Electronic Appendices

Table of contents

E-Appendix A: Tables 7

A1 Prognostic factors in HF 7

A2 Validation of HF prognostic models 8

A3 Causal criteria 9

A4 Final database search results 10

A5 Data extracted from each article that was included in the final review 12

A6a Formula for combining the mean and standard deviation of groups 13

A6b Alternative formula for combining the mean and standard deviation of groups 13

A7a QUIPS Domains 13

A7b Objective information assessed during quality appraisal and supplementary criteria 14

A8 Study characteristics: prognostic factors (chronic disease focus) studies 15

A9 Study characteristics: prognostic factors (general) studies 22

A10 Study characteristics of prognostic model studies 27

A11 Study Risk of bias assessment 31

A11 cont'd Study Risk of bias assessment: additional assessments for prognostic model studies 37

A12 Sensitivity analysis summary: Diabetes comorbidity 38

A13 Sensitivity analysis summary: CKD comorbidity 38

A14 Heart failure selection code set 39

A15 Exclusion criteria for CPRD heart failure cohort 40

A16 Baseline characteristics of the sample comparing the pre-match sample with the matched sample: mortality 41

A17 Baseline characteristics of the sample comparing the pre-match sample with the matched sample: first hospital admission 42

A18 COPD drug severity framework; extraction algorithms 43
A19 Missing data 45
A20 Exploration of missing data by mortality outcome 46
A21 Exploration of missing data by hospital admission outcome 47
A22 Pre and post imputed data: mortality outcome 48
A23 Pre and post imputed data: hospital admission linked sub-sample 49
A24 Summary of goodness of fit measures 50
A25 Baseline characteristics of the HF sample by mortality outcome in short, medium and long follow up periods 51
A26 Baseline characteristics of the HF sample by mortality outcome in two temporal periods of HF diagnosis (pre and post April 2006) 53
A27 Time-matched patient characteristics of the matched sample by comorbid COPD status 54
A28 Time-matched general characteristics of the matched sample by comorbid diabetes mellitus status 55
A29 Time-matched general characteristics of the matched sample by comorbid CKD status ..... **Error! Bookmark not defined.**
A30 Baseline Characteristics of the HF-HA sample by first hospital admission outcome in short, medium and long follow up periods 57
A31 Time-matched general characteristics of the matched hospital admission linked sample by comorbid COPD status 59
A32 Time-matched general characteristics of the matched sample by comorbid DM status 60
A33 Time-matched general characteristics of the matched sample by comorbid CKD status 61
A34 Unadjusted associations of each comorbidity with mortality by status (present or not) and then in strata of the potential confounders 62
A35 Adjusted comorbidity associations with all-cause mortality by each potential confounder 63
A36 Summary of linearity investigations for continuous variables and mortality 65
A37 Unadjusted associations of each comorbidity by status (present or not) with first hospital admission and then in strata of the potential confounders 66
A38 Adjusted comorbidity associations with first hospital admission by each potential confounder 67
A39 Summary of linearity investigations for continuous variables with risk of first hospital admission 69
E-Appendix B: Figures 70

B1 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid DM in HF 70
B2 Funnel plot for adjusted all-cause mortality risk associated with comorbid DM with pseudo 95% confidence intervals 70
B3 All-cause mortality associated with comorbid DM: prognostic factor (general) 71
B4 All-cause mortality associated with comorbid DM: prognostic model studies 71
B5 All-cause hospital admission risk associated with comorbid DM in HF 72
B6 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid COPD in HF 72
B7 Funnel plot for adjusted all-cause mortality risk associated with comorbid COPD with pseudo 95% confidence intervals 73
B8 All-cause mortality associated with comorbid COPD: prognostic factor (general) and prognostic model studies 73
B9 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid RD 74
B10 Funnel plot for adjusted all-cause mortality risk associated with any RD with pseudo 95% confidence intervals 74
B11 All-cause mortality associated with comorbid RD: prognostic factor (general) studies 75
B12 All-cause mortality associated with comorbid RD: prognostic model studies 75
B13 All-cause hospital admission associated with comorbid RD: prognostic factor (general) and model studies 75
B14 Comorbidities at baseline by mortality outcome 76
B15 Comorbidity combinations at baseline by mortality outcome 76
B16 Comorbidities at baseline by first hospital admission outcome 77
B17 Comorbidity combinations at baseline by event status 77
E-Appendix C: Statistical output 78
C1 Combined adjusted all-cause mortality risk associated with comorbid diabetes 78
C2 Sensitivity analysis removing From et al (2006) (combined adjusted all-cause mortality risk associated with diabetes) 78
C3 Sensitivity analysis removing Gustafsson et al (2004) (combined adjusted all-cause mortality risk associated with diabetes) 79
C4 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid diabetes). 79
C5 Sensitivity analysis removing Berry et al (2008) and Burger et al (2005) (combined adjusted all-cause mortality risk associated with comorbid diabetes). 80

C6 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid diabetes). 80
C7 Combined adjusted all-cause mortality risk associated with comorbid COPD 81
C8 Sensitivity analysis removing Lainscak (2009) (combined adjusted all-cause mortality risk associated with comorbid COPD) 81
C9 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid COPD). 82
C10 Combined adjusted all-cause mortality risk associated with any renal dysfunction 82
C11 Sensitivity analysis removing Campbell et al (2009) (combined adjusted all-cause mortality risk associated with comorbid RD) 83
C12 Sensitivity analysis removing Ismailov et al (2007) (combined adjusted all-cause mortality risk associated with comorbid RD) 83
C13 Sensitivity analysis removing Campbell et al (2009) and Ismailov et al (2007) (combined adjusted all-cause mortality risk associated with comorbid RD) 84
C14 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid COPD). 84
C15 Correlation matrix for covariates for mortality outcome 85
C16 Correlation matrix for centred covariates with quadratic extensions 86
C17 Correlation matrix of variables in hospital admission linked HF cohort 87
C18 Correlation matrix for centred covariates with quadratic extensions; hospital admission outcome 88
E-Appendix D: Protocols 89
D1 Systematic review: PROSPERO protocol 89
D2 CPRD scientific protocol 98
E-Appendix E: Miscellaneous 112
E1 Cochrane prognosis methods group letter 112
E2 Medline HF filter 112
E3 Heart failure string: database search results 113
E4 Heart failure search string 115
E5a Updated Haynes filter for MEDLINE 116
E5b Prognosis search filter for EMBASE 116

E5c Prognosis search filter for CINAHL 116
E6 Outcomes search string 117
E7 Inter-rater reliability assessment using Cohen's kappa 118
E8 Frequency of subject use in case control analyses 119
E9a Chronic obstructive pulmonary disease search strategy 120
E9b Diabetes mellitus search strategy 120
E9c Chronic kidney disease search strategy 120
E10 Chronic Obstructive Pulmonary Disease Code set 121
E11 Diabetes Mellitus Code set 125
E12 Chronic Kidney Disease Code set 145
E13 Comorbidity and covariate CPRD physiological data conversion and cleaning 152
E14 Exploration of continuous variables in the CPRD mortality sample 153
E15 Exploration of continuous variables in the CPRD hospital admission sample 156
E16 Testing the linearity assumption; continuous variable and all-cause mortality 160
E17 Testing the linearity assumption; continuous variable and first hospital admission 165
E18 Quality of life outcome study 1: HF and OA publication on QoL 169
E19 Quality of life outcome study 2: 2C_HF prospective hospital investigation 169
E20 Quality of life outcome study 3: Swedish HF registry study 183
E20 Trials acronyms 195
References 196

E-Appendix A: Tables

A1 Prognostic factors in HF(1,2)

Prognostic factors	Risk increasing factor
Environment	
Health care provision	Hospital admission Within hospital care, non specialist cardiology care
Treatments	No beta-blocker and/or ACEi
Deprivation	More deprived
Host	
Gender	Male
Age	Older age
Smoking	Current
BMI	Lower BMI
Cholesterol	Lower cholesterol
Functional class	Higher NYHA class
Exercise capacity	Lower peak exercise VO_2 Shorter distance in 6 minute walking test
Comorbidities	Chronic diseases (e.g. diabetes, COPD, renal disease, cardiovascular disease) and conditions (e.g. cachexia, anaemia, insulin resistance, depression)
Quality of life (QoL)	Patient reported lower quality of Life
HF Disease	
Aetiology	Ischemic heart disease Coronary artery disease
Cardiothoracic ratio	Higher ratio
Ejection fraction (EF)	In LVSD, lower EF
Hemodynamic variables	Reduced cardiac output Higher LV filling pressure or systemic vascular resistance Lower cardiac index Higher right atrial pressure
Neurohormones and blood chemistry	Higher plasma norepinephrine Low sodium Higher renin, aldosterone or angiotensin II Higher atrial natriuretic peptide Higher brain natriuretic factor, N-terminal pro-B-type natriuretic peptide Higher endothelin Higher cytokines (e.g beta interleukin-1, interleukin-6, C-reactive protein, alpha tumor necrosis factor) Higher uric acid
Arrhythmias	VT and AF
Heat rate variability	Reduced variability

A2 Validation of HF prognostic models

Model	Variables	Outcome and tool	Validation	Discrimination and calibration
HF survival score	Ischemic cardiomyopathy* QRS>120ms* LVEF HR Mean blood pressure Peak oxygen concentration Sodium	Outcome: Death OR urgent transplant/ ventricular assist device Tool: Score for three risk categories	8 Independent cohorts (2240 patients) Mean age 51-70 Men 65-82% Mean LVEF 20-30%	Discrimination: C-Index 0.56-0.79. Lower discrimination was found in more recent studies and where a higher percentage of beta blockers was prescribed or Implantable cardioverter defibrillator implanted (more contemporary interventions). Calibration: overestimated survival by 20% in low risk group in 1 study
Seattle HF model	Age, LVEF, NYHA, Systolic blood pressure, Diuretic dose (weight adjusted), Lymphocyte count Haemoglobin, Serum sodium Total cholesterol, Uric acid, Gender* Ischemic cardiomyopathy*, QRS>120ms* Beta blockers*, ACEi*, ARBs* Potassium sparing diuretic* Statins* Allopurinol*	Outcome: Death OR urgent transplant/ ventricular assist device Tool: Continuous risk score and predicted survival at 1, 2 and 5 years	14 independent cohorts (16,057 patients in total) Mean age 52-77 Men 61-82% Mean LVEF 17-45%	Discrimination: 0.63-0.81 (<0.7 in 50%). Lower discrimination where more ICD were implanted Calibration: High correlation between observed and predicted value (R-coefficient 0.97). Overestimated survival by 2% at one year and 10% at 5 years
Frankenstein et al's Model	Brain natriuretic peptide* 6-minute walk test (adjusted for gender and beta-blocker use)*	Outcome: All-cause mortality Tool: Three risk categories	1 independent cohort (676 patients) Mean age 74 Men 76%	Discrimination: 0.66-0.68 Calibration: not reported
PACE risk score (for ICD patients)	Peripheral vascular disease* Age>70yrs* Creatinine>2mg/dL*, LVEF<20%*	Outcome: all-cause mortality Tool: Continuous risk score from 1-5	1 independent (1812 patients) with ICD, Mean age 64 Men 77%, Mean LVEF 31-58%	Discrimination: 0.69 Calibration: not reported
SHOCK Predictors	Age>75yrs* NYHA>class II* Atrial fibrillation*, LVEF<20%* COPD*, Diabetes*	Outcome: Tool: Continuous risk score from 0-400 and estimates 1,2,3 and 4 year survival	1 independent ICD cohort (27,893 patients) Age: 39% >75yrs Men 75% 31% LVEF <20%	Discrimination: 0.74 Calibration: High correlation between observed and predicted value (R-coefficient 0.89). Goodness of fit inadequate at 2 and 3 years

Adapted from Alba et al (2013)(3)

A3 Causal criteria

Criterion	Meaning(4)	Considerations(5)
Strength	The magnitude of association between the exposure and effect.	The strength depends on the prevalence of other factors and can be confounded
Consistency	Whether the association is repeatedly observed by different persons and places	Causal relations have exceptions
Specificity	The exposure is related to a single outcome	There can have many effects from one cause
Temporality	The exposure needs to precede the effect	This can be difficult to measure
Biologic gradient	Changes to the exposure correspond to changes in the associated risk	This can be confounded and is often complicated by threshold effects
Plausibility	The possible causative relationship is biologically plausible	Subjective
Coherence	The possible causative relationship is coherent with general known facts or other population evidence	Similar to consistency and plausibility. Subjective and non-precise
Experimental evidence	The observed association is manipulated by experiment that assumes the causative relationship	Not always possible
Analogy	Other similar exposures produce similar outcomes	There are a lot of analogies

A4 Final database search results

No.	Search [Date of search]	MEDLINE 31/1/13	EMBASE 31/1/13	CINAHL 4/2/13
	POPULATION (title)			
1.	Heart failure	41834	57644	12229
2.	"Ventricular dysfunction"	3238	4278	698
3.	"Cardiac edema"	138	105	1
4.	"Heart edema"	1	1	0
5.	Cardiomyopathy	22000	28147	3514
6.	"Cardiac failure"	1957	2358	157
7.	"Myocardial failure"	137	145	8
8.	"Heart decompensation"	45	39	1
9.	"Ventric* failure"	4447	1044	91
10.	"Ventricular ejection fraction"	1235	1690	282
11.	"Cor Pulmonale"	2446	2339	67
12.	"diastolic dysfunction"	1340	2102	339
13.	"systolic dysfunction"	829	1239	303
14.	"congestive heart disease"	18	27	2
15	**1–14 combined using OR**	**74636**	**98484**	**17178**
	OUTCOMES (title/abstract)			
6	Mortalit*	421532	528340	60044
7	Death*	494668	604841	61670
8	Survival	531947	662909	40447
9	Admission*	124512	168010	26836
10	Readmission*	8561	11852	2780
11	Hospitalization* OR rehospitalization*	76726	103280	17013
12	"quality of life"	126212		
13	health	980189	180676	41997
14	"Kansas City Cardiomyopathy Questionnaire"	114	1165590	397359
15	KCCQ	81	186	46
16	"Minnesota Living with Heart Failure Questionnaire"	0	164	27
17	"Short form"	14951	512	107
18	Sf-36	11460	18119	4843
19	Sf36	663	15800	3643
20	Sf12	120	1286	3643
21	Sf-12	1769	275	606

22	EuroQol	1827	2561	606
23	EQ-5D	2309	2495	453
			3677	712
24	"Heart Failure Symptom Scale"	0	3	1
25	**6-24 combined using OR**	**2280022**	**2785858**	**557577**

No.	Medline Search Date of search	Hits	EMBASE Search	Hits	CINAHL Search	Hits
	PROGNOSIS					
26.	Predict[tiab]	177260	exp disease course/	1795632	TX "Disease course"	1735
27.	predictive value of tests[mh]	125552	risk*.mp	1978039	TX risk*	584679
28.	scor*[tiab]	467982	diagnos*.mp	2923603	TX diagnos*	688781
29.	observ*[tiab]	2261478	follow-up.mp	976807	TX follow-up	168955
30.	observer variation[mh]	28557	ep.fs	890615	MH "Epidemiology+"	332812
31.	"Stratification"	26322	outcome.tw	697229	TX outcome	230552
32.	"Roc curve"[Mesh]	24246				
33.	"Discrimination"	94561				
34.	"Discriminate"	36680				
35.	"c-statistic"	1288				
36.	"c statistic"	1288				
37.	"Area under the curve"	17482				
38.	"AUC"	30299				
39.	"Calibration"	56013				
40	"Indices"	104700				
41	"Algorithm"	88202				
42	"Multivariable"	24530				
43	Risk*[tiab]	1166759				
44	Hazard[tiab]	64704				
45	HR[tiab]	138588				
46	25–45 combined (OR)	4166006	26-31 combined (OR)	6687119	26-31 combined (OR)	1312829

COMBINED SEARCHES	**MEDLINE**	**EMBASE**	**CINAHL**
15 AND 24 AND 46	10616	23228	3397
LIMITED SEARCHES*	**6927**	**7789**	**2142**

*Medline: Human, Age>19, 1990> *Embase: Human, Age>18, 1990> *Cinahl: Adults, 1990>

A5 Data extracted from each article that was included in the final review

Data	Description
Study source	
- Author	First author surname
- Year	Year of publication
Methods	
-Design	Case-control, cohort, RCT, Other
-Trial/Database	Name of trial or database used
-Inclusion	Any important study inclusion criteria
-Exclusion	Any important study exclusion criteria
-Period	Date of recruitment period
-Follow-up length	Total, mean (SD)
Participants	
-Clinical definition	HF study definition used
- Setting	Community or hospital
-Sample size	Number of people in the study
-Centres/hospitals	Number of different centres/hospitals included
-Age	Mean (SD) or median (range)
-Gender	% male
-Systolic/LVF	% participants with EF<40% or study defined point)
-Ethnicity	% caucasian
-Ejection fraction	Mean (SD) or median (range)
-NYHA Stages	% with stage 3 and 4 HF
-Country	Country of residence
Exposure	
-Chronic Disease	Name of chronic disease included
-Study indicator	Type, severity, severity change measure
-Unit of measurement	Study definition of chronic disease factor
-No. included in study	Number of participants with the disease
-Prevalence	% of participants with the disease
Outcomes	Mortality, Hospital admission, Readmission, Health
Outcome definition	All-cause or health status measure
Primary or secondary outcome	Primary or secondary study outcome
Results	
- Participants included in the analysis	Number, Mean (SD) or median (range)
-Survival	Number of participants with the outcome
-Number outcome	Percentage of participants with the outcome
-Percentage outcome	Number of diseased participants with the outcome
-Number diseased who died	Percentage of diseased participants with the outcome
-Percentage diseased who died	Number with outcome per person years
-Rate	Odds, hazard, risk ratio or mean difference
- Effect type	Effect and confidence interval
-Unadjusted Effect estimate	
-P value	Significance level of confidence interval
-Significance level	Effect and confidence interval
-Adjusted Effect estimate	
-P value	Significance level of confidence interval
-Significance level	C statistic for model studies
-C statistic	
Analysis	
Study focus	Chronic disease focus, General predictor, prognostic model
Statistical technique	Logistic, linear, proportional hazards regression
Other factors adjusted for in the analysis	Yes or no

A6a Formula for combining the mean and standard deviation of groups (Adapted from Cochrane handbook)(6).

	Group 1 (e.g. males)	Group 2 (e.g. females)	Combined groups
Sample size	N_1	N_2	$N_1 + N_2$
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SD_1	SD_2	$\frac{\sqrt{(N_1 - 1)SD1^2 + (N_2 - 1){SD_2}^2}}{N1+N2 -1}$

A6b Alternative formula for combining the mean and standard deviation of groups(6)

	Group 1 (e.g. males)	Group 2 (e.g. females)	Combined groups
Sample size	N_1	N_2	$N_1 + N_2$
Mean	M_1	M_2	$\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$
SD	SD_1	SD_2	$\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}}$

A7a QUIPS Domains(7)

Domain	Goal
Study participation	To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants).
Study attrition	To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing participants).
Prognostic factor measurement	To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of outcome).
Outcome Measurement	To judge the risk of bias related to the measurement of outcome (differential measurement of outcome related to the baseline level of PF).
Study confounding	To judge the risk of bias due to confounding (i.e. the effect of PF is distorted by another factor that is related to PF and outcome).
Statistical analysis and reporting	To judge the risk of bias related to the statistical analysis and presentation of results.

A7b Objective information assessed during quality appraisal and supplementary criteria(8)

QUIPs Domains	Objective information assessed
Study participation	Baseline population discussed in some detail Sample described by key characteristics
Study attrition	Loss to follow-up <10%
Prognostic factor measurement	Description of chronic disease prognostic factor Method of missing data used
Outcome Measurement	Outcome measure/event is described
Study confounding	Confounders (or predictors for models) reported Confounders (or predictors for models) discussed/ rationale given
Statistical analysis and reporting	Adjusted AND unadjusted effects reported Interactions examined Linearity for continuous predictors assessed Proportional Hazards assumptions tested where relevant Predictor selection
Additional model factors considered	Correlations tested More than 10 events per variable Clinical tool developed Internal validation performed Discrimination assessed Calibration performed External validation

A8 Study characteristics: prognostic factors (chronic disease focus) studies

	Trial/ Database	Recruitment Period	Study Follow -up length	Follow-up Mean(SD)/ Median (IQR)* (R)ł	Heart Failure Clinical definition	Inclusions	Exclusions	Setting	Sample size (no. in analysis if different)	Centres/ hospitals	Country
DIABETES											
Ahmed 2007	DIG	1991-93	4.8y	38m*	Symptoms/signs or objective evidence		>=76y, Serious CM, high Cr, recent acute cardiac event/intervention	RCT	4112	Multicentre (n=302)	USA and Canada
Berry 2008		2000	33m	27(21-33)mł	Discharge code OR prescription +symptoms/signs or objective evidence	HF admission	Recent acute cardiac event/intervention	Hospital	454	Single	UK
Burger 2005	VMAC	1999-00		6m	Signs/ symptoms	Decompensated HF requiring diuretics	Low bp, high risk death	RCT	498	Multicentre (n=55)	USA
de Boer 2010	SENIORS			21(9)m	Clinical record + discharge code HF or low ef		<70y, significant renal dysfunction	RCT	2128	Multinational (n=11)	Europe
Flores-Le Roux 201		2000-02	6-9y		Discharge code			Hospital	400	Single	Spain
From 2006	REP	1979-99	20y	5(4.6)y	Discharge and Framingham criteria	Incident HF		Hospital/ Community	655	Regional	USA
Gerstein 2008	CHARM	1999-01		36.7m*	Clinical diagnosis	NYHA 2-4	Recent acute cardiac event/intervention, high CR, low bp, serious cardiac CM	RCT	2412	Multinational (n=26)	Multiple
Greenberg 2007	OPTIMIZE-HF	2003-04	6-9m		Clinical diagnosis			Hospital	5791	Multicentre (n=91)	USA
Gustafsson	DIAMOND	1993-95	5-8y		Symptoms/signs	NYHA 3-4	Recent acute	RCT	5491	Multicentre	Denmark

