.91 (0.88 - 0.94)
Valve disease	1.26 (1.22 - 1.30)
IHD	1.15 (1.11 - 1.18)
Hypertension	0.81 (0.79 - 0.84)
Diabetes	1.06 (1.03 - 1.10)
AF	0.98 (0.95 - 1.01)
NYHA (III/IV vs. I/II)	1.13 (1.08 - 1.18)
Place of care (cardiology vs. no cardiology ward)	0.69 (0.66 - 0.71)
EF	1.04 (1.01 - 1.08)
Random effects (Variance)	0.166
LR test p-value	p<0.001
Abbreviations AF= atrial fibrillation; BMI= Body Mass index; CI= confidence intervals; COPD= chronic obstructive pulmonary disease; EF= ejection fraction; IHD= ischemic heart disease; LR= Likelihood ratio test; NYHA= New York Heart Association; OR= Odds ratio; ref= reference	

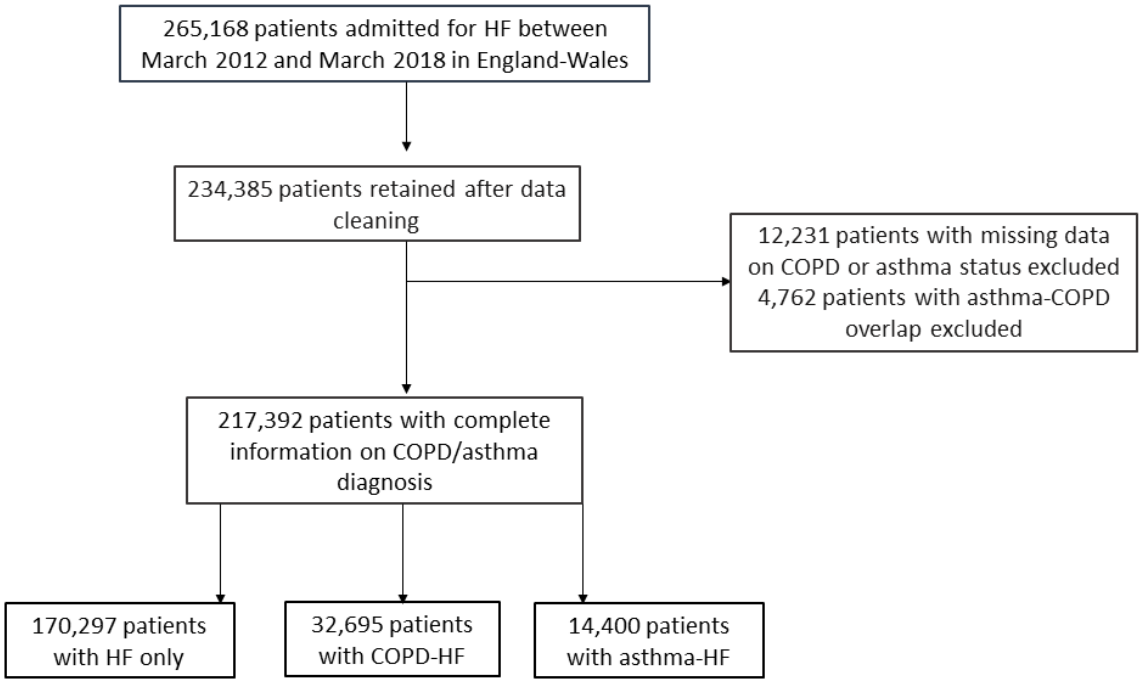
Table 7. Variables with considerable missingness in the National Heart Failure Audit 2012-2018