2004					or objective evidence		cardiac event/intervention			(n=34)	
Issa 2010	REMADHE	1999-07		3.6(2.2)y	Boston criteria	HF for >=6m	Recent acute cardiac event/intervention, serious CM	RCT	456	Single	Brazil
MacDonald 2008	Scottish morbidity data	1986-03	1y AND 5y		Discharge code	De novo HF		Hospital	55173 (MEN) 61383 (WOMEN)	Countrywide	UK
COPD											
De Blois 2010		2000-08	8y	13.3m	ESC guidelines			Hospital/ Community	4132 (3242)	Multicentre (n=22)	Norway
Iversen 1010	ECHOS			4.46(2.9-5.5)y‡	Symptoms/signs or objective evidence	Decompensated HF, NYHA 2-4	Recent acute cardiac event/intervention, serious cardiac CM	RCT	532	Multicentre (n=11)	Denmark
Lainscak 2009		2001-03	7y	2.9(2.1)y	Discharge code	X		Hospital	638	Single	Slovenia
Macchia 2007		2000-02	12m	9.6(4)m	Discharge code with prescription			Hospital	1020 (873)	Regional	Italy
Rusinaru 2008		2000,	5y		Framingham criteria amended by ESC	De novo HF	Severe cardiac disease	Hospital	799	Multicentre (n=11)	France
RENAL											
Aronson 2010	VMAC	1999-00	6m		Signs/ symptoms	Decompensated HF requiring diuretics	Low bp, high risk death	RCT	467	Multicentre (n=55)	USA
Breidthardt 2011		2001-2 and 2006-10	1y		ESC guidelines		Trauma, haemodialysis	Hospital	657	Multicentre (n=5)	Switzerland
Campbell 2009	DIG	1991-93	4.8y	38m*	Symptoms/signs or objective evidence		>=76y, Serious CM, high Cr , recent acute cardiac event/intervention,	RCT	4798	Multicentre (n=302)	United States and Canada

							rhythm				
Damman 2009	COACH	2002-07	18m		Symptoms/signs or objective evidence	Decompensated HF requiring diuretics	Recent acute cardiac event/intervention	RCT	1023	Multicentre (n=17)	Netherlands
Go 2006	Kaiser Permanente	1996-02		2.1(0.8-3.9)y*	Discharge code			Hospital/ Community	59772 (55170 known)	Regional	United States
Gotsman 2010		2001-02		6.5y	Symptoms/signs and/or reduced LVF		Heamodialysis	Hospital	355	Single	Israel
Hamaguchi 2009	JCARE-CARD	2004-05		2.4(0.7)y	Framingham criteria	Decompensated HF		Hospital	2013 (1617)	Multicentre (n=164)	Japan
Hillege 2006	CHARM	1999-01		34.4(1-45.2)mł	Clinical diagnosis	NYHA 2-4	Acute cardiac event or intervention, high CR, low bp, serious cardiac CM	RCT	2680	Multinational (n=26)	United States
Ismailov 2007		1995 and 2000	5 y		Framingham criteria		Recent acute cardiac event/intervention	Hospital	4350	Multicentre (n=11)	United States
Kimura 2010		2000-04	5 y	26.4(19.9)m	Framingham criteria	NYHA 2-4	Recent acute cardiac event/intervention, heamodyalisis, serious cardiac CM	Hospital	711	Single	Japan
Kociol	OPTIMIZE-HF	2003 -04	1 y		Discharge code		<65y, in-hosp death	Hospital	20063 (15792)	Multicentre (n=259)	United States
Maeder 2012	TIME-CHF	2003-06	18m		HF HA within 12 months, symptoms and BNP	NYHA 2-4, admission within 12mnths	<60y, high CR, serious CM, serious cardiac CM, BMI>35, recent acute cardiac event/intervention	RCT	566	Multicentre (n=15)	Switzerland/ Germany
Olandoski 2012		2005-06	4y	19.7(10.6)m	Clinical diagnosis	Incident admission with HF		Hospital	328	Regional	Brazil
Petretta		2002-05		15.2(0.3-	Framingham		Recent acute	Hospital	153	Single	Italy

2007			45.6)mł	criteria		cardiac event/intervention, list for device. Serious CM, serious cardiac CM, high CR, dialysis				
Takagi 2010	2002-05		20.3(1-54.2)mł	not specified	Acute HF	High risk of death, transplant, dialysis, serious cardiac CM	Hospital	194	Single	Japan
Testani 2011	2004-09		2.6(1.2-4.2)y*	Clinical diagnosis	BNP>100pg/mL	Acute cardiac event or intervention, dialysis	Hospital	903	Single	United States
Waldum 2010	2000-06	5y	9m*	ESC guidelines	NYHA 1-4		Hospital	3605	Multicentre (n=24)	Norway
RHEUMATOID ARTHRITIS										
Davis 2008	1979-00	1y		Framingham criteria	Incident Cases		Hospital Community	955	Single	United States

Follow up is expressed as mean(SD), median (IQR)* or median (range)ł years (y) or months (m). CM, comorbidity; RCT, randomised control trial; Cr, creatinine; bp, blood pressure; ef; ejection fraction; NYHA, New York Heart Association; BMI, body mass index; BNP, brain natriuretic peptide. **See appendix E20 for trial acronyms**.

A7 cont'd

	Age Mean(SD/ Median (IQR)*(R)ŧ	Gender (% male)	Systolic HF (% with EF <40%(or study defined)	Causcasian (%)	EF Mean(SD)/ Median (IQR)* (R)ŧ	NYHA Stages (% 3/4)	Study indicator	Unit of chronic disease exposure measurement	No. included in study	Prevalence	Outcome/s *secondary
DIABETES											
Ahmed 2007	64(11)	73		87	32(13)	36	Type	Clinical record	2056	29	AC Mortality/ Hospital admission
Berry 2008	72(13)	49	70				Type	Clinical record/Prescription/ admission glucose >11	110	24	AC Mortality
Burger 2005	62(14)	69	87		27(14)	84	Type	Patient reported/ Prescription/ Diet therapy	236	47	AC Mortality
de Boer 2010	76(5)	63	64(<=35%)		36(12)	41	Type	Clinical record/Prescription	555	26	AC Mortality*
Flores-Le Roux 2011	72(10)	51			46(18)		Type All then stratified by treatment	Undiagnosed(blood test) Clinical record/ Prescription/Diet..	63 149	16 37	AC Mortality
From 2006	77(12)	46			47(13)		Type	Blood test/Prescription	128	19	AC Mortality
Gerstein 2008	66	67			46	64	Severity	HbA1c (per 1% higher in all sample)	907	38% diabetes	AC Mortality*
Greenberg 2007	73(14)	48	49	74	39(18)		Type	All:Clinical record/Prescription Insulin treated	2464 986	42 17	AC Mortality
Gustafsson 2004	73*	60	47(<=35%)	100		63	Type	Clinical record/ Patient reported	900	16	AC Mortality
Issa 2010	50(11)	70			35(11)	43	Severity	Fasting glucose <=5.5 mmol/L (guideline and evidence driven cut point)	124 (diabetes)	27	AC Mortality
MacDonald 2008	72(12) 77(11)	100 0					Type	Discharge code	7356 7805	13 13	AC Mortality
COPD											
De Blois 2010	70(12)	71	83		33(11.7)	52	Type	GOLD guidelines	699	17	AC Mortality
Iversen 2010	72	63			39	67	Type and Severity	Self reported FEV1 <80%	107 182	22 35	AC Mortality

								FEV1 50-79% FEV1 <49% per 10% of predicted	92 90	18 17	
Lainscak 2009	73(10)	48	25		44(13)	74	Type	Discharge code	106	17	AC Mortality
Macchia 2007	80(75-87)*	50					Type	Prescriptions/ Discharge codes	241	24	AC Mortality
Rusinaru 2008	75(12)	51	55 (<50%)		50(16)	95	Type	Clinical record/ Patient reported AND prescription	156	20	AC Mortality
RENAL											
Aronson 2010	62(15)	68			27(12)	84	Severity change (0-30days). (stratified by transient and persistant change)	Increase CR (>=0.5 mg/dL) Reduction eGFR (>=25%)	115 159	25 34	AC Mortality
Breidthardt 2011	79(71-85)*	55			40(30-60)*		Severity change	Increase CR (>0.3mg/dl) (in-hosp)	136	21	AC Mortality*
Campbell 2009	65(9)	76		88	32(13)	32	Severity	"eGFR<60 eGFR30-59 eGFR <=30"	2399 2284 115	50 48 2	AC Mortality / Hospital admission
Damman 2009	71(11)	62			34(16)	38	Severity change	Increase Cr >26.5umol/L in-hosp 0-6m 6-12m	(or >25%) 106 101 43	 11 16 9	AC Mortality / Hospital admission*
Go 2006	72(12)	57	57	72			Severity (all pre admission – steady state measure)"	"eGFR >60 (ref) eGFR 45-59 eGFR 30-44 eGFR 15-29 eGFR <15 Dialysis	29240 13241 5958 1821 331 221	53 24 11 3 0.6 0.4	AC Mortality
Gotsman 2010	74(12)	53	64			58	Severity (All discharge values)	eGFR <53 eGFR <35 eGFR per ml/min	237 118	67 33	AC Mortality / Hospital readmission
Hamaguchi 2009	72(13)	59			44(16)		Severity (All baseline values)	"eGFR=>60 eGFR=30-59 eGFR <30ml or dialysis	478 831 308	30 51 19	AC Mortality

Hillege 2006	65(12)	67			39(16)	64	Severity (All baseline values) (decrease from 75) (decrease from 75)	eGFR >90 eGFR 89.9-75 eGFR 74.9-60 eGFR 59.9-45 eGFR <45 eGFR per 10ml/min eGFR per 20ml/min	577 519 618 547 419	22 19 23 20 16	AC Mortality
Ismailov 2007	76,	43		94			Severity (All admission values)	"eGFR >60 eGFR 45-59 eGFR 30-44 eGFR <30	 763 725 569	 18 17 13	AC Mortality
Kimura 2010	69(14)	56			40(15)		Severity	eGFR <60	388	55	AC Mortality
Kociol 2010	80*	44	36	90			Severity change (in hosp)	Increase Cr >=0.3mg/dL	3581	18	AC Mortality / Readmission
Maeder 2012	77(8)	60	81.6 (<45%)		35(13)	75	Severity change (baseline - 6 mnths)	Increase Cr of >0.5 mg/dL	124	22	AC Mortality
Olandoski 2012	68(12)	46	x				Severity change (over a month in 1 year pre or post hosp admission)	reduction in eGFR of >=1%	105	32	AC Mortality
Petretta 2007	64(19-87)ł	72	77		34	63	Type	per eGFR 1ml/min increase			AC Mortality
Takagi 2010	69(13)	71			36(11-81)ł		Type	eGFR <60	75	39	AC Mortality
Testani 2011	63(16)	54		34	29(15-45)*		Severity change (any time) (persisting at discharge)	 Increase eGFR >=20% Increase eGFR >=20%	 279 163	 31 18	AC Mortality
Waldum 2010	71(12)	70	72.8		33(12)	53	Type	eGFR per 5ml/min increase			AC Mortality*
RHEUMATOID ARTHRITIS											
Davies 2008	77(12)	45	51 (<50%)		44		Type	1987 American College of Rheumatology criteria	103	11	AC Mortality

Percentages are expressed as mean(SD), Median (IQR)* or Median (Range)ł. All outcomes are all-cause (AC). Ejection fraction (EF), New York Heart Association (NYHA). HbA1c, glycated haemoglobin; FEV1, forced expiratory volume in 1 second' eGFR, estimated glomerular filtration rate. Outcomes are all primary study outcomes except * where the study outcome was secondary.

A9 Study characteristics: prognostic factors (general) studies

	Trial/ Database	Recruitment Period	Study Follow-up length	Follow-up Mean(SD)/ Median (IQR)* (R)ł	Heart Failure Clinical definition	Inclusions	Exclusions	Setting	Sample size (no. in analysis if different)	Centres/ hospitals	Country
Ahluwalia 2012	Medicare	2001-02	5 y		Discharge code		<=65y	Hospital Community	9166 9166	National	USA
Ahmed 2006	DIG	1991-93	4.8y	37 (28-58)mł	Symptoms/signs or objective evidence	WOMEN	>=76y, Serious CM, high Cr,recent acute cardiac event/ intervention	RCT	1926	Multicentre (n=302)	USA and Canada
Aranda 2009	Medicare	2002-04	6-9 m		Discharge code			Hospital	28919 (27646)	National	USA
Barsheshet 2010	HSIS	2003	4 y		Symptoms/ objective evidence at rest			Hospital	1182 (>75y group) 1154 (<=75y group)	Multicentre (n=25)	Israel
Chaudhry 2010	Medicare	1998-99 or 2000-01	5y		Discharge code		<65y, heamodyalysis	Hospital	62330	Multistate (n=6)	USA
Chaudhry 2013	CHS	1989-99	20y	3.4(1.8-5.9)y*	Clinical history	Incident	Cancer	Hospital/ Community	758	Regional	USA
Dunlay 2009	REP	1987-06	19y	4.7(3.9)y	Discharge Code + Framingham criteria	Incident		Hospital/ Community	1077	Regional	USA
Fernandez-Berges 2013		2000-09	1y		Discharge Code			Hospital	2220	Single	Spain
Fonarow 2008	OPTIMIZE-HF	2003-04	6-9m		Clinical diagnosis. Symptoms/signs	HF admissions		Hospital	5791	Multicentre (n=91)	USA

Garty 2007	HSIS	2003	1y		Symptoms/signs and objective evidence	AHA stage B-D		Hospital	4102	Multicentre (n=117)	Israel
Gorelik 2009				47.5m	Modified Framingham criteria	Decompensated HF, NYHA 2-4	<60yrs, Serious cardiac CM, cancer, dialysis	Hospital	473	Single	Israel
Gotsman 2008		2001-02	1 y		Symptoms/signs and objective evidence	Clinical diagnosis of HF + echoe		Hospital	289	Single	Israel
Hamaguchi 2011	JCARE-CARD	2004-05		2.1(0.9)y	Framingham criteria	Decompensated HF	<80yrs	Hospital	765(620)	Multicentre (n=164)	Japan
Harjola 2010	EHFS	2004 -05	1 y		ESC guidelines	HF admissions	High output HF	Hospital	2981	Multinational (n=30)	Europe
MacIntyre 2000	Scottish morbidity data	1986-95	1-10y		Discharge code	De Novo HF		Hospital	31040(MEN) 35507(WOMEN)	Countrywide	United Kingdom
Mahjoub 2008		2000	5y		Framingham criteria amended byESC	De Novo HF	>=80yrs, serious cardiac CM	Hospital	305	Multicentre (n=11)	France
Mogensen 2011	DIAMOND and ECHOES	1993-96 2001-02	8 y		Symptoms/signs or objective evidence	NYHA 2-4	Recent acute cardiac event/intervention	Hospital	8507	Multicentre (n=43)	Denmark, Norway and Sweden
Mosterd 2001	Rotterdam study	1990-93	4.8-8.5y		Symptoms, signs and objective evidence		<55yrs, COPD	Community	181	Regional	Nether-lands
Pons 2010		2001-08		36(16.6-64.5)m*	Clinical diagnosis			Hospital	960	Single	Spain
Rusinaru 2009		2000	5y		Framingham criteria amended by ESC	De novo HF, women	Serious cardiac CM	Hospital	389 (306)	Multicentre (n=11)	France
Shiba	CHART	2000-03		1.88(0.92)y	Framingham			Hospital	1154	Multicentre	Japan

2004				criteria				(684)	(n=26)		
Tribouilloy 2010	2000	7yrs		Framingham criteria amended byESC	De novo HF	Serious cardiac CM	Hospital	735	Multicentre (n=11)	France	

Follow up is expressed as mean(SD), median (IQR)* or median (range)ł years (y) or months (m). CM, comorbidity; RCT, randomised control trial; Cr, creatinine; NYHA, New York Heart Association. **See appendix E20 for trial acronyms.**

A9 cont'd

	Age Mean(SD/ Median (IQR)*(R)ł	Gender (% male)	Systolic/ (% with EF <40% (or study defined)	Causcasian (%)	EF Mean(SD)/ Median (IQR)*(R)ł	NYHA Stages (% 3/4)	Chronic disease	Study indicator	Unit of chronic disease exposure measurement	No. included in study	Prevalence	Outcome/s
Ahluwalia 2012	81(75-86)* 81(75-86)*	41 41	x	86 85	x		Diabetes COPD Renal disease Arthritis Dementia Depression Osteoporosis Cancer- Prostate Cancer- Breast Cancer- Lung Cancer- Colorectal Cancer- Endometrial	Type	Discharge codes	7739 6129 5035 5399 4266 3173 2454 637 298 214 234 20	42 33 27 29 23 17 13 4 2 1 1 0.1	AC Mortality
Ahmed 2006	66(12)	0	79 (<45%)	82	35(14)		Diabetes Renal dysfunction	Type	Not specified eGFR per ml	650	34	Mortality Hospital admission
Aranda 2009	x	44	x	83	x		Diabetes	Type	Not specified	x	37	Readmission
Barsheshet 2010	82 (78-87)* 67 (59-72)*	47 63	48 53			48 42	Renal dysfunction Diabetes	Type	eGFR <60 Clinical record/ blood test/prescription	1361 1207	58 52	AC Mortality
Chaudhry 2010	80	42	.	87	x		Diabetes Dementia Cancer (any) COPD	Type	Clinical record	24745 6046 1496 21192	40 10 2 34	AC Mortality

Chaudhry 2013	80(6)	50	43 (<45%)	87	x	30	Renal disease COPD Depression Diabetes	Type	eGFR<60 Patient reported Depression scale Patient report/ Prescription/ Blood test	280 112 296 193	37 15 395 26	Hospital admission
Dunlay 2009	77(13)	46			46(18)		COPD Diabetes	Type	Clinical record National diabetes data group criteria	253 232	24 21	Hospital admission
Fernandez-Berges 2013	76(10)	47					Diabetes Renal disease COPD	Type	Clinical record	970 390 648	44 18 29	Mortality
Fonarow 2008	72(14)	51	53	78	37(17)		Renal dysfunction	Worsening Pre-admission	Clinical record	509	9	Mortality
Garty 2007	73(12)	57	52			40	Renal failure COPD	Type	Cr=>1.5mg/dl Clinical record	1672 803	41 20	Mortality
Gorelik 2009	73(10)	57	61 (<50%)		41(14)	46	Renal dysfunction Cancer – any	Severity	eGFR <60 (admission) Clinical record: Non advanced		70 12	Mortality
Gotsman 2008	73(12)	53	64			40	Diabetes Chronic renal disease	Type	Clinical record	122 110	42 38	Mortality
Hamaguchi 2011	85(4)	45			48(17)	12	Renal dysfunction	Severity	eGFR per ml/min decrease (baseline)			Mortality
Harjola 2010	72(62-79)*	62	65 (<45%)		38(15)		Diabetes	Type	Clinical record	987	33	Mortality
MacIntyre 2000	72* 78*	100 0					Arthritis Cancer – any Renal failure Diabetes Lung Disease	Type	Admission code (prior to HF admission)	3383 3330 454 1760 4818	5 5 1 3 7	Mortality

Mahjoub 2008	86(5)	37	39(<50%)	52(16)		Cancer – any Diabetes	Type	Clinical record	37 48	12 16	Mortality
Mogensen 2011	72(11)	60	55(<45%)			Diabetes COPD Renal dysfunction	Type	Clinical record/ Px Clinical record/ Px eGFR<30	1361 1948 970	16 23 11	Mortality
Mosterd 2001	77(8)	40		x		Diabetes	Type	Blood test/ Prescription	32	18	Mortality
Pons 2010	69*	71		31	39	Diabetes	Type	Not specified	377	39	Mortality
Rusinaru 2009	78(11)	n/a	36(<50%)	54(15)	96	Cancer Diabetes	Type	Clinical record	34 106	9 27	Mortality
Shiba2004	68(13)	67		49(16)	16	Diabetes	Type	Clinical record	223	19	Mortality
Tribouilloy 2010	75(12)	52	43 (<50%)	51(16)		Cancer Diabetes COPD	Type	Clinical record	75 181 146	10 25 20	Mortality

Percentages are expressed as mean(SD), Median (IQR)* or Median (Range)ł. All outcomes are all-cause (AC). Cr, creatinine; eGFR, estimated glomerular filtration rate. Outcomes are all primary study outcomes except * where the study outcome was secondary.

A10 Study characteristics of prognostic model studies

	Trial/ Database	Recruitment Period	Study Follow-up length	Follow-up Mean(SD)/ Median (IQR)* (R)ł	Heart Failure Clinical definition	Inclusions	Exclusions	Setting	Sample size (no. in analysis if different)	Centres/ hospitals	Country
Barlera 2013	GISSI-HF	2002-05	4y	3.9y*	ESC guidelines	NYHA 2-4	Recent acute cardiac event/intervention, serious CM	RCT	6975	Multicentre (n=357)	Italy
Bouvy 2003			18m		Discharge code		High risk of death	RCT	152	Multicentre (n=7)	Netherlands
Huynh 2006		1990-94	14y	2.5y*	Objective evidence OR signs/symptoms and response to diuresis		<70yrs, high risk of death	RCT	282	Single	United States
Krumholz 2000	Medicare	1994-95	6m		Discharge code, symptoms or objective evidence		<65yrs, serious cardiac CM, in-hopsital death	Hospital	1129 (derivation)	Multicentre (n=9)	United States
Lee 2003	EFFECT	1999-01	1y		Discharge code and modified Framingham criteria	HF admission		RCT	2624	Multicentre (n=34)	Canada
Martinez-Selles 2010	HOLA	1996	10y	5.2(4.2)y	Symptom and (Sign or objective evidence)		Recent acute cardiac event/intervention	Hospital	701	Single	Spain
O'Connor 2008	OPTIMIZE-HF	2003-04	60-90days	2.4(0.7)m	Clinical diagnosis	HF admissions		Hospital	5791(4402)	Multicentre (n=91)	United States
Pocock 2006	CHARM	1999-01		38m*	Clinical diagnosis	NYHA 2-4	Acute cardiac event or intervention, high CR, low bp, serious cardiac CM	RCT	7599	Multinational (n=26)	Multiple
Pocock	MAGIC			2.5y*				Hospital	39372	Multinational	Multiple

2013	database									
Senni 2006		2003	1yr	ESC guidelines		In-hosp death, heart surgery	Hospital/ Community	292 (derivation)	Multicentre (n=3)	Italy
Senni 2013		2002-06	1 yr	Symptoms, signs and objective evidence		In-hosp death, cancer	Hospital	2016 (derivation)	Multicentre (n=8)	Europe
Wang 2012	VHA	2009-10	1yr	Discharge codes	Chronic HF		Hospital/ Community	198640	National	United States

Follow up is expressed as mean(SD), median (IQR)* or median (range)ł years (y) or months (m). CM, comorbidity; RCT, randomised control trial; Cr, creatinine; bp, blood pressure; NYHA, New York Heart Association. **See appendix E20 for trial acronyms.**

A10 cont'd

	Age Mean(SD) Median (IQR)* (R)ł	Gender (% male)	Systolic/ LVF (% with EF <40% (or study defined)	Causcasian (%)	EF Mean(SD)/ Median (IQR)*(R)ł	NYHA Stages (% stage 3 or 4)	Chronic disease	Study indicator	Unit of chronic disease exposure measurement	No. included in study	Prevalence	Outcome/s
Barlera 2013	67(10)	78			33(9)	37	Diabetes COPD Renal dysfunction	Type	Clinical record Clinical examination eGFR per unit decrease<60	1974 1533	28 22	AC Mortality
Bouvy 2003	70(37-91)ł	34			x	41	Diabetes Renal dysfunction	Type	Clinical record	43 19	28 22	AC Mortality
Huynh 2006	79(6)	37	63 (<45%)	45	43(14)		Dementia	Type	Clinical record	13	5	AC Mortality
Krumholz 2000	78(8)	41	44	92			Diabetes	Type	Clinical record	412	36	Readmission
Lee 2003	76 (11)	50	53				Dementia COPD Liver cirrhosis Cancer	Type	Clinical record	225 543 34 234	9 21 1 9	AC Mortality
Martinez-Selles 2010	72(12)	45					COPD	Type	Clinical record	188	27	AC Mortality
O'Connor 2008	72(14)	51	53	78	37(17)		Liver disease Reactive airways disease	Type	Clinical record	126 498	2 9	AC Mortality
Pocock 2006	66(11)	68			39(15)	55	Diabetes	Type	Clinical record stratified by treatment	707	9	AC Mortality
Pocock 2013	67(11)	67		91	36(14)	44	Diabetes COPD	Type	Varies across studies	8919 4035	23 10	AC Mortality
Senni 2006	71(13)	62	61		38(13)	25	COPD Diabetes with target organ damage Renal dysfunction	Type, severity	Clinical record	45 40 41	15 14 14	AC Mortality

							(moderate to severe)						
							Cancer (metastatic or >2 tumors)				7	2	
Senni 2013	68 (58-76)*	70	90 (<50%)	35	(27-40)*	34	Diabetes with target organ damage	Severity	Clinical record	304	15	AC Mortality
							Renal dysfunction			157	8	
Wang 2012	73	98					Renal failure	Type	Clinical record	50454	25	Hospital admission
							COPD			61380	31	
							Diabetes			98724	50	
							Dementia			16487	8	
							Cancer*			5363	3	
							Liver cirrhosis			5363	3	

Percentages are expressed as mean(SD), Median (IQR)* or Median (Range)ł. All outcomes are all-cause (AC). Ejection fraction (EF), New York Heart Association (NYHA). Outcomes are all primary study outcomes except * where the study outcome was secondary.

A11 Study Risk of bias assessment

	Study participation			Study attrition		Prognostic factor measurement			Outcome Measurement		Study confounding		
	Baseline population level of detail provided	Sample described	Risk level	Loss to follow-up	**Risk level**	Chronic disease exposure description	Method of missing data	Risk level	Outcome measure description	Risk level	Confounders (or predictors for models) reported	Confounders Rationale provided	Risk level
Diabetes													
Ahmed 2007	Brief	Yes	Med	NR	**Med**	Yes	NR	Med	Yes	Low	Yes	No	Low
Berry 2008	Brief	Yes	Med	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Burger 2005	Brief	Yes	Med	<10%	**Low**	Yes	NR	Med	Yes	Med	Yes	No	Med
de Boer 2010	Brief	Yes	Med	NR	**Med**	Yes	NR	Med	Yes	Med	Yes	No	Med
Flores-Le Roux 2011	Brief	Yes	Med	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
From 2006	Detailed	Yes	Low	<10%	**Low**	Yes	Single imputation	Low	Yes	Low	Yes	No	Med
Gerstein 2008	Brief	Yes	Med	<10%	**Low**	Yes	No missing data	Low	Yes	Low	Yes	No	Med
Greenberg 2007	Detailed	yes	Low	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
Gustafsson 2004	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Issa 2010	Brief	Yes	High	<10%	**Low**	Yes	NR	Med	Yes	Med	Yes	No	Med
MacDonald 2008	Detailed	Yes	Low	NR	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
COPD													
De Blois 2010	Brief	Yes	Med	>10%	**Med**	Yes	No missing data	Low	Yes	Med	Yes	No	Low
Iversen 2010	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Low	Yes	Low	Yes	No	Med
Lainscak 2009	Brief	Yes	High	<10%	**Low**	Yes	NR	High	Yes	Low	Yes	No	Med
Macchia 2007	Brief	yes	Med	NR	**Low**	Yes	NR	Med	Yes	low	Yes	No	High
Rusinaru 2008	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	low	Yes	No	Low
Renal													
Aronson 2010	Brief	Yes	Med	<10%	**Low**	Yes	Single imputation	Low	Yes	Low	Yes	No	Med
Breidthardt 2011	Brief	Yes	Med	>10%	**High**	Yes	No missing data	Low	Yes	Low	Yes	No	Med
Campbell 2009	Brief	Yes	Med	<10%	**Low**	Yes	NR	Low	Yes	Low	Yes	No	Low

Damman 2009	Brief	Yes	Med	<10%	**Low**	Yes	Single imputation	Low	Yes	Low	No	Yes	Low
Go 2006	Detailed	Yes	Low	NR	**Med**	Yes	Full case analysis	Med	Yes	Low	Yes	Yes	Low
Gotsman 2010	Brief	Yes	Med	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
Hamaguchi 2009	Brief	Yes	Med	>10%	**Med**	Yes	NR	Med	Yes	Low	Yes	Yes	Med
Hillege 2006	Detailed	Yes	Low	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	Yes	Low
Ismailov 2007	Brief	Yes	Med	NR	**Med**	Yes	NR	Med	Yes	Med	Yes	No	Med
Kimura 2010	Brief	Yes	Med	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
Kociol 2010	Detailed	Yes	Low	NR	**Low**	Yes	Single imputation	Med	Yes	Low	Yes	No	Low
Maeder 2012	Brief	Yes	Med	<10%	**Low**	Yes	NR	Low	Yes	Low	Yes	No	Med
Olandoski 2012	Brief	Yes	Med	NR	**Med**	Yes	NR	High	Yes	Med	No	No	High
Petretta 2007	Brief	Yes	Med	NR	**Med**	Yes	NR	Med	Yes	Low	No	No	High
Takagi 2010	None	Yes	High	NR	**Med**	Yes	NR	Med	Yes	Low	Yes	No	High
Testani 2011	Brief	Yes	Med	NR	**Med**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Waldum 2010	Brief	Yes	Med	<10%	**Low**	Yes	Full case analysis	Med	Yes	Med	Yes	No	Med
Davis 2008	Brief	Yes	Low	NR	**Low**	Yes	NR	Med	Yes	Low	Yes	No	High
Prognostic factors (general)													
Ahluwalia 2012	Brief	Yes	Med	<10%	**Low**	Yes	No missing data	Med	Yes	Med	Yes	No	Med
Ahmed 2006	Brief	Yes	Med	NR	**Med**	No	NR	Med	Yes	Low	Yes	No	Low
Aranda 2009	Brief	Yes	Med	NR	**High**	Yes	NR	Med	Yes	Med	No	No	High
Barsheshet 2010	Detailed	Yes	Low	NR	**Med**	Yes	Full case analysis	Low	Yes	Low	Yes	Yes	Low
Chaudhry 2010	Brief	Yes	Med	<10%	**Low**	No	Missings catagorised	Med	Yes	Low	Yes	No	Med
Chaudhry 2013	Detailed	Yes	Low	<10%	**Low**	Yes	Missings catagorised	Med	Yes	Low	Yes	Yes	Low
Dunlay 2009	Detailed	Yes	Low	<10%	**Low**	Yes	Multiple imputation	Low	Yes	Low	Yes	No	Med
Fernandez-Berges 2013	Brief	Yes	Med	<10%	**Low**	No	NR	High	Yes	Med	Yes	Yes	Med
Fonarow 2008	Detailed	Yes	Low	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
Garty 2007	Brief	Yes	Med	<10%	**Low**	No	NR	Med	Yes	Low	No	No	High
Gorelik 2009	Brief	Yes	High	NR	**Med**	Yes	NR	Med	Yes	Low	Yes	No	Med
Gotsman 2008	Brief	Yes	Med	NR	**Med**	Yes	NR	Med	yes	Low	Yes	No	Med
Hamaguchi 2011	Brief	Yes	Med	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med

Harjola 2010	Brief	Yes	Med	<10%	**Low**	Yes	Single imputation	Low	Yes	Low	Yes	No	Med
MacIntyre 2000	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Mahjoub 2008	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Mogensen 2011	Brief	Yes	Low	<10%	**Low**	Yes	NR	Med	Yes	Low	Yes	No	Med
Mosterd 2001	Detailed	Yes	Med	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	No	No	High
Pons 2010	Brief	Yes	Med	<10%	**Low**	No	NR	Med	Yes	Low	Yes	No	Med
Rusinaru 2009	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	No	Med
Shiba 2004	Detailed	Yes	Low	<10%	**Low**	No	Full case analysis	High	Yes	Med	Yes	No	Med
Tribouilloy 2010	Detailed	Yes	Low	<10%	**Low**	No	Full case analysis	Med	Yes	Low	Yes	No	Med
Prognostic model studies													
Barlera 2013	Brief	Yes	Med	<10%	**Low**	Yes	Multiple imputation	Low	Yes	Low	Yes	No	Low
Bouvy 2003	Brief	Yes	Med	<10%	**Low**	No	Single imputation	Med	Yes	Low	Yes	Yes	Med
Huynh 2006	Brief	Yes	High	<10%	**Low**	No	Full case analysis	Med	Yes	Low	Yes	No	Med
Krumholz 2000	Brief	Yes	Med	NR	**Med**	No	Missings catagorised	Med	Yes	Low	Yes	Yes	Low
Lee 2003	Detailed	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	Yes	Low
Martinez-Selles 2010	Brief	Yes	Med	NR	**Med**	No	NR	Med	Yes	Low	Yes	No	Med
O'Connor 2008	Detailed	Yes	Low	<10%	**Low**	No	Full case analysis	Med	Yes	Low	Yes	No	Med
Pocock 2006	Detailed	Yes	Low	NR	**Med**	Yes	NR	Med	Yes	Low	Yes	No	Low
Pocock 2013	Brief	Yes	Med	NR	**Med**	No	Multiple imputation	Med	Yes	Med	Yes	No	Med
Senni 2006	Brief	Yes	Med	<10%	**Low**	Yes	Single imputation	Low	Yes	Low	Yes	Yes	Med
Senni 2013	Brief	Yes	Low	<10%	**Low**	Yes	Full case analysis	Med	Yes	Low	Yes	Yes	Low
Wang 2012	Brief	Yes	Med	NR	**Med**	Yes	Single imputation	Med	Yes	Med	Yes	No	Med

A11 Cont'd

	Statistical analysis and reporting						Overall study risk
	Adjusted AND unadjusted effects reported	Interactions examined	Linearity for continuous predictors assessed	Proportional Hazards assumptions tested	Predictor selection	Risk level	Risk Level
Diabetes							
Ahmed 2007	Yes	Yes	N/A	NR	Full model	Low	Med
Berry 2008	Yes	NR	NR	NR	Selected by significance level + stepwise	Med	Med
Burger 2005	No	NR	NR	NR	Full model	Low	Med
de Boer 2010	Yes	Yes	N/A	NR	Full model	Low	Med
Flores-Le Roux 2011	No	NR	No	NR	Pre-specified predictors	Med	Med
From 2006	No	Yes	N/A	NR	Full model	Low	Low
Gerstein 2008	No	NR	NR	Yes	Full model	Med	Med
Greenberg 2007	No	Yes	Yes	NR	Stepwise	Med	Low
Gustafsson 2004	Yes	Yes	Yes	Yes	Pre-specified predictors	Low	Low
Issa 2010	No	Yes	No	NR	Selected by significance level	Med	Med
MacDonald 2008	No	Yes	No	NR	Full model	Med	Low
COPD							
De Blois 2010	Yes	NR	N/A	NR	Selected by significance level	Med	Med
Iversen 2010	Yes	Yes	yes	Yes	Backward selection	Low	Low
Lainscak 2009	Yes	NR	NR	NR	Selected by significance level	Med	Med
Macchia 2007	Yes	NR	NR	NR	Selected by significance level	Med	Med
Rusinaru 2008	Yes	NR	NR	NR	Backward selection	Med	Low
Renal							
Aronson 2010	Yes	NR	NR	NR	Selected by significance level	Med	Med
Breidthardt 2011	Yes	NR	N/A	NR	Selected by significance level	Med	Med
Campbell 2009	N/A	Yes	N/A	Yes	N/A	Low	Low
Damman 2009	Yes	NR	N/A	NR	Full model	Med	Low
Go 2006	No	Yes	N/A	NR	Pre-specified predictors	Low	Low

Gotsman 2010	No	Yes	Yes	NR	Pre-specified predictors	Med	Med
Hamaguchi 2009	Yes	NR	NR	NR	Pre-specified predictors	Med	Med
Hillege 2006	Yes	Yes	Yes	Yes	Pre-specified predictors	Low	Low
Ismailov 2007	Yes	NR	NR	NR	Selected by significance level	Med	Med
Kimura 2010	No	NR	NR	NR	Selected by significance level	High	Med
Kociol 2010	No	NR	NR	NR	Full model	Med	Low
Maeder 2012	No	Yes	NR	NR	Selected by significance level	Med	Med
Olandoski 2012	No	Yes	No	NR	Pre-specified predictors	High	High
Petretta 2007	Yes	Yes	Yes	Yes	Selected by significance level + stepwise	Med	Med
Takagi 2010	No	NR	NR	NR	Full model	High	Med
Testani 2011	Yes	Yes	NR	NR	Selected by significance level + backwards	Med	Med
Waldum 2010	No	Yes	Yes	Yes	Selected by significance level	Med	Med
Rheumatoid arthritis							
Davis 2008	No	NR	N/A	NR	Full model	High	Med
Prognostic factors (general)							
Ahluwalia 2012	No	Yes	N/A	Yes	Full model	Med	Med
Ahmed 2006	No	NR	NR	NR	Full model	Med	Med
Aranda 2009	No	NR	NR	N/A	Full model	High	High
Barsheshet 2010	No	Yes	NR	NR	Selected by significance level	Med	Low
Chaudhry 2010	Yes	NR	Yes	N/A	Stepwise	Low	Med
Chaudhry 2013	Yes	NR	NR	N/A	Selected by significance level + backwards	Low	Low
Dunlay 2009	Yes	Yes	Yes	N/A	Full model	Low	Low
Fernandez-Berges 2013	Yes	NR	NR	NR	Selected by significance level	Med	Med
Fonarow 2008	No	NR	Yes	NR	Stepwise	Med	Med
Garty 2007	No	NR	NR	N/A	Stepwise	High	Med
Gorelik 2009	No	NR	NR	NR	Selected by significance level	High	Med
Gotsman 2008	No	NR	NR	NR	Pre-specified predictors	High	Med
Hamaguchi 2011	No	NR	NR	NR	Pre-specified predictors	Med	Med

Harjola 2010	Yes	NR	yes	yes	Selected by significance level	Low	Low
MacIntyre 2000	No	Yes	N/A	Yes	Full model	Low	Low
Mahjoub 2008	No	NR	NR	NR	Selected by significance level + backwards	Med	Low
Mogensen 2011	No	Yes	Yes	Yes	Backward selection	Low	Low
Mosterd 2001	No	NR	No	NR	Pre-specified predictors	High	Med
Pons 2010	Yes	NR	NR	NR	Backward selection	Med	Med
Rusinaru 2009	No	NR	NR	NR	Pre-specified predictors	Med	Med
Shiba 2004	No	NR	NR	NR	Backward selection	High	Med
Tribouilloy 2010	No	NR	Yes	Yes	Full model	Med	Med
Prognostic models							
Barlera 2013	No	Yes	Yes	Yes	Stepwise	Low	Low
Bouvy 2003	Yes	NR	NR	N/A	Selected by significance level	Med	Med
Huynh 2006	Yes	NR	NR	NR	Selected by significance level + forwards	High	Med
Krumholz 2000	No	NR	NR	Yes	Stepwise	Med	Med
Lee 2003	Yes	yes	yes	N/A	Selected by significance level	Low	Low
Martinez-Selles 2010	No	Yes	NR	NR	Selected by significance level + backwards	Med	Med
O'Connor 2008	yes	yes	Yes	Yes	Stepwise	low	Low
Pocock 2006	No	Yes	Yes	NR	Forward selection	Low	Low
Pocock 2013	No	Yes	Yes	NR	Forward selection	Med	Med
Senni 2006	No	NR	NR	N/A	Selected by significance level	Med	Med
Senni 2013	No	Yes	NR	N/A	Other e.g. LASSO, bootstrap	Low	Low
Wang 2012	No	Yes	Yes	N/A	Backward selection	Med	Med

A11 cont'd Study Risk of bias assessment: additional assessments for prognostic model studies

	Internal validity				External validity		
	Correlations tested	More than 10 events per variable	Clinical tool developed	Internal validation (bootstrap, cross validation, random split-sample)	Performance (AUC/ ROC)	Calibration (Goodness of fit/ Hosmer-Lemeshow test/ Score categories tested)	External validation
Barlera 2013	NR	Yes	Score	Yes	Yes	Yes	No
Bouvy 2003	NR	No	Score	No	Yes	Yes	No
Huynh 2006	No	Yes	Score	Yes	Yes	No	No
Krumholz 2000	NR	Yes	Score	Yes	NR	Yes	No
Lee 2003	Yes	Yes	Score	Yes	Yes	Yes	Yes
Martinez-Selles 2010	NR	Yes	Score	No	Yes	Yes	No
O'Connor 2008	NR	Yes	Score	Yes	Yes	NR	Yes
Pocock 2006	NR	Yes	Score	Yes	Yes	Yes	No
Pocock 2013	NR	Yes	Score	Yes	NR	Yes	No
Senni 2006	NR	No	Score	Yes	Yes	Yes	No
Senni 2013	NR	Yes	Score	Yes	Yes	Yes	Yes
Wang 2012	Yes	Yes	Score	Yes	Yes	Yes	No

A12 Sensitivity analysis summary: DM comorbidity

Study	Reason for removal	Combined all-cause mortality risk associated with diabetes	Test
All		HR 1.34 (1.24, 1.46)	Chi^2 (p=0.008) I^2 = 61% Egger's (p=0.119)
From et al (2006)	More community patients	HR 1.34 (1.22, 1.47)	Chi^2 (p=0.004), I^2=66%
Gustafsson et al (2004)	More chronically severe patients, Galbraith plot	HR 1.30 (1.21, 1.39)	Chi^2 (p=0.15), I^2=35%
Berry et al (2008) and Burger et al (2005)	Small study effects, funnel plot	HR 1.31(1.22, 1.41)	Eggers's (p=0.431)

A13 Sensitivity analysis summary: CKD comorbidity

Study	Reason for removal	Combined all-cause mortality risk associated with renal dysfunction	Test
All		HR 1.52 (1.34, 1.71)	Chi^2 (p=<0.0001) I^2 = 88% Egger's (p=0.56)
Cambell et al (2009)	More males, lower ejection fraction, Galbraith plot	HR 1.59(1.41, 1.78)	Chi^2 (p=<0.0001), I^2=83%
Ismailov et al (2007)	Older, less males, Galbraith plot	HR 1.57 (1.35, 1.84)	Chi^2 (p=<0.0001), I^2=81%
Campbell et al (2009) and Ismailov et al (2007)		HR 1.62(1.59, 1.67)	Chi^2 (p=0.823), I^2=0%

A14 Heart failure selection code set

			Validation		Code type	
Medcode	**Read code**	**Read term**	**Previous literature**	**QOF listed**	**Read code type**	**Study code type**
398	G580.00	Congestive heart failure	√	√	Diagnostic	Index
884	G581.00	Left ventricular failure	√	√	Diagnostic	Index
2062	G58..00	Heart failure	√	√	Diagnostic	Index
2906	G580.11	Congestive cardiac failure	√	√	Diagnostic	Index
4024	G58z.00	Heart failure NOS	√	√	Diagnostic	Index
1223	G58..11	Cardiac failure	√	√	Diagnostic	Index
5942	G581.13	Impaired left ventricular function	√	√	Diagnostic	Index
5255	G581000	Acute left ventricular failure	√	√	Diagnostic	Index
32671	G580100	Chronic congestive heart failure	√	√	Diagnostic	Index
10079	G580.12	Right heart failure	√	√	Diagnostic	Index
9524	G580.14	Biventricular failure	√	√	Diagnostic	Index
17278	G58z.12	Cardiac failure NOS	√	√	Diagnostic	Index
23707	G580000	Acute congestive heart failure	√	√	Diagnostic	Index
10154	G580.13	Right ventricular failure	√	√	Diagnostic	Index
27964	G582.00	Acute heart failure	√	√	Diagnostic	Index
27884	G580200	Decompensated cardiac failure	√	√	Diagnostic	Index
23481	G581.11	Asthma – cardiac	√	√	Diagnostic	Index
43618	G581.12	Pulmonary oedema – acute	√	√	Diagnostic	Index
11424	G580300	Compensated cardiac failure	√	√	Diagnostic	Index
22262	G58z.11	Weak heart	√	√	Diagnostic	Index
12590	G583.00	Heart failure with normal ejection fraction		√	Diagnostic	Index
101138	G580400	Congestive heart failure due to valvular disease		√	Diagnostic	Index
94870	G584.00	Right ventricular failure		√	Diagnostic	Index
104275	G583.11	HFNEF - heart failure with normal ejection fraction		√	Diagnostic	Index
101137	G1yz100	Rheumatic left ventricular failure		√	Diagnostic	Index
9913	101..00	Heart Failure confirmed			Process	Index
21837	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure			Diagnostic	Index

A15 Exclusion criteria for CPRD heart failure cohort

		Frequency	Percent
Valid	**Included patients**	50,114	62.9
	Excluded patients:		
	(1) current registration date or up to standard date was less than 3 years before the index date	14,633	17.9
	(2) current registration date or up to standard date was after the index date	12,346	16.0
	(3) transfer out of the practice date was before the index date	169	0.2
	(4) Unexplained gaps	74	0.02
	(5) Current registration date, up to standard date, transfer out date or index date greater than one month after death date	2,002	2.6
	(6) Office of National Statistics death and CPRD death date differ >93days	102	0.1
	(7) HES identified multiple patid for same patient	189	0.2
	Total	79,629	100.0

A16 Baseline characteristics of the sample comparing the pre-match sample with the matched sample: mortality

	Pre matched cohort (n=50,114)	Matched cohort (133,645 observations)	Absolute difference in units
Age, years	78(IQR 71-85)	77[IQR 69-83]	1
Women	23,595 (47.1)	61,732(46.2)	0.9
IMD quintile			
1	5,846 (19.5)	15,908(20.0)	0.5
2	6,952 (23.2)	18,089(22.8)	0.4
3	6,340 (21.1)	16,666(21)	0.1
4	6,235 (20.8)	16,451(20.7)	0.1
5	4,613 (15.4)	12,269(15.5)	0.1
Systolic BP (mmHg)	137.3 ±21.5	138.4±21.4	1.1
Diastolic BP (mmHg)	76.7 ±12	77.4±11.9	0.7
BMI (Kg/m^2)	27(IQR 23.8-31)	27.3[24.1-31.2]	0.3
Cholesterol (mmol/L)	4.7 ±1.2	4.7±1.2	0
HB (g/dL)	13.1 ±1.9	13.2±1.8	0.1
Smoking status			
yes	6,841 (14.2)	18833(14.7)	0.5
No	22,618 (46.9)	59492(46.5)	0.4
Ex	18,757 (38.9)	49670(38.8)	0.1
Alcohol status			
Yes	31,228 (70.9)	84370(72)	1.1
No	11,093 (25.2)	28557(24.4)	0.8
Ex	1,746 (4.0)	4260(3.6)	0.4
Diuretics	32,071(64.0)	91,068(68.1)	4.1
Beta blocker	16,382 (32.7)	47581(35.6)	2.9
ACEi	22,582 (45.1)	62,074(46.5)	1.4
ARB	6,118 (12.2)	16,225(12.1)	0.1
COPD	5,848 (11.7)	14483(10.8)	0.9
FEV1 (pp) (in COPD only)	53.2(IQR 39-69.6)	54.1(39.7-70.0)	0.9
Diabetes	10,533 (21.0)	27,175(20.3)	0.7
HbA1c (%) (in diabetes only)	7.1(IQR 6.4-8.1)	7.1[6.4-8.2]	0
Renal disease at baseline (medical code)	7,621 (15.2)	16,801(12.6)	2.6
Renal disease (eGFR<60) at baseline	20,084 (49.8)	50,834(48.9)	0.9
eGFR ($ml/min/1.73m^2$)	60.9 ±20.3	61.3±19.6	0.4
Number of the listed comorbidities at baseline (renal code)			
0	30,358 (60.6)	84795(63.5)	2.9
1	15,810 (31.6)	39892(29.9)	1.7
2	3,646 (7.3)	8307(6.2)	1.1
3	300 (0.6)	651(0.5)	0.1
Number of the listed comorbidities at baseline (egfr definition)			
0	13565 (33.6)	35930(34.6)	1
1	19471 (48.3)	50,181(48.3)	0
2	6,795 (16.8)	16700(16.1)	0.7
3	515 (1.3)	1169(1.1)	0.2