	HF alone (N=170297)	COPD + HF (N=32695)	Asthma + HF (N=14400)	Overall (N=217392)
Cerebrovascular accident	2882 (1.7%)	582 (1.8%)	244 (1.7%)	3708 (1.7%)
Missing	145636 (85.5%)	28115 (86.0%)	12279 (85.3%)	186030 (85.6%)
Alcohol units/week				
Median [Q1, Q3]	0 [0, 1.00]	0 [0, 2.00]	0 [0, 0]	0 [0, 1.00]
Missing	159233 (93.5%)	30570 (93.5%)	13314 (92.5%)	203117 (93.4%)
Smoking status				
Current smoker	1869 (1.1%)	911 (2.8%)	143 (1.0%)	2923 (1.3%)
Ex-smoker	8371 (4.9%)	2505 (7.7%)	715 (5.0%)	11591 (5.3%)
Never-smoker	8823 (5.2%)	673 (2.1%)	896 (6.2%)	10392 (4.8%)
Missing	151234 (88.8%)	28606 (87.5%)	12646 (87.8%)	192486 (88.5%)
Chest X-ray (pulmonary oedema)	3954 (2.3%)	692 (2.1%)	334 (2.3%)	4980 (2.3%)
Missing	157253 (92.3%)	30528 (93.4%)	13311 (92.4%)	201092 (92.5%)
Medications at admission				
ACEi	6316 (3.7%)	1116 (3.4%)	513 (3.6%)	7945 (3.7%)
Contraindicated	592 (0.3%)	140 (0.4%)	59 (0.4%)	791 (0.4%)
Missing	152642 (89.6%)	29598 (90.5%)	12903 (89.6%)	195143 (89.8%)
ARB	2392 (1.4%)	453 (1.4%)	305 (2.1%)	3150 (1.4%)
Not applicable	2570 (1.5%)	513 (1.6%)	240 (1.7%)	3323 (1.5%)
Stopped	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Contraindicated	338 (0.2%)	88 (0.3%)	32 (0.2%)	458 (0.2%)
Missing	151870 (89.2%)	29463 (90.1%)	12781 (88.8%)	194114 (89.3%)
Beta-blocker	9516 (5.6%)	1446 (4.4%)	598 (4.2%)	11560 (5.3%)
Not applicable	762 (0.4%)	144 (0.4%)	88 (0.6%)	994 (0.5%)
Contraindicated	153 (0.1%)	136 (0.4%)	74 (0.5%)	363 (0.2%)
Missing	151820 (89.2%)	29481 (90.2%)	12831 (89.1%)	194132 (89.3%)
Loop diuretic	5519 (3.2%)	1202 (3.7%)	490 (3.4%)	7211 (3.3%)

Missing	160255 (94.1%)	30820 (94.3%)	13532 (94.0%)	204607 (94.1%)
Thiazide or Metolazone	925 (0.5%)	140 (0.4%)	81 (0.6%)	1146 (0.5%)
Stopped*	-	-	-	-
Missing	152559 (89.6%)	29604 (90.5%)	12891 (89.5%)	195054 (89.7%)
MRA	2356 (1.4%)	502 (1.5%)	221 (1.5%)	3079 (1.4%)
Not applicable	225 (0.1%)	45 (0.1%)	27 (0.2%)	297 (0.1%)
Contraindicated	36 (0.0%)	*	*	42 (0.0%)
Missing	152494 (89.5%)	29570 (90.4%)	12885 (89.5%)	194949 (89.7%)
Digoxin	1700 (1.0%)	399 (1.2%)	168 (1.2%)	2267 (1.0%)
Missing	152631 (89.6%)	29622 (90.6%)	12874 (89.4%)	195127 (89.8%)
CCB	2847 (1.7%)	479 (1.5%)	280 (1.9%)	3606 (1.7%)
Missing	155279 (91.2%)	30261 (92.6%)	13150 (91.3%)	198690 (91.4%)
Bronchodilators	919 (0.5%)	1390 (4.3%)	750 (5.2%)	3059 (1.4%)
Missing	155316 (91.2%)	30248 (92.5%)	13136 (91.2%)	198700 (91.4%)
Ivabradine	186 (0.1%)	64 (0.2%)	31 (0.2%)	281 (0.1%)
Missing	153320 (90%)	29666 (90.7%)	12845 (89.2%)	195831 (90.1%)
BMI				
Median [Q1, Q3]	26.5 [22.9, 31.1]	27.1 [22.8, 32.2]	28.0 [23.6, 33.7]	26.7 [22.9, 31.4]
Missing	125287 (73.6%)	23693 (72.5%)	10274 (71.3%)	159254 (73.3%)
BNP				
Median [Q1, Q3]	428 [1.00, 1100]	350 [1.00, 985]	353 [1.00, 871]	412 [1.00, 1070]
Missing	153043 (89.9%)	29385 (89.9%)	12978 (90.1%)	195406 (89.9%)
NT_proBNP				
Median [Q1, Q3]	2790 [404, 7530]	2490 [349, 6820]	2440 [426, 6330]	2700 [393, 7320]
Missing	153022 (89.9%)	29161 (89.2%)	12818 (89.0%)	195001 (89.7%)

*not shown due to small numbers policy
ACEi= angiotensin-converting-enzyme inhibitors; ARB= angiotensin receptor blockers; BMI= Body mass index; BNP= brain natriuretic peptide; NT_proBNP= N-terminal (NT)-pro hormone BNP; MRA=mineralocorticoid receptor antagonist

Figure 1. Study flow
HF= heart failure; COPD=chronic obstructive pulmonary disease



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