Data are number patients (%) or mean± standard deviation or median[IQR]. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index; HB, haemoglobin

A17 Baseline characteristics of the sample comparing the pre-match sample with the matched sample: first hospital admission

	Pre matched cohort (n=30,061)	Matched cohort (110,789 observations)	Absolute difference in units
Age, years	79[IQR 71-85]	78(70-84)	1
Women	14,163 (47.1)	53,804(48.6)	1.5
IMD quintile			
1	5,844 (19.5)	22,493(20.4)	0.9
2	6,946 (23.2)	26,525(24.0)	0.8
3	6,340 (21.2)	22,936(20.8)	0.4
4	6,232 (20.8)	22,505(20.4)	0.4
5	4,612 (15.4)	15,988(14.5)	0.9
Prior Hospital admission			
<3 months	11,719 (39)	26,461 (23.9)	15.1
3-6 months	2,471 (8.2)	10,143 (9.2)	1
>6months to 1 year	2,711 (9.0)	11,400 (10.3)	1.3
Systolic BP (mmHg)	137.4 ±21.4	138.8 ±21.1	1.4
Diastolic BP (mmHg)	76.8 ±12	`77.8±11.6	1
BMI (Kg/m^2)	26.9[IQR 23.7-30.8]	27.3(24.1-31.2)	0.4
Cholesterol (mmol/L)	4.7 ±1.2	4.7±1.2	0
HB (g/dL)	13.1 ±1.9	13.4±1.7	0.3
Smoking status			
yes	3,866 (13.3)	13,034(12.2)	1.1
No	13,614 (47.0)	51,480(48.2)	1.2
Ex	11,504 (39.7)	42,293(39.6)	0.1
Alcohol status			
Yes	19,296 (72.8)	73,125(74.6)	1.8
No	6,152 (23.2)	21,497(21.9)	1.3
Ex	1,060 (4.0)	3,364(3.4)	0.6
Diuretics	19,359(64.4)	74,394(67.2)	2.8
Beta blocker	9,683 (32.2)	38,717(35.0)	2.8
ACEi	13,589 (45.2)	54,985(49.6)	4.4
ARB	3,779 (12.6)	15,325(13.8)	1.2
COPD	3,504 (11.7)	10,843(9.8)	1.9
FEV1 (pp) (in COPD only)	53.5[IQR 38.8-70.7]	53(IQR 37.4-68.4)	0.5
Diabetes	6,298 (21.0)	19,793(17.9)	3.1
HbA1c (%) (in diabetes only)	7.1[IQR 6.4-8.1]	7.1(IQR 6.4-8.0)	0
Renal disease (eGFR<60) at baseline	12,687 (50.1)	43,967(47.2)	2.9
eGFR (ml/min/1.73m^2)	60.8 ±20.3	62.1±18.8	1.3
Number of the listed comorbidities at baseline (egfr definition)			
0	8,518 (33.6)	35,133(37.7)	4.1
1	12,290 (48.5)	45,013(48.3)	0.2
2	4,202 (16.6)	12,279(13.2)	3.4
3	322 (1.3)	823(0.9)	0.4

Data are number patients (%) or mean± standard deviation or median(IQR). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index; HB, haemoglobin

A18 COPD drug severity framework; extraction algorithms

Cont'd on next page

KEY

Drug class	BNF chapter	CPRD category code
Beta2-antagonists: SHORT	3.1.1.1	1
Beta2-antagonists: LONG	3.1.1.1	2
Anti-cholinergics: SHORT	3.1.2	3
Anti-cholinergics: LONG	3.1.2	4
Methylxanthines	3.1.3	5
Compound inhalers (SHORT x2)	3.1.4	6
Inhaled steroids	3.2	7
Inhaled steroids + beta2-antagonist:SHORT	3.2	8
Inhaled steroids + beta2-antagonist:LONG	3.2	9
Oral steroids – prednisolone	6.3.2	10
Oral steroids – methylprednisolone	6.3.2	11
Oxygen	3.6	12

COPD drug severity CPRD extraction algorithms

Severity Group	Severity category description	Extraction algorithm using CPRD category codes
A Short acting	Any short acting bronchodilators	At least one of (1,3 or 6) and NOT (2, 4, 5, 7-9 or 12 or more)
B Monotherapy	Any one long acting bronchodilator on its own or Methylxanthines monotherapy (without other step up therapy) or inhaled steroid on its own. May be in addition to short acting inhalers	One of [2 OR 4 OR 5] OR [7 OR 8 OR both]) AND NOT [9 or more]
C Dual therapy	Any long acting bronchodilator and an inhaled steroid (separate or combined). Methylxanthines may replace one of the bronchodilators	2 AND [7 or 8 or 9 – any or all] AND NOT [4, 5 or 10 or more] **OR** One of [4 OR 5] AND [7 OR 8 OR both] AND NOT [2 or 9 or more] **OR** 9 but NOT [4, 5, or 10 or more]
	Or both long acting bronchodilators without inhaled steroid	[2 AND 4] AND NOT [5, 7,8 ,9 or more] [2 AND 5] AND NOT [4, 7,8 ,9 or more] [5 AND 4] AND NOT [2, 7,8 ,9 or more]
D Triple therapy	Both long acting bronchodilators and an inhaled steroid Methylxanthines may replace one of the bronchodilators or be additional to both	Two of [2, 4 or 5] AND one or all of [7 or 8 or 9] AND NOT 10 or more **OR** 9 AND [4 or 5] AND NOT [10, 11 or 12]
E Additional therapy	On long term oxygen therapy or oral steroids	Any or all of 10,11 or 12

A19 Missing data

	Total missing; Mortality	Total missing; Hospital admission linked sub sample
IMD quintile	54262(40.6)	342(0.31)
BMI (Kg/m2)	11,855(8.9)	10,596(9.6)
Cholesterol (mmol/L)	19,194(14.4)	19,600(17.7)
HB (g/dL)	15,565(11.6)	12,165(11.0)
Systolic and Diastolic BP (mmHg)	736(0.6)	521(0.47)
Smoking status	2480(1.9)	2,634(2.4)
Alcohol status	12279(9.2)	11,132(10.1)
HbA1c (%) compared to no diabetes	3097 (2.3% total sample, 9.7% in diabetes)	6,713 (6.1% total sample, 31.5% in diabetes)
HbA1c change compared to no diabetes	5788 (4.3% total sample, 18.1% in diabetes)	9,049 (8.2% total sample, 42.5% in diabetes)
FEV_1(pp)	9,963 (7.5% total sample, 53.9% in COPD)	10,031(9.1% total sample, 84.3% in COPD)
FEV_1 (pp) severity change	13,796 (10.3% total sample, 74.7% in COPD)	11,250 (10.2% total sample, 94.5% in COPD)
eGFR	14030(10.5)	38,390(34.7)
eGFR change	28761(21.5)	56,017(50.6)

IMD, Index Multiple Deprivation; BMI, body mass index; HB, haemoglobin, FEV1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate. Shaded area = values to be imputed.

A20 Exploration of missing data by mortality outcome

	Total missing	Controls	Cases	Absolute difference in %*
IMD quintile	54262(40.6)	43,915(41.1)	10,347(38.7)	-2.4*
Systolic and Diastolic BP (mmHg)	736(0.6)	542(0.5)	194(0.7)	0.2
BMI (Kg/m2)	11,855(8.9)	8485(7.9)	3370(12.6)	4.7*
Cholesterol (mmol/L)	19,194(14.4)	14094(13.2)	5100(19.1)	5.9*
HB (g/dL)	15,565(11.6)	12877(12.0)	2688(10.1)	-1.9*
Smoking status	2480(1.9)	1823(1.7)	657(2.5)	0.8
Alcohol status	12279(9.2)	9294(8.7)	2985(11.2)	2.5*
FEV_1(pp)	9,963 (7.5% total sample)	8192 (7.7% total sample)	1771 (6.6% total sample)	-1.1
	(53.9% in COPD)	(59.2 in COPD)	(38.3 in COPD)	-20.9*
FEV_1 (pp) severity change	13,796 (10.3% total sample)	10,861 (10.2% total sample)	2,935 (11.0% total sample)	1.2
	(74.7% in COPD)	(78.4% in COPD)	(63.4% in COPD)	-15*
HbA1c (%) compared to no diabetes	3097 (2.3% total sample)	2356 (2.2% total sample)	741 (2.8% total sample)	0.6
	(9.7% in diabetes)	(9.3% in diabetes)	(9.4% in diabetes)	0.1
HbA1c change compared to no diabetes	5788 (4.3% total sample)	4548 (4.3% total sample)	1240 (4.6% total sample)	0.3
	(18.1% in diabetes)	(18.0% in diabetes)	(18.5% in diabetes)	0.5
eGFR	14030(10.5)	11216(10.5)	2814(10.5)	0
eGFR change	28761(21.5)	23310(21.8)	5451(20.4)	-1.4

FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index; HB, haemoglobin . *Missing data was compared for cases and controls to identify whether missing values differed significantly between the groups. Given the large sample size rather than using a statistical test, difference was assessed using the absolute difference in the percent of missing data with >1.5% difference considered important

A21 Exploration of missing data by hospital admission outcome

	Total missing	Controls	Cases	Absolute difference in %
IMD quintile	342(0.31)	272(0.31)	70(0.29)	-0.2
Systolic and Diastolic BP (mmHg)	521(0.47)	362(0.42)	159(0.7)	0.28
BMI (Kg/m2)	10,596(9.6)	8,019(9.3)	2,577(10.6)	1.3
Cholesterol (mmol/L)	19,600(17.7)	14,934(17.3)	4,666(19.2)	1.9
HB (g/dL)	12,165(11.0)	9,627(11.4)	2,538(10.4)	-1.0
Smoking status	2,634(2.4)	2,013(2.3)	621(2.6)	0.3
Alcohol status	11,132(10.1)	8,587(9.9)	2,545(10.5)	0.6
FEV_1(pp)	10,031(9.1% total sample)	7,348(8.5% total sample)	2,683 (11% total sample)	2.5
	(84.3% in COPD)	(84.7% in COPD)	(83.1% in COPD)	-1.6
FEV_1 (pp) severity change	11,250 (10.2% total sample)	8,213 (9.5% total sample)	3,037(12.5% total sample)	3.0
	(94.5% in COPD)	(94.7% in COPD)	(94 % in COPD)	-0.7
HbA1c (%) compared to no diabetes	6,713 (6.1% total sample)	4,757 (5.5% total sample)	1,956 (8.0% total sample)	2.5
	(31.5% in diabetes)	(30.2% in diabetes)	(35.1% in diabetes)	4.9
HbA1c change compared to no diabetes	9,049 (8.2% total sample)	6,507 (7.5% total sample)	2,542 (10.4% total sample)	2.9
	(42.5% in diabetes)	(41.4% in diabetes)	(45.6% in diabetes)	4.2
eGFR	38,390(34.7)	29,943(34.6)	8,447(34.7)	0.1
eGFR change	56,017(50.6)	43,995(50.9)	12,022(49.4)	-1.5

FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BMI, body mass index; HB, haemoglobin . *Missing data was compared for cases and controls to identify whether missing values differed significantly between the groups. Given the large sample size rather than using a statistical test, difference was assessed using the absolute difference in the percent of missing data with >1.5% difference considered important

A22 Pre and post imputed data: mortality outcome

	Pre imputation ALL	Post imputation ALL (n=133,645)	Pre imputation cases	Post imputation cases (n= 26,729)	Pre imputation controls	Post imputation controls (n=106,916)
BMI (Kg/m2)	26.9(IQR 23.7-31)	26.9(23.5-31)	25.4(22.2-29.3)	25.4(22.1-29.3)	27.3(24-31.3)	27.3(24-31.3)
Cholesterol (mmol/L)	4.5±1.2	4.5±1.2	4.4±1.2	4.4±1.2	4.5±1.2	4.5±1.2
HB (g/dL)	12.9±1.9	13.0±1.9	12.2±2.0	12.3±2.0	13.1±1.2	13.1±1.8
Systolic BP (mmHg)	131.4±20.5	131.4±20.5	126.9±22.3	126.9±22.3	132.5±19.9	132.5±19.9
Diastolic BP (mmHg)	73.3±11.4	73.3±11.4	71.1±11.4	71.1±12	73.9±11.1	73.9±11.1
Smoking status						
yes	14,737(11.2)	15,002(11.2)	3066(11.8)	3,127 (11.7)	11671(11.1)	11,875 (11.1)
No	60,527(46.1)	61,936(46.3)	12177(46.7)	12,573 (47.0)	48350(46.0)	49,363 (46.2)
Ex	55901(42.6)	56,707(42.4)	10829(41.5)	11,029(41.3)	45072(42.9)	45,678(42.7)
Alcohol status						
Yes	84,114(69.3)	92,438(69.2)	15744(66.3)	17,740(66.4)	68370(70.0)	74,698(69.9)
No	31330(25.8)	34,755(26.0)	6730(28.3)	7,611(28.5)	24600(25.2)	27,144(25.4)
Ex	5922(4.9)	6,452(4.8)	1270(5.4)	1,378(5.2)	4652(4.8)	5,074(4.8)

BMI, body mass index; HB, haemoglobin. Shaded area = final values following imputation.

A23 Pre and post imputed data: hospital admission linked sub-sample

	Pre imputation ALL	Post imputation ALL (n=110,789)	Pre imputation cases	Post imputation cases	Pre imputation controls	Post imputation controls (n=84,450)
IMD quintile						
1	22,493 (20.4)	22,567(20.4)	4,659(19.2)	4,676(19.2)	17,834(20.7)	17,891(20.7)
2	26,525 (24.0)	26,602(24.0)	5,597(23.1)	5,612(23.1)	20,928(24.3)	20,990(24.3)
3	22,936 (20.8)	23,003(20.8)	5,142(21.2)	5,155(21.2)	11,794(20.7)	17,848(20.6)
4	22,505 (20.4)	22,579(20.4)	5,046(20.8)	5,060(20.8)	17,459(20.7)	17,519(20.3)
5	15,988 (14.5)	16,038(14.5)	3,825(15.8)	3,836(15.8)	12,163(14.1)	12,202(14.1)
BMI (Kg/m2)	27.2(IQR 24-31.2)	27.2(23.9-31.2)	26.8(23.5-30.6)	26.7(23.5-30.6)	27.3(24.2-31.4)	27.3(24.1-31.3)
Cholesterol (mmol/L)	4.7±1.2	4.7±1.2	4.6±1.2	4.7±1.2	4.7±1.2	4.7±1.2
Hb (g/dL)	13.3±1.7	13.3±1.7	12.9±1.9	12.9±1.9	13.4±1.6	13.4±1.6
Systolic BP (mmHg)	135.6±20.2	135.6±20.2	134.1±21.6	134.1±21.5	136.0±19.8	136.0±19.8
Diastolic BP (mmHg)	75.7±11.2	75.7±11.2	74.7±12.0	74.7±12.0	75.9±11.0	75.9±11.0
Smoking status						
yes	11,796(10.9)	12,028(10.9)	2,965(12.5)	3,025 (12.4)	8,831(10.5)	9,003 (10.4)
No	51,774(47.9)	53,310(48.1)	10,899(46.0)	11,240(46.2)	40,875(48.4)	42,070 (48.7)
Ex	44,585(41.2)	45,451(41.0)	9,854(41.6)	10,074(41.4)	34,731(41.1)	35,377(40.9)
Alcohol status						
Yes	73,560(73.8)	81,676(73.7)	15678(71.9)	17,500(71.9)	57,882(74.3)	64,176(74.2)
No	22,167(22.2)	24,783(22.4)	5,161(23.7)	5,779(23.7)	17,006(21.8)	19,004(22.0)
Ex	3,930 (3.9)	4,330(3.9)	955(4.4)	1,060(4.4)	2,975(3.8)	3,270(3.8)

IMD, index of multiple deprivation; BMI, body mass index; Hb, haemoglobin. Shaded area = final values following imputation.

A24 Summary of goodness of fit measures

Test	**Description**	**Interpretation**
ROC/ c-index	How well does the model separate those who do and do not have the event?	C-index 0.5 = no discrimination
Log-likelihood	How likely is the data given the model?	Higher = better fit
Likelihood ratio test	How many times more likely the data are under one model than the other? Should the null model be rejected in favour of the alternative model?	$p \leq 0.01$ = reject the null model
AIC/ BIC	How well does the model fit the data given the number of parameters in the model?	Lower = better fit Difference of 2 AIC between models = model with smaller AIC preferred
McFadden's R^2	How much improved id the fitted model from the null model?	0.2 to 0.4 = excellent fit

A25 Baseline characteristics of the HF sample by mortality outcome in short, medium and long follow up periods

	Cohort upto 1 year follow up (n=50114)			Cohort 1-5 years follow up (n=36161)			Cohort > 5 years follow up (n=12336)		
Characteristics	Dead (n=11661)	Alive (n=38453)	*P*	Dead (n=11609)	Alive (n=24552)	*P*	Dead (n=3459)	Alive (n=8877)	*P*
Person and socio demographic factors									
Age, years	83[IQR 76-88]	77[69-84]	<0.001	81[74-86]	75[67-81]	<0.001	78[71-83]	72[64-78]	<0.001
Women	5919(50.76)	17,676(46)	<0.001	5,447(46.9)	10999(44.8)	<0.001	1608(46.5)	3914(44.1)	0.02
IMD quintile			0.003			0.003			0.31
1	1374(18.3)	4472(19.9)		1287(18.8)	2919(20.4)		403(19.8)	1069(20.6)	
2	1720(22.9)	5232(23.3)		1545(22.6)	3351(23.5)		443(21.8)	1210(23.3)	
3	1678(22.4)	4662(20.7)		1455(21.3)	2939(20.6)		437(21.5)	1057(20.3)	
4	1594(21.2)	4641(20.7)		1420(20.8)	2943(20.6)		413(20.3)	1069(20.6)	
5	1141(15.2)	3472(15.5)		1131(16.5)	2134(14.9)		341(16.7)	796(15.3)	
Anthropometric and clinical factors									
Systolic BP (mmHg)	134.9±22.2	138±21.2	<0.001	138.7±21.8	137.8±20.9	<0.001	141.1±21.9	138.5±20.9	<0.001
Diastolic BP (mmHg)	74.7±12	77.3±11.9	<0.001	76.3±11.6	77.8±12.0	<0.001	77.9±11.9	79.1±12	<0.001
BMI (Kg/m^2)	25.5[IQR22.4-29.3]	27.4[24.3-31.4]	<0.001	26.5[23.4-30.3]	27.9[24.7-31.9]	<0.001	27.2[24.4-31]	28.1[25-32.1]	<0.001
Cholesterol (mmol/L)	4.6±1.3	4.7±1.2	<0.001	4.6±1.2	4.7±1.2	<0.001	4.8 1.2	4.8 1.2	0.51
HB (g/dL)	12.5±2	13.2±1.8	<0.001	12.9±1.9	13.5±1.7	<0.001	13.3 1.7	13.7 1.7	<0.001
Lifestyle factors									
Smoking status			<0.001			0.03			0.288
yes	1637(14.8)	5204(14)		1641(14.8)	3282(13.8)		520(16.9)	1284(15)	
No	5341(48.2)	17277(46.5)		5070(45.7)	11.65(46.4)		1487(46)	3958(46.17)	
Ex	4098(37)	14659(39.5)		4381(39.5)	9501(39.8)		1224(37.9)	3330(38.9)	
Alcohol status			<0.001			<0.001			<0.001
Yes	6759(67.9)	24469(71.7)		6928(68.9)	16230(73.7)		2135(72.3)	5956(75.4)	
No	2755(27.7)	8338(24.4)		2739(27.2)	4975(22.6)		735(24.9)	1677(21.2)	
Ex	441(4.4)	1305(3.8)		392(4)	830(3.8)		82(2.8)	266(3.4)	
Drug factors									
Diuretics	8,277(71.0)	23,794(61.9)	<0.001	8,519(73.4)	14,485(59.0)	<0.001	2,515(72.7)	5,381(60.6)	<0.001
Beta blocker	3219(27.6)	13,163(34.2)	<0.001	3638(31.3)	9129(37.2)	<0.001	1076(31.11)	3513(39.6)	<0.001
ACEi	4366(37.4)	18216(47.4)	<0.001	5227(45)	11996(48.9)	<0.001	1636(47.3)	4384(49.4)	0.04
ARB	1061(9.1)	5057(13.2)	<0.001	1408(12.1)	3407(13.9)	<0.001	380(11)	1147(12.92)	0.003
Comorbidity exposures									
COPD	1615(13.9)	4233(11)	<0.001	1659(14.3)	2337(9.5)	<0.001	366(10.6)	663(7.47)	<0.001
FEV_1 (pp) (COPD only)	52.3[IQR 38.0-69.5]	54.0[40.3-69.8]	0.1239	52.3[37.9-68]	57.1[45-71]	<0.01	55.0[42.5-70.8]	57[45-69.6]	0.8059
Diabetes	2461(21.1)	8072(21)	<0.001	2723(23.5)	4900(20.0)	<0.001	699(20.2)	1476(16.6)	<0.001

HbA1c (%) (diabetes only)	7[IQR6.3-8]	7.1[6.4-8.1]	<0.001	7.1[6.4-8.2]	7.1[6.4-8.1]	0.4721	7.3[6.4-8.4]	7.2[6.5-8.1]	0.2104
Renal disease (medical code)	2106(18.1)	5515(14.3)		1909(16.4)	3218(13.1)		179(5.2)	810(9.1)	
Renal disease (eGFR<60)	5568(59.4)	14516(46.9)	<0.001	5277(56.9)	8259(41.8)	<0.001	1287(52.8)	2643(39.5)	<0.001
eGFR (ml/min/1.73m^2)	56.4±21.9	62.4±19.7	<0.001	57.8±20.1	64.7±19.0	<0.001	59.4±17.6	65.1±17.2	<0.001
Number of listed comorbidities			<0.001			<0.001			<0.001
0	2425(25.9)	11140 (36)		2442(26.3)	8039(40.6)		756(31.0)	2946(44.1)	
1	4929(52.5)	14542(47)		4740(51.1)	8904(45)		1247(51.2)	2995(44.8)	
2	1863(19.9)	4932(15.9)		1949(21)	2668(13.5)		412(16.9)	714(10.7)	
3	165(1.8)	350(1.1)		152(1.64)	173(0.9)		22(0.9)	32(0.5)	

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; HB, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate. Number of comorbidities is based on those listed (COPD, DM, CKD [eGFR]). HbA1c and FEV_1 were measured in the respective diabetes and COPD groups only. eGFR was measured in all HF patients.

A26 Baseline characteristics of the HF sample by mortality outcome in two temporal periods of HF diagnosis (pre and post April 2006)

Factors and exposures	Pre April 2006 (22,351)	Post April 2006 (27,763)	*P*
Person and socio-demographic factors			
Age, years	79(IQR 71-84)	78(IQR 70-85)	0.2113
Women	10,866(48.6)	12,729(45.9)	<0.001
IMD quintile			0.297
1	2,645(19.6)	3201(19.4)	
2	3055(22.7)	3,897(23.6)	
3	2,897(21.5)	3,443(20.9)	
4	2,794(20.7)	3,441(20.9)	
5	2,095(15.5)	2,518(15.3)	
Anthropometric and clinical factors			
BMI (Kg/m^2)	26.8.9[IQR 23.7-26.8]	27.2[23.9-31.3]	<0.001
Cholesterol (mmol/L)	4.9±1.2	4.5±1.2	<0.001
HB (g/dL)	13.1±1.9	13.0±1.9	<0.001
Systolic BP (mmHg)	140.9±22.2	134.4`±20.4	<0.001
Diastolic BP (mmHg)	`78.3±11.9	75.4±11.9	<0.001
Lifestyle factors			
Smoking status			<0.001
yes	3422(16.6)	3419(12.4)	
No	10,044(48.7)	12574(45.6)	
Ex	7177(34.8)	11580(42.0)	
Alcohol status			<0.001
Yes	13412(72.0)	17816(70.1)	
No	4665(25.0)	6,428(25.3)	
Ex	557(3.0)	1189(4.7)	
Drug factors			
Diuretics	15,301(68.5)	16,770(60.4)	<0.001
Beta blocker	6118(27.4)	10264(37.0)	<0.001
ACEi	9460(42.3)	13122(47.3)	<0.001
ARB	2005(9.0)	4113(14.8)	<0.001
Comorbidity exposures			
Diabetes	4,165(18.6)	6368(22.9)	<0.001
HbA1c (%) (in diabetes only)	7.2[IQR 6.5-8.3]	7[IQR 6.3-8]	<0.001
COPD	2,248(10.1)	3600(13.0)	<0.001
FEV1 (pp) (in COPD only)	51.4[IQR 36-68]	54[40.6-70]	0.0028
Renal disease (medical code)	655(2.9)	6966(25.1)	<0.001
Renal disease (eGFR<60)	8590(55.0)	11494(46.5)	<0.001
eGFR (mL/min/1.73m^2)	58.3±18.8	62.7±21.2	<0.001
Number of listed comorbidities			<0.001
0	4820(30.9)	8745(35.4)	
1	8,022(51.4)	11449(46.3)	
2	2,614(16.8)	4181(17.0)	
3	154(1.0)	361(1.5)	

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; HB, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate. Number of comorbidities is based on those listed (COPD, DM, HF).

A27 Time-matched patient characteristics of the matched sample by comorbid COPD status

Factors	COPD (n=18,478)	No COPD (n=115,167)
Age, years	76[IQR 69-81]	77[69-84]
Women	7,247(39.2)	54,485(47.3)
IMD quintile		
1	1,664(15.0)	14,244(20.9)
2	2237(20.2)	15,852(23.2)
3	2291(20.7)	14,375(21.04)
4	2520(22.8)	13,931(20.4)
5	2,361(21.3)	9,908(14.5)
BMI (Kg/m2)	26.7[23-31.1]	26.9 [23.6-30.9]
Cholesterol (mmol/L)	4.5±1.1	4.5±1.2
Hb (g/dL)	13.1±1.9	12.9±1.8
Systolic BP (mmHg)	128.9±19.9	131.8±20.6
Diastolic BP (mmHg)	72.1±11.2	73.5±11.4
Smoking status		
yes	3820(20.7)	11,182(9.7)
No	3191(17.3)	58,745(51.01)
Ex	11467(62.1)	45,240(39.3)
Alcohol status		
Yes	12856(69.6)	76582(69.1)
No	4502(24.4)	30253(26.3)
Ex	1120(6.1)	5332(4.6)
Beta blocker	6786(36.7)	67,435(58.6)
ACEi	9960(53.9)	64413(55.9)
ARB	3036(16.4)	19717(17.1)
ACEi or ARB	12725(68.9)	81822(71.1)
Diuretics	14,957(80.9)	88,326(76.7)
Diabetes	4276(23.1)	27686(24.0)
Renal disease (eGFR <60)	8384(49.9)	57917(56.3)
eGFR (ml/min/$m^{2)}$	61.0±22.4	57.3±20.9

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; Hb, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; eGFR, estimated glomerular filtration rate.

A28 Time-matched general characteristics of the matched sample by comorbid diabetes mellitus status

Factors	Diabetes (n= 31,962)	No diabetes (n=101,683)
Age, years	75[IQR 67-81]	78[70-84]
Women	13,127(41.1)	48605(47.8)
IMD quintile		
1	3,181(16.8)	12,727(21.1)
2	4,033(21.3)	14,056(23.3)
3	4,009(21.2)	12,657(20.9)
4	4,251(22.5)	12,200(20.2)
5	3,448(18.2)	8,821(14.6)
BMI (Kg/m2)	29.2[25.5-33.7]	26.3 [23.1-30]
Cholesterol (mmol/L)	4.1±1.1	4.6±1.2
Hb (g/dL)	12.7±1.9	13.0±1.8
Systolic BP (mmHg)	131.3±20.1	131.4±20.6
Diastolic BP (mmHg)	71.7±11.1	73.8±11.4
Smoking status		
yes	3153(9.9)	11,849(11.7)
No	13492(42.2)	47444(47.6)
Ex	15,317(47.9)	41390(40.7)
Alcohol status		
Yes	20805 (65.1)	71633(70.5)
No	9101(28.5)	25654(25.2)
Ex	2056(6.4)	4396(4.3)
Beta blocker	19,663(61.5)	54,558(53.7)
ACEi	19,104(59.8)	55,269(54.4)
ARB	6,727(21.1)	16,026(15.8)
ACEi or ARB	24,900(77.9)	6,9647(68.5)
Diuretics	26,361 (82.5)	76,922(75.7)
COPD	14276(13.4)	14,202(14.0)
Renal disease (eGFR <60)	18345(60.2)	47,956(53.8)
eGFR (ml/min/$m^{2)}$	55.6±22.4	58.6±20.7

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; Hb, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

A29 Time-matched general characteristics of the matched sample by comorbid CKD status

Factors	CKD (n= 66,301)	No CKD (n=53,314)
Age, years	80[IQR 73-85]	74[65-81]
Women	34847(52.6)	20264(38)
IMD quintile		
1	8344(20.4)	16462(20.0)
2	9471(23.1)	7314(22.6)
3	8758(21.4)	6637(20.5)
4	8453(20.6)	6705(20.7)
5	5979(14.6)	5206(16.1)
BMI (Kg/m2)	26.8[23.5-30.8]	27.2[23.8-31.3]
Cholesterol (mmol/L)	4.5±1.2	4.5±1.1
Hb (g/dL)	12.5±1.8	13.4±1.8
Systolic BP (mmHg)	130.7±21.0	131.2±19.4
Diastolic BP (mmHg)	72.0±11.4	74.2±10.9
Smoking status		
yes	5326(8.0)	7061(13.2)
No	32750(49.4)	22598(42.4)
Ex	28225(42.6)	23,655(44.4)
Alcohol status		
Yes	44246(66.7)	38405(72.0)
No	18785(28.3)	12222(22.9)
Ex	3270(4.9)	2687(5.0)
Beta blocker	19,663(61.5)	54,558(53.7)
ACEi	19,104(59.8)	55,269(54.4)
ARB	6,727(21.1)	16,026(15.8)
ACEi or ARB	24,900(77.9)	6,9647(68.5)
Diuretics	26,361 (82.5)	76,922(75.7)
COPD	8384(12.7)	8422(15.8)
Diabetes	18345(27.7)	12125(22.7)
eGFR (ml/min/$m^{2)}$	42.7±11.7	76.6±14.0

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; Hb, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate..

A30 Baseline characteristics of the HF-HA sample by first hospital admission outcome in short, medium and long follow up periods

	Cohort up to ≤1 month (n=30,061)			Cohort >1 month and ≤ 1 year (n=18,749)			Cohort > 1 year (n=8,291)		
Factors and exposures	First admission (n=9,911)	Not admitted (n=18,749)	*P*	First admission (n=9,478)	Not admitted (n=8,291)	*P*	First admission (n=5,149)	Not admitted (n=3,142)	*P*
Person and socio-demographic factors									
Age, years	80[72-86]	79[IQR 71-85]	<0.001	78[70-85]	78[71-84]	0.875	78[71-84]	77[68-83]	<0.001
Women	4,734(47.8)	9,429(46.8)	0.113	4,242(44.8)	4,476(48.3)	<0.001	2,509(48.7)	1,455(46.3)	0.03
IMD quintile			0.143			<0. 01			0.23
1	1,851(18.7)	3,993(19.9)		1,827(19.4)	1,893(20.5)		1,020(19.9)	665(21.3)	
2	2,276(23.0)	4,670(23.3)		2,143(22.7)	2,225(24.1)		1,221(23.8)	749(23.9)	
3	2,119(21.4)	4,221(21.0)		1,993(21.1)	1,921(20.8)		1,069(20.8)	657(21.0)	
4	2,094(21.2)	4,138(20.6)		1,943(20.6)	1,888(20.4)		1,053(20.5)	638(20.4)	
5	1,545(15.6)	3,067(15.3)		1,538(16.3)	1,319(14.3)		776(15.1)	421(13.5)	
Anthropometric and clinical factors									
BMI (Kg/m^2)	26.6[23.4-30.4]	27.1[IQR 23.9-31]	<0.001	27[23.8-30.8]	27.4[24.2-31.3]	<0.001	27.4[24.2-31.2]	27.7[24.5-32.9]	<0.01
Cholesterol (mmol/L)	4.7±1.2	4.7±1.2	0.049	4.6±1.2	4.7±1.2	<0.001	4.8±1.2	4.7±1.2	<0.001
Hb (g/dL)	12.8±2	13.2±1.8	<0.001	13.1±1.8	13.4±1.7	<0.001	13.4±1.7	13.5±1.7	0.39
Systolic BP (mmHg)	137.0±22.1	137.6±21.1	0.023	136.9±21.0	138.6±21	<0.001	140.2±21.1	136.6±20.5	<0.001
Diastolic BP (mmHg)	76.3±12.5	77.0±11.7	<0.001	76.6±11.8	77.7±11.5	<0.001	78±11.6	77.5±11.4	0.04
Prior Hospital admission			<0.01			<0.001			0.450
<3 months	3,914 (39.5)	7,805 (38.7)		4,248 (44.8)	3,021 (32.6)		1,617 (31.4)	1,003 (31.9)	
3-6 months	861 (8.7)	1,610 (8.0)		818 (8.6)	696 (7.5)		385 (7.5)	254 (8.1)	
>6months-1 year	940 (9.5)	1,771 (8.8)		845(8.9)	825 (8.9)		472 (9.2)	262 (8.3)	
Lifestyle factors									
Smoking status			<0.001			<0.01			0.163
yes	1,393(14.6)	2,473(12.7)		1,175(12.8)	1,076(12.1)		630(12.8)	351(11.4)	
No	4,361(45.6)	9,253(47.6)		4,263(46.3)	4,336(48.6)		2,339(47.6)	1,501(48.9)	
Ex	3,806(39.8)	7,698(39.6)		3,764(40.9)	3,502(39.3)		1,941(39.5)	1,218(39.7)	
Alcohol status			<0.001			0.03			0.612
Yes	6,197(71.1)	13,099(73.7)		6,182(73.1)	6,121(74.9)		3,411(75.5)	,2120(75.1)	
No	2,142(24.6)	4,010(22.6)		1,949(23.1)	1,753(21.5)		952(21.1)	594(21.0)	
Ex	383(4.4)	677(3.8)		325(3.9)	299(3.7)		156(3.5)	110(3.9)	
Drug factors									
Diuretics	5,773(58.3)	13,586(67.4)	<0.001	6,569(69.3)	6,241(67.3)	<0.01	3,747(72.8)	1,879(59.8)	<0.001
Beta blocker	2,898(29.2)	6,785(33.7)	<0.001	3,215(33.9)	3,257(35.1)	0.08	1,764(34.3)	1,242(39.5)	<0.001
ACEi	3,701(37.3)	19,888(49.1)	<0.001	4,705(49.6)	4,720(50.9)	0.08	2,638(51.2)	1,649(52.5)	0.27

ARB	1,180(11.9)	2,599(12.9)	0.015	1,236(13.0)	1,266(13.7)	0.216	675(13.1)	481(15.3)	<0.01
Comorbidity exposures									
Diabetes	2,340(23.6)	3,958(19.6)	<0.001	2,061(21.8)	1,649(17.8)	<0.001	944(18.3)	554(17.6)	0.421
HbA1c (%) (diabetes only)	7.1(6.3-8.1)	7.1(IQR 6.4-8.0)	0.8243	7.1(6.4-8.)	7 (6.4-8)	0.34	7.2(6.5-8.2)	6.9(6.3-7.7)	<0.001
COPD	1,243(12.5)	2,261(11.2)	<0.01	1,226(12.9)	890(9.6)	<0.001	499(9.7)	287(9.1)	0.401
FEV_1 (pp) (COPD only)	52.9[IQR 37.7-70.3]	54.1[39.6-71]	0.2378	54[40.4-71]	54.1[38.6-68.7]	0.58	54.1[38-70.3]	54.6[39-66]	0.943
Renal disease (medical code)	1,669(16.8)	2,851 (14.1)	<0.001	1,462(15.4)	1,204(13.0)	<0.001	531(10.3)	501(16.0)	<0.001
Renal disease (eGFR<60)	4,455(53.4)	8,232(48.5)	<0.001	4,088(50.2)	3,597(46.2)	<0.001	2,073(49.6)	1,108(39.6)	<0.001
eGFR (ml/min/1.73m^2)	59.2±21.3	61.6±19.7	<0.001	60.8±20.0	62.7±18.9	<0.001	61.1±17.8	65.7±19.6	<0.001
Number of comorbidities (renal code)			<0.001			<0.001			<0.01
0	5,661(57.1)	12,591(62.5)		5,574(58.1)	6,098(65.8)		3,445(66.9)	2,030(64.6)	
1	33,16(33.5)	6,164(30.6)		3,128(33)	2,634(28.4)		1,449(28.1)	894(28.5)	
2	866(8.7)	1,289(6.4)		707(7.5)	508(5.5)		240(4.7)	206(6.6)	
3	68(0.7)	106(0.5)		69(0.7)	31(0.3)		15(0.3)	12(0.4)	
Number of listed comorbidities (eGFR definition)			<0.001			<0.001			<0.001
0	2,497(29.9)	6,021 (35)		2,676(32.9)	2,986(38.4)		1,456(34.8)	1,244(44.5)	
1	4,089(49.0)	8,201(48.3)		3,951(48.5)	3,734(48)		2,121(50.7)	1,211(43.3)	
2	1,630(19.5)	2,572(15.1)		1,400(17.2)	1,007(12.9)		571(13.7)	328(11.7)	
3	128(1.5)	194(1.1)		119(1.5)	59(0.8)		36(0.9)	15(0.5)	

Data are number patients (%) or mean± standard deviation or median[IQR]. First hospital admission is the first all-cause admission following the incident HF date. BMI, body mass index; Hb, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; Number of comorbidities is based on those listed (COPD, DM, HF).

A31 Time-matched general characteristics of the matched hospital admission linked sample by comorbid COPD status

Factors	COPD (n= 11,903)	No COPD (n=98,886)
Current age, years	77(70-82)	79(70-85)
Women	4,982(41.9)	48,822(49.4)
IMD quintile		
1	1,784(15.0)	20,783(21.02)
2	2,366(19.9)	24,236(24.5)
3	2,460(20.7)	20,543(20.8)
4	2,717(22.8)	19,862(20.10)
5	2,576(21.6)	13,462(13.6)
BMI (Kg/m2)	27[23.5-31.4]	27.2 [24-31.2]
Cholesterol (mmol/L)	4.7±1.1	4.7±1.2
HB (g/dL)	13.5±1.8	13.3±1.7
Systolic BP (mmHg)	132.7±19.8	135.9±20.3
Diastolic BP (mmHg)	74.2±11.3	75.9±11.2
Prior Hospital admission		
<3 months	1,104 (9.27)	7,559(7.6)
3-6 months	1,005(8.44)	7,382 (7.5)
>6 months to 1 year	1,550(13.02)	11,380 (11.5)
Smoking status		
yes	2,534(21.3)	9,494(9.6)
No	2,038(17.1)	51,272(51.9)
Ex	7,331(61.6)	38,120(38.6)
Alcohol status		
Yes	8,670 (72.8)	73,006 (73.8)
No	2,666 (22.4)	22,117 (22.4)
Ex	567 (4.8)	3,763 (3.8)
Beta blocker	2,391(20.1)	42,076(42.6)
ACEi	6,915(58.1)	56,992(57.6)
ARB	1,892(15.9)	17,432(17.6)
ACEi or ARB	8,586(72.1)	71,834(72.6)
Diuretics	9,025(75.8)	70,835(71.6)
Diabetes	2,107(17.7)	19,184(19.4)
Renal disease (eGFR <60)	3,686(46.6)	34,098(52.9)
eGFR (ml/min/$m^{2)}$	62.0±20.0	59.2±19.3

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; HB, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; pp, percent predicted; eGFR, estimated glomerular filtration rate

A32 Time-matched general characteristics of the matched sample by comorbid DM status

Factors	Diabetes (n=21,291)	No diabetes (n=89,498)
Current age, years	76[68-82]	79[71-85]
Women	8,918(41.9)	44,886(50.2)
IMD quintile		
1	3,617(17.0)	18,950(21.2)
2	4,788(22.5)	21,814(24.4)
3	4,509(21.1)	18,494(20.7)
4	4,457(21.4)	18,032(20.2)
5	3,830(18.0)	12,208(13.6)
BMI (Kg/m2)	29.6[26-34.1]	26.6[23.5-30.4]
Cholesterol (mmol/L)	4.3±1.1	4.8±1.2
HB (g/dL)	13.1±1.9	13.4±1.7
Systolic BP (mmHg)	135.2±19.8	135.7±20.3
Diastolic BP (mmHg)	73.4±11.0	76.2±11.2
Prior Hospital admission		
<3 months	2,084(9.8)	6,579(7.4)
3-6 months	1,787(8.4)	6,600(7.4)
>6 months to 1 year	2,573(12.1)	10,357(11.6)
Smoking status		
yes	2,124(10.0)	9,904(11.1)
No	8,785(41.3)	44,525(49.8)
Ex	10,382(48.8)	35,069(39.2)
Alcohol status		
Yes	14,122 (66.3)	67,554(75.5)
No	5,858(27.5)	18,925(21.2)
Ex	1,311(6.2)	3,019(3.4)
Beta blocker	9,772(45.9)	34,695(38.8)
ACEi	13,603(63.9)	50,304(56.2)
ARB	4,716(22.2)	14,608(16.3)
ACEi or ARB	17,475(82.1)	62,945(70.3)
Diuretics	16,291(76.5)	63,569(71.0)
COPD	2,107(9.9)	9,796(11.0)
Renal disease (eGFR <60)	9.024(54.3)	28,760(51.6)
eGFR (ml/min/$m^{2)}$	58.6±20.7	59.7±19.0

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; HB, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

A33 Time-matched general characteristics of the matched sample by comorbid CKD status

Factors	Renal dysfunction (n= 37,784)	No renal dysfunction (n=34,618)
Current age, years	81[75-86]	75[66-82]
Women	21,027(55.7)	13,546 (39.1)
IMD quintile		
1	7,730(20.5)	7,135 (20.6)
2	8,977(23.8)	8,338(24.1)
3	8,233(21.8)	7,084(20.5)
4	7,633(20.2)	7,009(20.3)
5	5,211(13.8)	5,049(14.6)
BMI (Kg/m2)	27.1[23.8-31]	27.6[24.3-31.8]
Cholesterol (mmol/L)	4.7±1.2	4.6±1.1
Hb (g/dL)	12.8±1.7	13.7±1.6
Systolic BP (mmHg)	135.1±20.9	134.5±19.3
Diastolic BP (mmHg)	74.1±11.4	76.2±10.9
Prior Hospital admission		
<3 months	3,214 (8.5)	2,441 (7.1)
3-6 months	3,031(8.0)	3,020(8.7)
>6 months to 1 year	4,689(12.4)	4,260 (12.3)
Smoking status		
yes	2,985(7.9)	4,199(12.1)
No	19,107(50.6)	15,100(43.6)
Exf	15,692(41.5)	15,316(44.3)
Alcohol status		
Yes	26,630(70.5)	26,612(76.9)
No	9,584(25.4)	6,583(19.0)
Ex	1,570(4.2)	1,420(4.1)
Beta blocker	16,067(42.5)	14,807(42.8)
ACEi	22,194(58.7)	22,087(63.8)
ARB	7,590(20.1)	5,900(17.0)
ACEi or ARB	28,681(75.9)	26,889(77.7)
Diuretics	30,773 (81.4)	23,472(67.8)
Diabetes	9,024(23.9)	7,597(22.0)
COPD	3,686(9.8)	4,218(12.2)
eGFR (ml/min/$m^{2)}$	44.7±10.5	75.6±13.1

Data are number patients (%) or mean± standard deviation or median[IQR]. BMI, body mass index; Hb, haemoglobin; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

A34 Unadjusted associations of each comorbidity with mortality by status (present or not) and then in strata of the potential confounders

Potential confounders	Diabetes	COPD	CKD
Unadjusted RR	1.09 (1.05, 1.12)	1.41 (1.36, 1.46)	1.77 (1.72, 1.82)
Person and socio-demographic factors			
Age quartile			
1	1.54 (1.38, 1.71)*	2.03 (1.78, 2.30)*	2.22 (1.98, 2.50)*
2	1.32 (1.21, 1.44)	1.70 (1.53, 1.88)	1.41 (1.29, 1.54)
3	1.21 (1.11, 1.33)	1.65 (1.49, 1.84)	1.36 (1.24, 1.50)
4	1.16 (1.06, 1.13)	1.17 (1.05, 1.31)	1.21 (1.12, 1.31)
Male	1.10 (1.05, 1.16)	1.47 (1.39, 1.55)	1.94 (1.85, 2.03)*
Female	1.13 (1.07, 1.19)	1.36 (1.27, 1.46)	1.55 (1.47, 1.63)
Anthropometric and clinical factors			
BMI quartile			
1	1.36 (1.24, 1.50)*	1.24 (1.13, 1.36)*	1.45 (1.34, 1.57)*
2	1.34 (1.22, 1.47)	1.45 (1.30, 1.62)	1.72 (1.57, 1.88)
3	1.29 (1.17, 1.41)	1.37, 1.22, 1.54)	2.02 (1.83, 2.23)
4	1.25 (1.14, 1.37)	1.52 (1.35, 1.72)	2.19 (1.98, 2.43)
Cholesterol >=4.3	1.09 (1.03, 1.16)	1.39 (1.31, 1.48)	1.71 (1.62, 1.80)
Cholesterol <4.3	1.04 (0.99, 1.09)	1.39 (1.31, 1.47)	1.84 (1.75, 1.93)
Haemoglobin >=13	1.10 (1.03, 1.17)	1.59 (1.49, 1.70)*	1.74 (1.65, 1.84)
Haemoglobin <13	0.96 (0.91, 1.00)*	1.36 (1.28, 1.44)	1.38 (1.31, 1.44)*
Systolic BP >=130mmHg	1.07 (1.02, 1.12)	1.45 (1.36, 1.54)	1.67 (1.59, 1.76)
Systolic BP <130mmHg	1.08 (1.03, 1.14)	1.34 (1.26, 1.42)	1.84 (1.75, 1.94)
Lifestyle factors			
Smoking yes	1.05 (0.87, 1.26)	1.43 (1.20, 1.70)	1.83 (1.51, 2.22)
Smoking no	1.08 (1.05, 1.12)	1.39 (1.33, 1.45)	1.78 (1.72, 1.84)
Alcohol yes	1.09 (1.05, 1.14)	1.43 (1.36, 1.50)	1.79 (1.72, 1.87)
Alcohol no	1.03 (0.97, 1.11)	1.33 (1.22, 1.45)	1.66 (1.55, 1.78)
Drug factors			
Beta blocker yes	1.21 (1.15, 1.26)*	1.37 (1.28, 1.47)	2.10 (2.00, 2.21)*
Beta blocker no	1.01 (0.96, 1.07)	1.15 (1.09, 1.22)*	1.56 (1.48, 1.64)
ACEi or ARB yes	1.18 (1.13, 1.23)	1.51 (1.43, 1.58)	1.90 (1.82, 1.98)
ACEi or ARB no	1.11 (1.03, 1.20)	1.14 (1.05, 1.23)*	1.51 (1.40, 1.61)*
Diuretic yes	1.02 (0.99, 1.06)	1.39 (1.33, 1.45)	1.66 (1.60, 1.72)
Diuretic no	1.23 (1.10, 1.38)*	1.31 (1.14, 1.49)	1.81 (1.63, 2.02)
Comorbidity exposures			
Diabetes	-	1.51 (1.35, 1.69)	1.95 (1.78, 2.13)*
No diabetes	-	1.42 (1.36, 1.48)	1.76 (1.69, 1.82)
COPD	1.06 (0.92, 1.21)	-	1.29 (1.13, 1.47)*
No COPD	1.10 (1.06, 1.13)	-	1.91 (1.85, 1.98)
eGFR<60	1.08 (1.03, 1.13)	1.29 (1.22, 1.37)	-
eGFR60	1.05 (0.98, 1.13)	1.79 (1.66, 1.93)*	-

*10% Difference in comorbidity effect in at least one of the strata of the confounder. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; BMI, body mass index;

A35 Adjusted comorbidity associations with all-cause mortality by each potential confounder

	Diabetes							COPD							
	Diabetes Status	HbA1c 6.5-7.5%	HbA1c >7.5%	HbA1c <6.5%	No drugs	Oral (+/- Insulin)	Insulin only	COPD Status	FEV_1 ≥80%	FEV_1 50-79%	FEV_1 30-49%	FEV_1 <30%	No steroids/ oxygen	Steroids /no oxygen	Oxygen
Unadjusted RR	1.09	1.01	1.01	1.24	1.30	0.93	1.32	1.41	1.88	1.87	2.47	2.84	1.19	1.79	3.14
Adjusted by:															
Age	1.28	1.15	1.32	1.38	1.38	1.12	1.74	1.56	1.95	2.00	2.78	3.89	1.30	2.02	3.80
Sex	1.09	1.02	1.01	1.24	1.30	0.94	1.33	1.42	1.89	1.90	2.52	2.91	1.21	1.80	3.17
IMD	1.05	0.99	0.95	1.21	1.3	0.89	1.25	1.36	1.77	1.83	2.49	2.77	1.17	1.74	2.85
BMI (Kg/m2)	1.32	1.21	1.28	1.41	1.41	1.15	1.68	1.39	1.79	1.89	2.35	2.56	1.19	1.75	3.10
Cholesterol (mmol/L)	1.05	0.97	0.98	1.19	1.27	0.90	1.27	1.41	1.87	1.85	2.47	2.87	1.19	1.81	3.15
Hb (g/dL)	0.98	0.92	0.93	1.06	1.23	0.84	1.12	1.50	1.95	1.93	2.59	3.63	1.26	1.90	3.37
Systolic BP (mmHg)	1.10	1.02	1.03	1.24	1.31	0.94	1.34	1.37	1.79	1.80	2.37	2.71	1.17	1.73	2.95
Diastolic BP (mmHg)	1.05	0.97	0.97	1.18	1.28	0.90	1.23	1.38	1.82	1.80	2.38	2.78	1.16	1.76	3.03
Smoking status	1.09	1.01	1.01	1.24	1.30	0.93	1.33	1.45	1.95	1.94	2.55	2.95	1.23	1.85	3.25
Alcohol status	1.08	1.00	0.99	1.23	1.30	0.92	1.30	1.41	1.89	1.88	2.47	2.86	1.20	1.79	3.12
Not on beta blocker	1.12	1.05	1.04	1.26	1.33	0.96	1.37	1.24	1.68	1.67	2.13	2.34	1.07	1.53	2.69
Not on ACEi	1.12	1.04	1.03	1.26	1.3	0.97	1.33	1.40	1.84	1.88	2.47	2.80	1.19	1.75	3.03
Not on ARB	1.11	1.03	1.04	1.25	1.31	0.95	1.38	1.40	1.91	1.87	2.44	2.78	1.19	1.78	3.01
Diuretic	1.07	0.99	0.98	1.22	1.29	0.91	1.29	1.39	1.87	1.84	2.42	2.82	1.18	1.76	3.06
COPD/ Diabetes	1.09	1.01	1.01	1.24	1.30	0.93	1.33	1.41	1.88	1.87	2.47	2.86	1.20	1.79	3.15
eGFR <60ml/min)	1.05	0.98	0.97	1.19	1.28	0.91	1.20	1.47	1.97	1.90	2.70	3.44	1.23	1.97	3.41
eGFR (ml/min/m2)	1.03	0.96	0.95	1.16	1.25	0.91	1.09	1.51	1.98	1.93	2.81	3.74	1.25	2.06	3.52

All Diabetes and COPD exposure measures are compared to the reference group of no diabetes or no COPD respectively. Red text indicates a ≥10% adjustment to the OR. IMD, Index Multiple Deprivation; Hb, haemoglobin; BMI, body mass index ; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate..

A35 cont'd Adjusted comorbidity associations with all-cause mortality by each potential confounder

	Renal any (eGFR<60)	>105	90-105	45-59	30-44	15-29	<15
Unadjusted RR	1.77	1.59	1.09	1.30	1.99	3.60	5.53
Adjusted by:							
Age	1.34	2.12	1.37	1.07	1.48	2.71	5.30
Sex	1.76	1.60	1.09	1.29	1.98	3.59	5.52
IMD quintiles*	1.72	1.69	1.07	1.25	1.96	3.58	5.42
BMI (Kg/m2)	1.74	1.57	1.10	1.28	1.95	3.61	5.59
Cholesterol (mmol/L)	1.77	1.59	1.09	1.30	1.98	3.58	5.46
HB (g/dL)	1.42	1.57	1.11	1.16	1.58	2.51	3.47
Systolic BP (mmHg)	1.75	1.58	1.08	1.29	1.95	3.59	5.72
Diastolic BP (mmHg)	1.69	1.62	1.10	1.26	1.89	3.35	5.19
Smoking status	1.78	1.57	1.08	1.30	2.00	3.62	5.54
Alcohol status	1.76	1.59	1.09	1.29	1.97	3.57	5.48
Not on beta blocker	1.79	1.51	1.06	1.30	2.00	3.71	5.76
Not on ACEi	1.73	1.58	1.10	1.29	1.95	3.40	5.04
ot on ARB	1.79	1.56	1.08	1.31	2.01	3.65	5.47
Diuretic	1.72	1.62	1.10	1.27	1.93	3.48	5.55
Diabetes	1.76	1.59	1.09	1.30	1.99	3.60	5.53
COPD	1.79	1.55	1.07	1.31	2.01	3.66	5.65

Renal status eGFR <60 is compared to eGFR ≥60 mls/min/m2. Renal severity exposures are compared to the reference group of eGFR 60-89 mls/min/m^2. Red text indicates a ≥10% adjustment to the OR. IMD, Index Multiple Deprivation; Hb, haemoglobin; BMI, body mass index ; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

A36 Summary of linearity investigations for continuous variables and mortality

Continuous factor	Margins-plots	Likelihood ratio tests	Fitted lines	Eccles plots	Decision
Age	Some departure from linearity	Quadratic extension significant but change to log-likelihood small (53.26)	Linear fit close to observed data for most of age distribution	Good fit between observed data and model with age (linear) and model with age (quadratic)	Age linear
BMI	Curved line	Quadratic extension significant with large change in log-likelihood (121.69). Cubic extension significant with small change in log-likelihood (4.59).	Quadratic line fit close to observed data for most of BMI distribution (IQR 23.5-31kg/m2)	Good fit between observed data and model with BMI (quadratic) and model with BMI (cubic)	BMI + BMI^2
Cholesterol	Small departure from linearity in lower deciles	Quadratic extension significant but change to log-likelihood small (50.7)	Linear fit close to observed data for most of CH distribution (mean 4.5±1.2)	Good fit between observed data and model with CH (linear) and model with CH (quadratic)	CH linear
Haemoglobin	Curved line	Quadratic extension significant with large change in log-likelihood (114.53). Cubic extension significant with a smaller change in log-likelihood (71.37). Log transformation non-significant.	Quadratic line fit close to observed data for most of Hb distribution (mean 13.1±1.9)	Good fit between observed data and model with Hb (quadratic) and model with Hb (cubed)	Hb + Hb^2
Systolic blood pressure	Curved line	Quadratic extension significant with large change in log-likelihood (297.25). Cubic extension significant with small change in log-likelihood (27.3).	Quadratic line fit close to observed data for most of systolic distribution (mean 137.3±21.5)	Reasonable fit between observed data and model with systolic (quadratic) and model with systolic (cubed)	systolic + $systolic^2$
Diastolic blood pressure	Curved line	Quadratic extension significant with large change in log-likelihood (97.66). Cubic extension significant with small change in log-likelihood (5.93).	Quadratic line fit close to observed data for diastolic	Good fit between observed data and model with diastolic (quadratic) and model with diastolic (cubed)	diastolic + $diastolic^2$
eGFR	Curved line	Quadratic extension significant with large change in log-likelihood (385.06). Cubic extension significant with small change in log-likelihood (9.53).	Quadratic extension fit close to observed data	Good fit between observed data and model with eGFR (quadratic)	eGFR + $eGFR^2$

A37 Unadjusted associations of each comorbidity by status (present or not) with first hospital admission and then in strata of the potential confounders

Potential confounders	Diabetes	COPD	CKD
Unadjusted	1.33 (1.28, 1.37)	1.36 (1.31, 1.43)	1.34 (1.29, 1.40)
Person and socio-demographic factors			
Age quartile 1	1.31 (1.19, 1.45)	1.40 (1.23, 1.59)	1.69 (1.46, 1.96)*
2	1.36 (1.23, 1.50)	1.55 (1.37, 1.76)*	1.21 (1.08, 1.37)*
3	1.54 (1.38, 1.72)*	1.60 (1.40, 1.83)*	1.18 (1.04, 1.34)*
4	1.52 (1.35, 1.72)*	1.41 (1.21, 1.64)	1.16 (1.02, 1.32)*
Male	1.24 (1.18, 1.31)	1.36 (1.28, 1.46)	1.53 (1.44, 1.64)*
Female	1.44 (1.35, 1.53)	1.38 (1.27, 1.50)	1.17 (1.09, 1.26)*
IMD quintile 1	1.37 (1.19, 1,57)	1.29 (1.07, 1,55)	1.47 (1.26, 1,71)*
2	1.32 (1.18, 1.48)	1.39 (1.20, 1.61)	1.34 (1.18, 1.53)
3	1.33 (1.18, 1.51)	1.17 (1.00, 1.37)*	1.40 (1.21, 1.62)
4	1.45 (1.29, 1.64)	1.50 (1.29, 1.74)*	1.37 (1.18, 1.60)
5	1.18 (1.01, 1.38)*	1.38 (1.15, 1.65)	1.19 (0.97, 1.46)*
Anthropometric and clinical factors			
No hospital admissions in previous year	1.28 (1.22, 1.35)	1.33 (1.25, 1.42)	1.35 (1.28, 1.43)
Hospital admission ≤3 months ago	1.16 (0.97, 1.40)*	1.56 (1.23, 1.97)*	1.38 (1.10, 1.73)
Hospital admission >3-6 months ago	1.36 (1.11, 1.66)	1.31 (1.02, 1.69)	1.03 (0.81, 1.29)*
Hospital admission >6months to 1 year ago	1.41 (1.19, 1.66)	1.66 (1.34, 2.04)*	1.15 (0.95, 1.40)*
BMI quartile 1	1.45 (1.28, 1.65)	1.45 (1.28, 1.64)	1.20 (1.06, 1.35)*
2	1.50 (1.34, 1.69)*	1.28 (1.12, 1.47)	1.29(1.13, 1.46)
3	1.20 (1.08, 1.33)*	1.33 (1.15, 1.53)	1.31 (1.15, 1.50)
4	1.38 (1.26, 1.52)	1.36 (1.19, 1.56)	1.41 (1.25, 1.60)
Cholesterol <4.6	1.30 (1.24, 1.37)	1.37 (1.27, 1.47)	1.44 (1.35, 1.54)
Cholesterol ≥4.6	1.29 (1.20, 1.38)	1.40 (1.30, 1.51)	1.25 (1.17, 1.35)
Haemoglobin <13.4	1.33 (1.26, 1.40)	1.40 (1.30, 1.50)	1.20 (1.13, 1.28)*
Haemoglobin ≥13.4	1.14 (1.07, 1.21)*	1.39 (1.29, 1.49)	1.22 (1.13, 1.31)*
Systolic BP <131mmHg	1.28 (1.21, 1.35)	1.37 (1.28, 1.47)	1.40(1.32, 1.49)
Systolic BP≥135mmHg	1.39 (1.31, 1.48)	1.33 (1.23, 1.43)	1.31 (1.22, 1.41)
Lifestyle factors			
Smoking yes	1.09 (0.87, 1.38)*	1.33 (1.08, 1.65)	1.04 (0.77, 1.41)*
Smoking no	1.34 (1.29, 1.40)	1.36 (1.29, 1.42)	1.34 (1.28, 1.39)
Alcohol yes	1.34 (1.28, 1.40)	1.37 (1.30, 1.45)	1.34 (1.28, 1.41)
Alcohol no	1.26 (1.15, 1.37)	1.33 (1.18, 1.51)	1.30 (1.15, 1.46)
Drug factors			
Beta blocker yes	1.37 (1.28, 1.47)	1.37 (1.28, 1.47)	1.40 (1.30, 1.52)
Beta blocker no	1.38 (1.31, 1.45)	1.15 (1.09, 1.22)*	1.31 (1.23, 1.39)
ACEi or ARB yes	1.40 (1.34, 1.46)	1.51 (1.43, 1.58)*	1.34 (1.28, 1.41)
ACEi or ARB no	1.45 (1.31, 1.61)	1.14 (1.05, 1.23)*	1.37 (1.22, 1.54)
Diuretic yes	1.31 (1.25, 1.36)	1.39 (1.33, 1.45)	1.33 (1.27, 1.40)
Diuretic no	1.48 (1.34, 1.63)*	1.31 (1.14, 1.49)	1.49 (1.31, 1.69)*
Comorbidity exposures			
Diabetes	-	1.54 (1.30, 1.82)*	1.50 (1.31, 1.70)*
No diabetes	-	1.38 (1.32, 1.46)	1.29 (1.22, 1.35)
COPD	1.28 (1.03, 1.60)	-	1.38 (1.06, 1.79)
No COPD	1.34 (1.29, 1.39)	-	1.35 (1.29, 1.41)
Renal dysfunction	1.24 (1.14, 1.35)	1.43 (1.29, 1.58)	-
No renal dysfunction	1.32 (1.23, 1.42)	1.37 (1.24, 1.53)	-

First hospital admission is the first all-cause admission following the incident HF date. *10% Difference in comorbidity effect in at least one of the strata of the confounder. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; BMI, body mass index;

A38 Adjusted comorbidity associations with first hospital admission by each potential confounder

	Diabetes							COPD							
	Diabetes Status	HbA1c 6.5-7.5%	HbA1c >7.5%	HbA1c <6.5%	No drugs	Oral (+/- Insulin)	Insulin only	COPD Status	FEV_1 ≥80%	FEV_1 50-79%	FEV_1 30-49%	FEV_1 <30%	No steroids or oxygen	Steroids /no oxygen	On oxygen
Unadjusted	1.33	1.14	1.31	1.25	1.17	1.34	1.63	1.36	1.38	1.59	1.43	1.28	1.20	1.74	3.34
Adjusted by:															
Age	1.37	1.17	1.39	1.27	1.18	1.39	1.75	1.39	1.39	1.61	1.44	1.34	1.22	1.78	3.41
Sex	1.32	1.13	1.30	1.24	1.17	1.33	1.62	1.36	1.38	1.57	1.42	1.26	1.19	1.73	3.35
IMD quintiles	1.32	1.13	1.30	1.23	1.16	1.33	1.62	1.35	1.36	1.55	1.42	1.26	1.18	1.71	3.31
Prior admissions	1.27	1.13	1.29	1.21	1.10	1.32	1.46	1.35	1.50	1.52	1.41	1.36	1.21	1.67	2.89
BMI (Kg/m2)	1.42	1.23	1.44	1.32	1.22	1.45	1.78	1.36	1.38	1.60	1.40	1.22	1.20	1.73	3.27
Cholesterol (mmol/L)	1.30	1.11	1.29	1.22	1.16	1.31	1.60	1.37	1.38	1.58	1.44	1.29	1.20	1.75	3.36
Hb (g/dL)	1.26	1.08	1.26	1.15	1.16	1.25	1.55	1.43	1.44	1.62	1.45	1.49	1.25	1.83	3.53
Systolic BP (mmHg)	1.33	1.14	1.32	1.24	1.17	1.34	1.65	1.35	1.38	1.58	1.41	1.24	1.18	1.71	3.18
Diastolic BP (mmHg)	1.29	1.11	1.29	1.21	1.15	1.30	1.57	1.34	1.38	1.56	1.41	1.26	1.18	1.72	3.20
Smoking status	1.32	1.14	1.31	1.24	1.16	1.34	1.64	1.33	1.37	1.54	1.39	1.24	1.17	1.70	3.28
Alcohol status	1.31	1.13	1.30	1.24	1.16	1.32	1.62	1.36	1.38	1.60	1.43	1.28	1.20	1.73	3.31
Not on beta blocker	1.34	1.16	1.33	1.27	1.18	1.36	1.66	1.32	1.35	1.53	1.38	1.21	1.16	1.66	3.20
Not on ACEi	1.36	1.18	1.34	1.29	1.18	1.38	1.68	1.37	1.40	1.60	1.45	1.26	1.21	1.72	3.32
Not on ARB	1.34	1.16	1.33	1.26	1.18	1.35	1.67	1.20	1.40	1.58	1.41	1.26	1.20	1.73	3.33
Diuretic	1.34	1.15	1.33	1.26	1.17	1.35	1.65	1.37	1.38	1.60	1.46	1.30	1.21	1.75	3.35
COPD	1.33	1.14	1.33	1.25	1.17	1.34	1.66	1.37	1.41	1.59	1.45	1.31	1.20	1.76	3.43
eGFR <60ml/min)	1.29	1.17	1.33	1.23	1.05	1.35	1.54	1.39	1.40	1.87	1.51	1.18	1.22	1.86	3.03
eGFR (ml/min/m2)	1.29	1.17	1.32	1.21	1.04	1.36	1.50	1.40	1.40	1.88	1.50	1.24	1.23	1.87	2.99

First hospital admission is the first all-cause admission following the incident HF date. All Diabetes and COPD exposure measures are compared to the reference group of no diabetes or no COPD respectively. Red text indicates a ≥10% adjustment to the OR. IMD, Index Multiple Deprivation; Hb, haemoglobin; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Table A38 cont'd Adjusted comorbidity associations with first hospital admission by each potential confounder

	Renal any (eGFR<60)	>105	90-105	45-59	30-44	15-29	<15
Unadjusted	1.34	1.19	1.15	1.16	1.41	2.50	9.17
Adjusted by:							
Age	1.29	1.23	1.18	1.13	1.36	2.39	9.01
Sex	1.37	1.19	1.14	1.19	1.45	2.58	9.42
IMD quintiles*	1.35	1.18	1.14	1.16	1.41	2.50	9.10
Prior admission	1.30	1.22	1.10	1.16	1.34	2.22	7.48
BMI (Kg/m2)	1.33	1.19	1.15	1.15	1.40	2.47	9.13
Cholesterol (mmol/L)	1.35	1.19	1.15	1.17	1.42	2.51	9.08
Hb (g/dL)	1.15	1.22	1.19	1.08	1.18	1.85	6.08
Systolic BP (mmHg)	1.34	1.19	1.15	1.16	1.41	2.51	9.29
Diastolic BP (mmHg)	1.31	1.21	1.15	1.15	1.37	2.43	8.87
Smoking status	1.36	1.16	1.13	1.17	1.43	2.56	9.21
Alcohol status	1.33	1.19	1.15	1.16	1.40	2.48	9.04
Not on beta blocker	1.35	1.17	1.15	1.16	1.41	2.52	9.12
Not on ACEi	1.33	1.18	1.14	1.16	1.39	2.41	8.77
Not on ARB	1.35	1.19	1.15	1.17	1.42	2.52	9.22
Diuretic	1.35	1.19	1.14	1.17	1.43	2.55	9.25
COPD	1.36	1.18	1.15	1.17	1.43	2.53	9.27
Diabetes	1.34	1.18	1.14	1.16	1.40	2.47	8.88

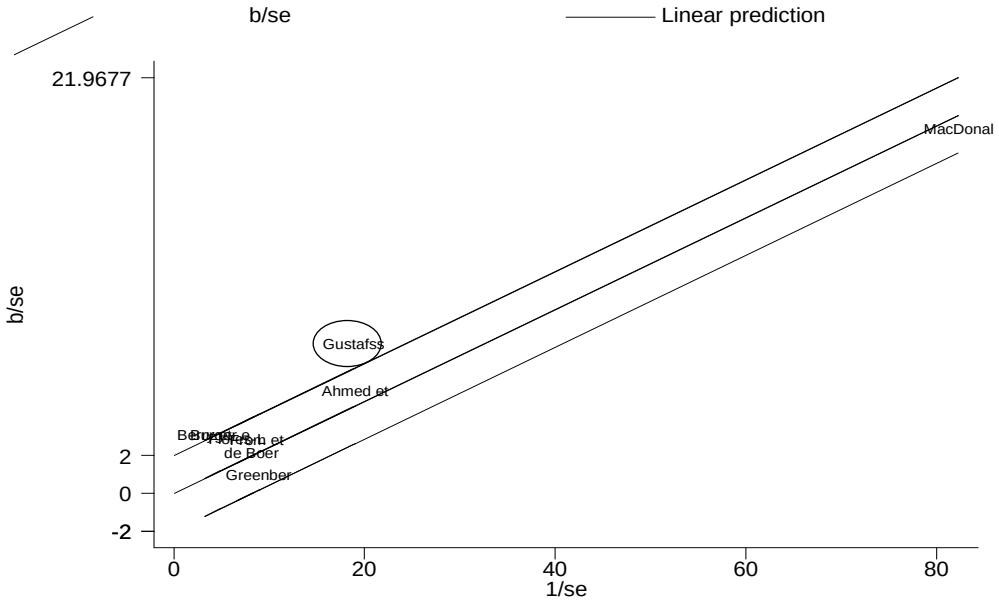
First hospital admission is the first all-cause admission following the incident HF date. Renal status eGFR <60 is compared to eGFR ≥60 mls/min/m2. Renal severity exposures are compared to the reference group of eGFR 60-89 mls/min/m^2. Red text indicates a ≥10% adjustment to the OR. IMD, Index Multiple Deprivation; Hb, haemoglobin; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

A39 Summary of linearity investigations for continuous variables with risk of first hospital admission

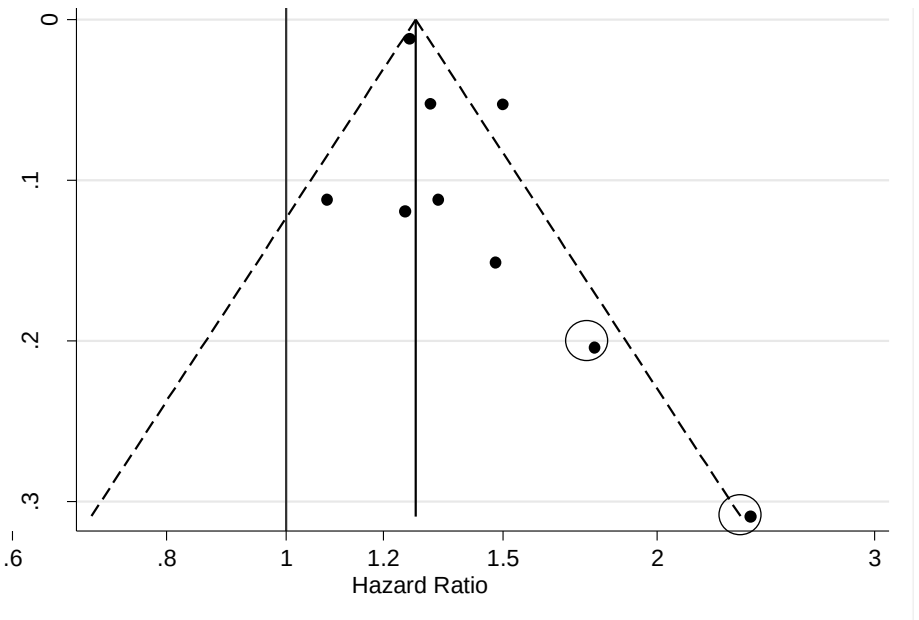
Continuous factor	Margins-plots	Log-likelihood ratio tests	Fitted lines	Eccles plots	Decision
Age	Some departure from linearity	Quadratic extension significant but change to log-likelihood small (11.78)	Linear fit close to observed data for most of age distribution	Good fit between observed data and model with age (linear) and model with age (quadratic)	Age linear
BMI	Curved line	Quadratic extension significant but with minimal change to log-likelihood (8.48). Cubic extension non-significant.	Linear fit close to observed data for most of BMI distribution (IQR 23.9-31.2 kg/m2)	Good fit between observed data and model with BMI (linear) and model with BMI (quadratic)	BMI linear
Cholesterol	Small departure from linearity in lower deciles	Quadratic extension significant but change to log-likelihood small (8.91)	Linear fit close to observed data for most of CH distribution (mean 4.7±1.2)	Good fit between observed data and model with CH (linear) and model with CH (quadratic)	CH linear
Haemoglobin	Curved line	Quadratic extension significant with large change in log-likelihood (122.32). Cubic extension and log transformation non-significant.	Quadratic line fit close to observed data for most of Hb distribution (mean 13.3±1.7)	Good fit between observed data and model with Hb (quadratic) and model with Hb (cubed)	Hb + Hb^2
Systolic blood pressure	Curved line	Quadratic extension significant with change in log-likelihood (77.05). Cubic extension significant with small change in log-likelihood (5.5).	Quadratic line fit close to observed data for most of systolic distribution (mean 135.6±20.2)	Good fit between observed data and model with systolic (quadratic)	systolic + $systolic^2$
eGFR	Curved line	Quadratic extension significant change in log-likelihood (84.67). Cubic extension significant with small change in log-likelihood (19.25).	Quadratic extension fit close to observed data	Good fit between observed data and model with eGFR (linear) and eGFR (quadratic)	eGFR + $eGFR^2$

E-Appendix B: Figures

B1 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid DM in HF



B2 Funnel plot for adjusted all-cause mortality risk associated with comorbid DM with pseudo 95% confidence intervals



B3 All-cause mortality associated with comorbid DM: prognostic factor (general)

Study	Sample size (n)	Diabetes (n)	Prevalence (%)	Adjusted	ES (95% CI)	Effect
Ahluwalia et al (2012) (Community)	9166	3122	34	A, G, E	1.22 (1.15, 1.31)	HR
Ahluwalia et al (2012) (Hospital)	9166	4617	50	A, G, E	1.16 (1.11, 1.22)	HR
Ahmed et al (2006)	1926	650	34	A, G,E,C,At,Sv,D,L,P,Ef	1.63 (1.36, 1.95)	HR
Barsheshet et al (2010) (<75 years)	1154	706	61	A, G,C,At,Sv,D,L,P,Ef	1.43 (1.15, 1.77)	HR
Barsheshet et al (2010) (>75 years)	1182	501	42	A, G,C,At,Sv,D,L,P,Ef	1.28 (1.07, 1.53)	HR
Chaudhry et al (2010)	62330	24745	40	A, G,E,C,L,P,Ef	1.28 (1.23, 1.34)	OR
Fernandez-Berges et al (2013)	2220	970	44	A, R,C,D	1.35 (1.11, 1.66)	HR
Gotsman et al (2008)	289	122	42	A, G,S,C,L,Ef	1.68 (1.03, 2.74)	HR
Harjola et al (2010)	2981	987	33	A, G,C,At,L,P	1.38 (1.08, 1.76)	HR
MacIntyre et al (2000) (Men)	31040	*		A, S,C	1.55 (1.41, 1.70)	HR
MacIntyre et al (2000)(Women)	35507	*		A, S,C	1.50 (1.38, 1.62)	HR
Mogensen et al (2011)	8507	1361	16	A, G,R,C,Ef	1.47 (1.37, 1.58)	HR
Mosterd et al (2001)	181	32	18	A,	3.19 (1.80, 5.65)	HR
Pons et al (2010)	960	377	40	A, G,C,At,Sv,D,Ef	1.60 (1.27, 2.01)	HR
Rusinaru et al (2009)	389	106	27	A, G,R,C,Sv,Ef	2.05 (1.41, 3.00)	HR
Shiba et al (2004)	1154	223	19	A, S,C,Sv,L	1.94 (1.26, 2.99)	HR
Tribouilloy et al (2010)	735	181	25	A, G,R,C,D,L	1.53 (1.22, 1.92)	HR

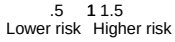


Fig B3 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(EF) *not reported

B4 All-cause mortality associated with comorbid DM: prognostic model studies

Study	Sample size (n)	Diabetes (n)	Prevalence (%)	Adjusted	ES (95% CI)	Effect
Barlera et al (2013)	6975	1974	28	A,G,R,C,Sv,L,P,Ef	1.34 (1.22, 1.48)	HR
Bouvy et al (2003)	152	43	28	A,G,C,D,P	2.37 (1.15, 4.85)	OR
Pocock et al (2006) (Other)	7599	2164	29	A,G,R,C,Sv,P,Ef	1.50 (1.34, 1.68)	HR
Pocock et al (2006) (Insulin group)	7599	707	9	A,G,R,C,Sv,P,Ef	1.80 (1.56, 2.08)	HR
Pocock et al (2013)	39372	8919	23	A,G,R,C,Sv,D,P,Ef	1.42 (1.37, 1.48)	HR
Senni et al (2006)	292	40	14	A,C,Sv,D,Ef	2.41 (0.28, 8.80)	LogOR
Senni et al (2013)	2016	304	15	A,C,Sv,D,Ef	1.62 (1.40, 1.80)	OR

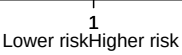


Fig B4 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(EF)

B5 All-cause hospital admission risk associated with comorbid DM in HF

Study	Sample size (n)	Diabetes (n)	Prevalence (%)	Adjusted variables	ES (95% CI)	Effect
Prognostic factors (general)						
Ahmed et al (2006)	1926	650	34	A,G,E,C,At,Sv,D,L,P,Ef	1.44 (1.27, 2.63)	HR
Aranda et al (2009)	28919	10700	37	*	1.13 (1.07, 1.20)	OR
Chaudhry et al (2013)	758	193	26	A,G,S,C,Sv,D,Ef	1.36 (1.13, 1.64)	HR
Dunlay et al (2009)	1077	232	21	A,G,C,Ef	1.53 (1.31, 1.79)	HR
Prognostic model						
Krumholz et al (2000)	1129	412	36	Sv,L	1.17 (0.99, 1.39)	HR

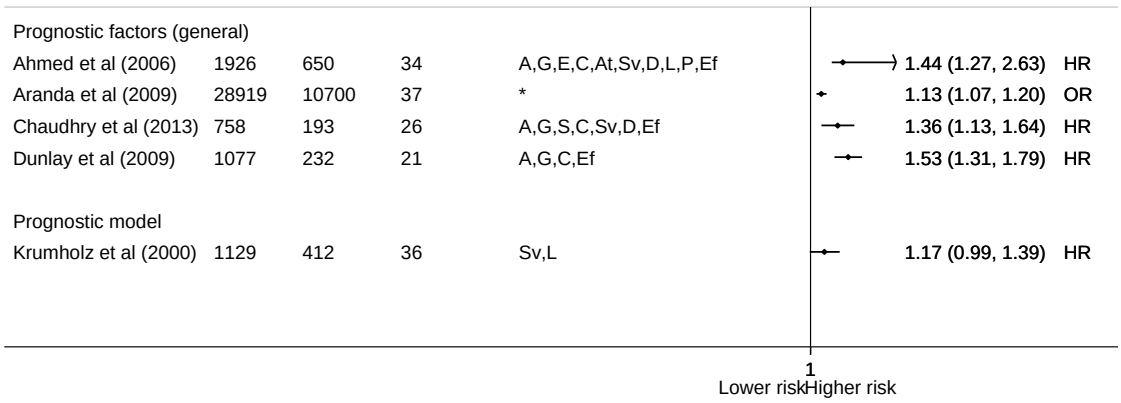
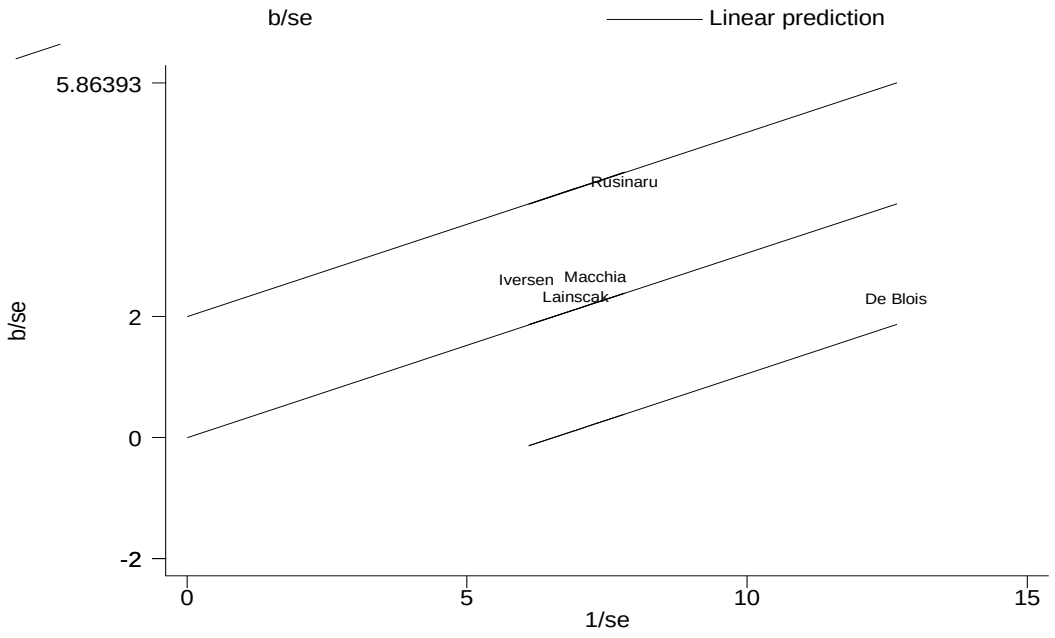
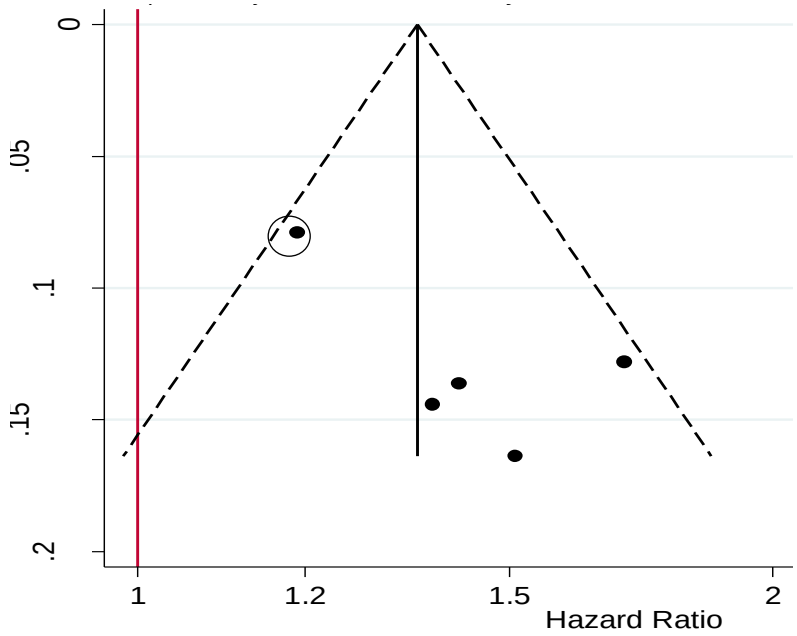


Fig B5 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(Ef) *not reported

B6 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid COPD in HF



B7 Funnel plot for adjusted all-cause mortality risk associated with comorbid COPD with pseudo 95% confidence intervals



B8 All-cause mortality associated with comorbid COPD: prognostic factor (general) and prognostic model studies

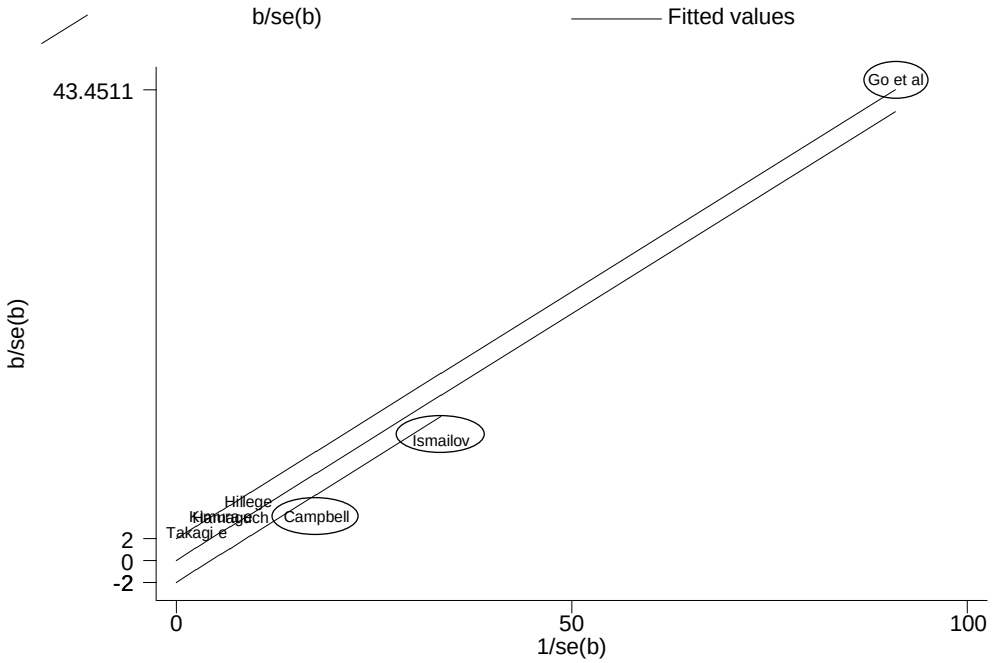
All-cause mortality associated with COPD: prognostic factor (general) and model studies

Study	Sample (n)	COPD (n)	Prevalence (%)	Adjusted variables	ES (95% CI)	Effect type	C-statistic
Prognostic factors (general)							
Ahluwalia et al (2012) (Community)	9166	1866	20	A,G,E,C	1.70 (1.58, 1.82)	HR	
Ahluwalia et al (2012) (Hospital)	9166	4263	47	A,G,E,C	1.24 (1.19, 1.31)	HR	
Chaudhry et al (2010)	62330	21192	34	A,G,E,C,L,P,Ef	1.51 (1.44, 1.57)	OR	
Garty et al (2007)	4102	803	20	A,G,C,Sv,D	1.25 (1.04, 1.50)	OR	
Mogensen et al (2011)	8507	1948	23	A,G,R,C,Ef	1.46 (1.37, 1.55)	HR	
Tribouilloy et al (2010)	735	146	20	A,S,R,C,D,L	1.44 (1.13, 1.84)	HR	
Prognostic model							
Barlera et al (2013)	6975	1533	22	A,G,R,C,Sv,L,P,Ef	1.43 (1.30, 1.58)	HR	.75
Lee et al (2003)	2624	543	21	A,C,L,P	1.41 (1.13, 1.75)	OR	.77
Martinez-Selles et al (2010)	701	188	27	A,C,L,Ef	1.60 (1.30, 1.90)	HR	.75
Pocock et al (2013)	39372	4035	10	A,G,R,C,Sv,D,P,Ef	1.23 (1.15, 1.31)	HR	*
Senni et al (2006)	292	45	15	A,G,R,C,D,L	1.41 (0.99, 2.35)	LogOR	0.82

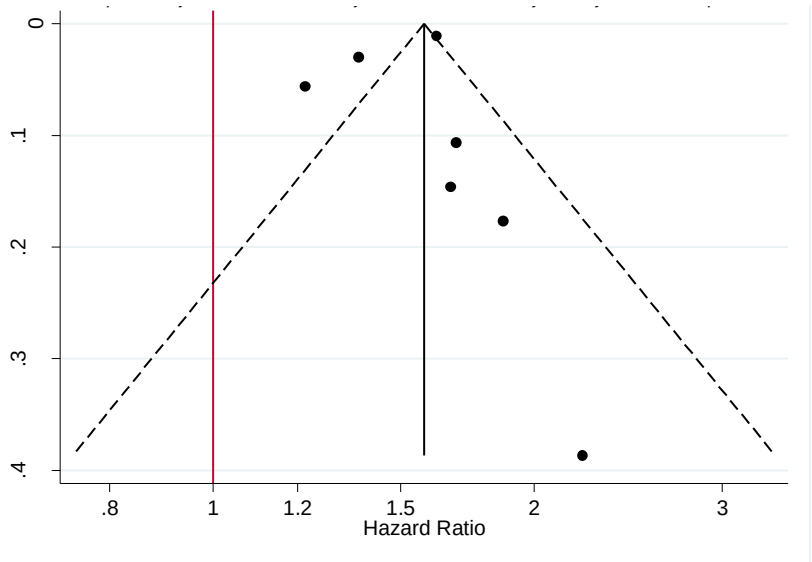
Fig 4.15

Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(Ef)
*not reported

B9 Galbraith Plot of studies investigating all-cause mortality risk associated with comorbid RD

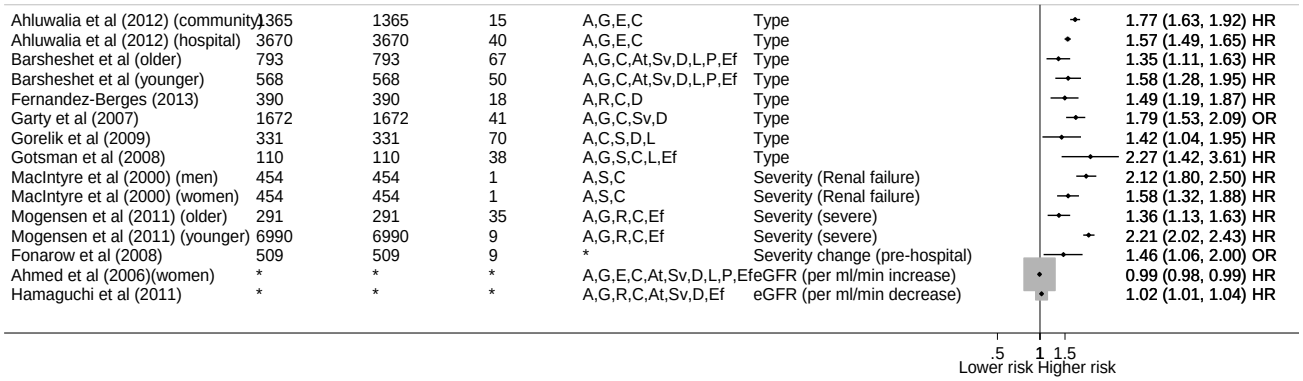


B10 Funnel plot for adjusted all-cause mortality risk associated with any RD with pseudo 95% confidence intervals



B11 All-cause mortality associated with comorbid RD: prognostic factor (general) studies

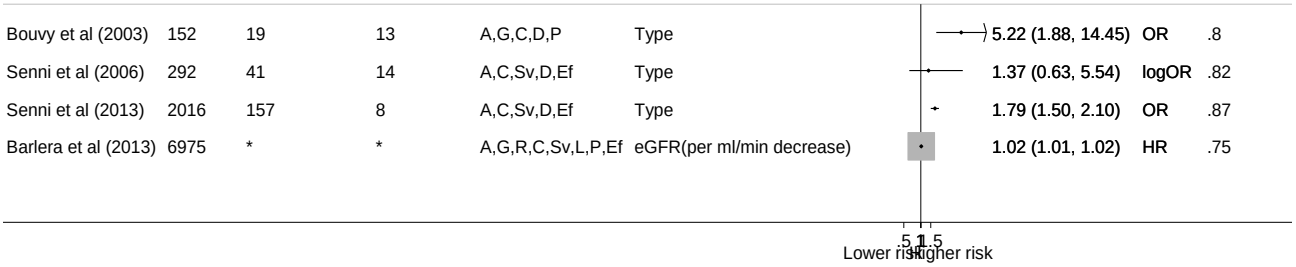
Study	Renal dysfunction (n)	Renal dysfunction (n)	Prevalence (%)	Adjusted variables	Measure	Hazard Ratio (95% CI)	Effect type
Ahluwalia et al (2012) (community)	1365	1365	15	A,G,E,C	Type	1.77 (1.63, 1.92)	HR
Ahluwalia et al (2012) (hospital)	3670	3670	40	A,G,E,C	Type	1.57 (1.49, 1.65)	HR
Barsheshet et al (older)	793	793	67	A,G,C,At,Sv,D,L,P,Ef	Type	1.35 (1.11, 1.63)	HR
Barsheshet et al (younger)	568	568	50	A,G,C,At,Sv,D,L,P,Ef	Type	1.58 (1.28, 1.95)	HR
Fernandez-Berges (2013)	390	390	18	A,R,C,D	Type	1.49 (1.19, 1.87)	HR
Garty et al (2007)	1672	1672	41	A,G,C,Sv,D	Type	1.79 (1.53, 2.09)	OR
Gorelik et al (2009)	331	331	70	A,C,S,D,L	Type	1.42 (1.04, 1.95)	HR
Gotsman et al (2008)	110	110	38	A,G,S,C,L,Ef	Type	2.27 (1.42, 3.61)	HR
MacIntyre et al (2000) (men)	454	454	1	A,S,C	Severity (Renal failure)	2.12 (1.80, 2.50)	HR
MacIntyre et al (2000) (women)	454	454	1	A,S,C	Severity (Renal failure)	1.58 (1.32, 1.88)	HR
Mogensen et al (2011) (older)	291	291	35	A,G,R,C,Ef	Severity (severe)	1.36 (1.13, 1.63)	HR
Mogensen et al (2011) (younger)	6990	6990	9	A,G,R,C,Ef	Severity (severe)	2.21 (2.02, 2.43)	HR
Fonarow et al (2008)	509	509	9	*	Severity change (pre-hospital)	1.46 (1.06, 2.00)	OR
Ahmed et al (2006)(women)	*	*	*	A,G,E,C,At,Sv,D,L,P,Ef	eGFR (per ml/min increase)	0.99 (0.98, 0.99)	HR
Hamaguchi et al (2011)	*	*	*	A,G,R,C,At,Sv,D,Ef	eGFR (per ml/min decrease)	1.02 (1.01, 1.04)	HR



B11 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(Ef) *not reported

B12 All-cause mortality associated with comorbid RD: prognostic model studies

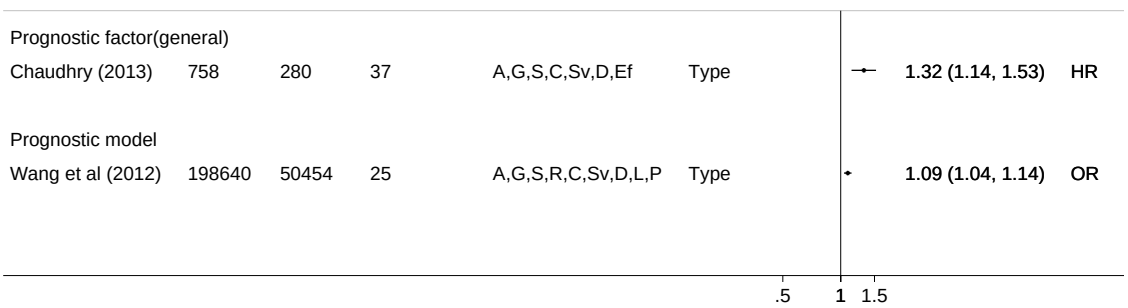
Study	Sample size	Renal dysfunction (n)	Prevalence (%)	Adjusted variables	Measure	Hazard Ratio (95% CI)	Effect type	C-statistic
Bouvy et al (2003)	152	19	13	A,G,C,D,P	Type	5.22 (1.88, 14.45)	OR	.8
Senni et al (2006)	292	41	14	A,C,Sv,D,Ef	Type	1.37 (0.63, 5.54)	logOR	.82
Senni et al (2013)	2016	157	8	A,C,Sv,D,Ef	Type	1.79 (1.50, 2.10)	OR	.87
Barlera et al (2013)	6975	*	*	A,G,R,C,Sv,L,P,Ef	eGFR(per ml/min decrease)	1.02 (1.01, 1.02)	HR	.75



B12 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(Ef)
*not reported

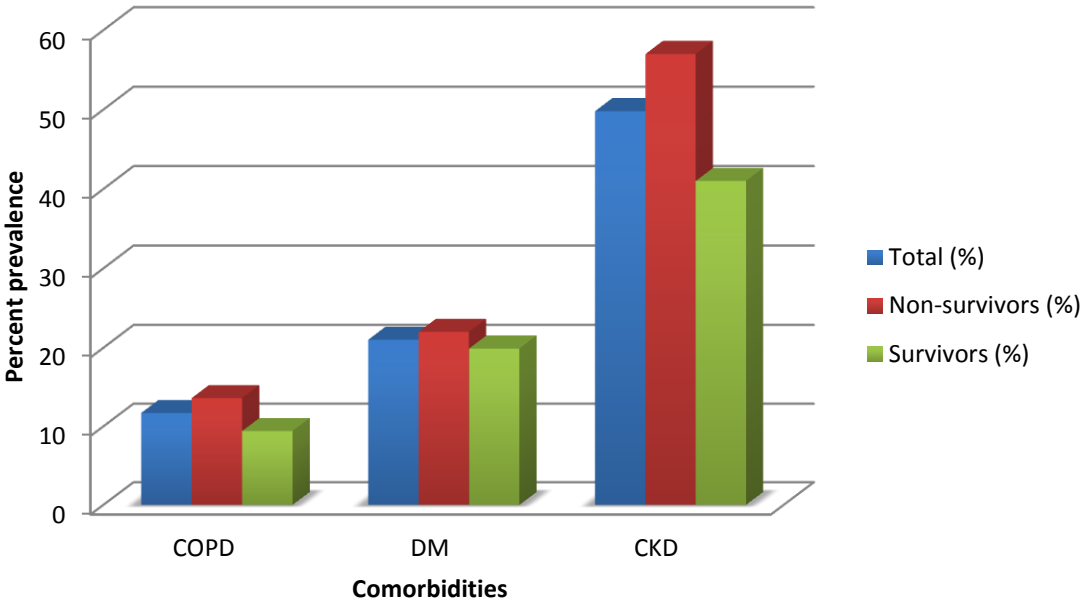
B13 All-cause hospital admission associated with comorbid RD: prognostic factor (general) and model studies

Study	Sample (n)	Renal dysf (n)	Prevalence (%)	Adjusted	Measure	ES (95% CI)	Effect type
Prognostic factor(general)							
Chaudhry (2013)	758	280	37	A,G,S,C,Sv,D,Ef	Type	1.32 (1.14, 1.53)	HR
Prognostic model							
Wang et al (2012)	198640	50454	25	A,G,S,R,C,Sv,D,L,P	Type	1.09 (1.04, 1.14)	OR

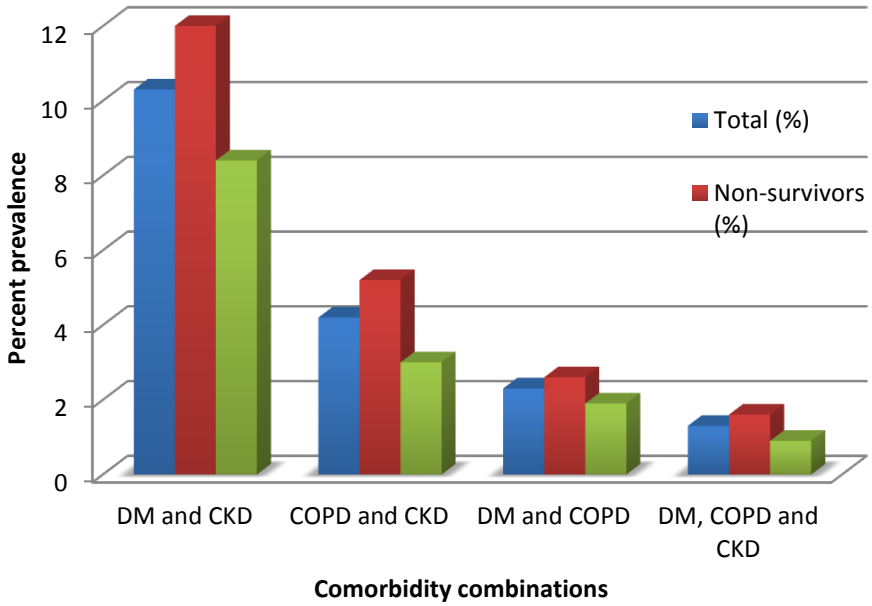


B13 Adjusted variables: age(A), gender(G), ethnicity(E), social(S), risk factors(R), comorbidities(C), aetiology(At), HF severity(Sv), drugs(D), laboratory(L), physical(P), ejection fraction(Ef)

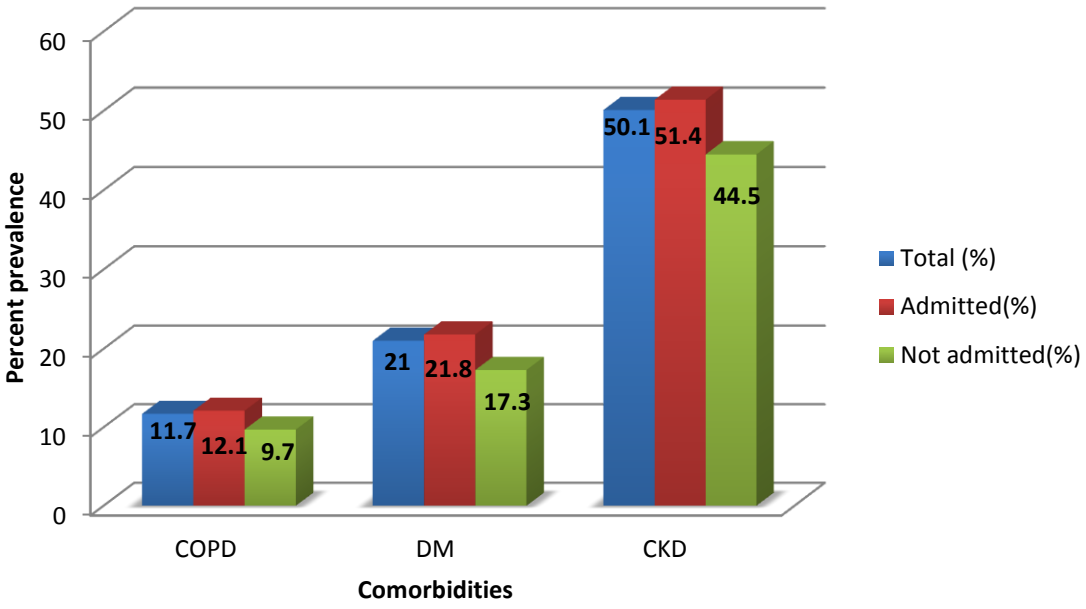
B14 Comorbidities at baseline by mortality outcome



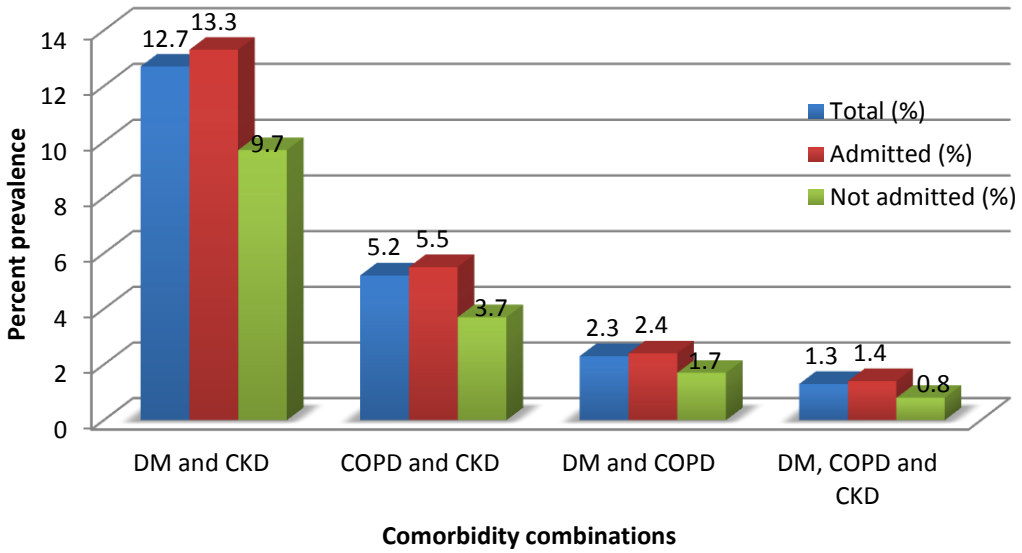
B15 Comorbidity combinations at baseline by mortality outcome



B16 Comorbidities at baseline by first hospital admission outcome



B17 Comorbidity combinations at baseline by event status



E-Appendix C: Statistical output

Meta-analysis supplementary tables

C1 Combined adjusted all-cause mortality risk associated with comorbid diabetes

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Ahmed et al          |  1.310       1.180     1.450         18.44
Berry et al          |  2.380       1.300     4.370          1.71
Burger et al         |  1.780       1.190     2.650          3.62
de Boer et al        |  1.250       0.990     1.580          8.36
Flores-Le Roux et al |  1.480       1.100     1.990          5.92
From et al           |  1.330       1.070     1.660          9.09
Greenberg et al      |  1.080       0.870     1.350          9.08
Gustafsson et al     |  1.500       1.300     1.600         18.35
MacDonald et al      |  1.260       1.230     1.290         25.42
---------------------+-------------------------------------------------
D+L pooled ES        |  1.341       1.235     1.456        100.00
I-V pooled ES        |  1.275       1.247     1.303        100.00
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  20.70 (d.f. = 8) p = 0.008
  I-squared (variation in ES attributable to heterogeneity) =  61.4%
  Estimate of between-study variance Tau-squared =  0.0068

  Test of ES=1 : z=   7.01 p = 0.000
```

C2 Sensitivity analysis removing From et al (2006) (combined adjusted all-cause mortality risk associated with diabetes)

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Ahmed et al          |  1.310       1.180     1.450         20.07
Berry et al          |  2.380       1.300     4.370          2.05
Burger et al         |  1.780       1.190     2.650          4.28
de Boer et al        |  1.250       0.990     1.580          9.62
Flores-Le Roux et al |  1.480       1.100     1.990          6.91
Greenberg et al      |  1.080       0.870     1.350         10.40
Gustafsson et al     |  1.500       1.300     1.600         19.99
MacDonald et al      |  1.260       1.230     1.290         26.69
---------------------+-------------------------------------------------
D+L pooled ES        |  1.344       1.228     1.471        100.00
I-V pooled ES        |  1.274       1.246     1.303        100.00
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  20.56 (d.f. = 7) p = 0.004
  I-squared (variation in ES attributable to heterogeneity) =  65.9%
  Estimate of between-study variance Tau-squared =  0.0078

  Test of ES=1 : z=   6.43 p = 0.000
```

C3 Sensitivity analysis removing Gustafsson et al (2004) (combined adjusted all-cause mortality risk associated with diabetes)

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
Ahmed et al          |  1.310       1.180     1.450         23.17
Berry et al          |  2.380       1.300     4.370          1.36
Burger et al         |  1.780       1.190     2.650          2.99
de Boer et al        |  1.250       0.990     1.580          7.77
Flores-Le Roux et al |  1.480       1.100     1.990          5.17
From et al           |  1.330       1.070     1.660          8.60
Greenberg et al      |  1.080       0.870     1.350          8.60
MacDonald et al      |  1.260       1.230     1.290         42.33
---------------------+-------------------------------------------------
D+L pooled ES        |  1.295       1.205     1.391        100.00
I-V pooled ES        |  1.265       1.236     1.294        100.00
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  10.80 (d.f. = 7) p = 0.148
  I-squared (variation in ES attributable to heterogeneity) =  35.2%
  Estimate of between-study variance Tau-squared =  0.0030

  Test of ES=1 : z=   7.06 p = 0.000
```

C4 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid diabetes).

```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  9                                Root MSE      =   1.429
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2206232	.0203807	10.83	0.000	.1724305	.2688158
bias	1.063904	.5999956	1.77	0.119	-.3548604	2.482668

```
Test of H0: no small-study effects          P = 0.119
```

C5 Sensitivity analysis removing Berry et al (2008) and Burger et al (2005) (combined adjusted all-cause mortality risk associated with comorbid diabetes).

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Ahmed et al          |  1.310       1.180     1.450         19.76
de Boer et al        |  1.250       0.990     1.580          7.57
Flores-Le Roux et al |  1.480       1.100     1.990          5.16
From et al           |  1.330       1.070     1.660          8.32
Greenberg et al      |  1.080       0.870     1.350          8.31
Gustafsson et al     |  1.500       1.300     1.600         19.64
MacDonald et al      |  1.260       1.230     1.290         31.24
---------------------+---------------------------------------------------
D+L pooled ES        |  1.313       1.220     1.413        100.00
I-V pooled ES        |  1.272       1.244     1.301        100.00
---------------------+---------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  13.92 (d.f. = 6) p = 0.030
  I-squared (variation in ES attributable to heterogeneity) =  56.9%
  Estimate of between-study variance Tau-squared =  0.0044

  Test of ES=1 : z=   7.27 p = 0.000
```

C6 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid diabetes).

```
. drop in 2/3
(2 observations deleted)

. metabias logHRa SElogHRa, egger

Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  7                                  Root MSE      =   1.558
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   .2275579   .0234434     9.71   0.000     .1672948     .287821
        bias |   .6686409   .7808384     0.86   0.431    -1.338568     2.67585
------------------------------------------------------------------------------

Test of H0: no small-study effects          P = 0.431

.
```

C7 Combined adjusted all-cause mortality risk associated with comorbid COPD

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
De Blois et al       |  1.190       1.020     1.390         32.19
Iversen et al        |  1.510       1.100     2.090         13.83
Lainscak et al       |  1.380       1.040     1.830         16.61
Macchia et al        |  1.420       1.090     1.860         17.92
Rusinaru et al       |  1.700       1.320     2.180         19.46
---------------------+-------------------------------------------------
D+L pooled ES        |  1.395       1.214     1.602        100.00
I-V pooled ES        |  1.357       1.224     1.504        100.00
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   6.42 (d.f. = 4) p = 0.170
  I-squared (variation in ES attributable to heterogeneity) =  37.7%
  Estimate of between-study variance Tau-squared =  0.0093

  Test of ES=1 : z=   4.71 p = 0.000
```

C8 Sensitivity analysis removing Lainscak (2009) (combined adjusted all-cause mortality risk associated with comorbid COPD)

```
           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+-------------------------------------------------
De Blois et al       |  1.190       1.020     1.390         34.87
Iversen et al        |  1.510       1.100     2.090         18.35
Macchia et al        |  1.420       1.090     1.860         22.64
Rusinaru et al       |  1.700       1.320     2.180         24.15
---------------------+-------------------------------------------------
D+L pooled ES        |  1.410       1.184     1.680        100.00
I-V pooled ES        |  1.353       1.211     1.512        100.00
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   6.40 (d.f. = 3) p = 0.094
  I-squared (variation in ES attributable to heterogeneity) =  53.1%
  Estimate of between-study variance Tau-squared =  0.0166

  Test of ES=1 : z=   3.85 p = 0.000
```

C9 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid COPD).

```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  5                                  Root MSE      =   .9114
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.063053	.1760321	-0.36	0.744	-.6232657	.4971596
bias	3.249777	1.495121	2.17	0.118	-1.508366	8.00792

```
Test of H0: no small-study effects          P = 0.118
```

C10 Combined adjusted all-cause mortality risk associated with any renal dysfunction

```
           Study     |     ES    [95% Conf. Interval]
---------------------+-------------------------------------------------
Campbell et al       |  1.220       1.090     1.360
Go et al             |  1.620       1.590     1.660
Hamaguchi et al      |  1.670       1.250     2.220
Hillege et al        |  1.690       1.370     2.080
Ismailov et al       |  1.370       1.290     1.450
Kimura et al         |  1.870       1.300     2.600
Takagi et al         |  2.220       1.040     4.730
---------------------+-------------------------------------------------
D+L pooled ES        |  1.517       1.344     1.711
I-V pooled ES        |  1.577       1.546     1.608
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  51.20 (d.f. = 6) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  88.3%
  Estimate of between-study variance Tau-squared =  0.0160

  Test of ES=1 : z=   6.76 p = 0.000
```

C11 Sensitivity analysis removing Campbell et al (2009) (combined adjusted all-cause mortality risk associated with comorbid RD)

```
           Study     |     ES    [95% Conf. Interval]
---------------------+-------------------------------------------------
Go et al             |  1.620       1.590     1.660
Hamaguchi et al      |  1.670       1.250     2.220
Hillege et al        |  1.690       1.370     2.080
Ismailov et al       |  1.370       1.290     1.450
Kimura et al         |  1.870       1.300     2.600
Takagi et al         |  2.220       1.040     4.730
---------------------+-------------------------------------------------
D+L pooled ES        |  1.586       1.411     1.782
I-V pooled ES        |  1.590       1.559     1.623
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  29.85 (d.f. = 5) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  83.2%
  Estimate of between-study variance Tau-squared =  0.0109

  Test of ES=1 : z=   7.74 p = 0.000
```

C12 Sensitivity analysis removing Ismailov et al (2007) (combined adjusted all-cause mortality risk associated with comorbid RD)

```
           Study     |     ES    [95% Conf. Interval]
---------------------+-------------------------------------------------
Campbell et al       |  1.220       1.090     1.360
Go et al             |  1.620       1.590     1.660
Hamaguchi et al      |  1.670       1.250     2.220
Hillege et al        |  1.690       1.370     2.080
Kimura et al         |  1.870       1.300     2.600
Takagi et al         |  2.220       1.040     4.730
---------------------+-------------------------------------------------
D+L pooled ES        |  1.574       1.348     1.838
I-V pooled ES        |  1.606       1.573     1.640
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =  26.07 (d.f. = 5) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  80.8%
  Estimate of between-study variance Tau-squared =  0.0225

  Test of ES=1 : z=   5.73 p = 0.000
```

C13 Sensitivity analysis removing Campbell et al (2009) and Ismailov et al (2007) (combined adjusted all-cause mortality risk associated with comorbid RD)

```
           Study     |     ES    [95% Conf. Interval]
---------------------+-------------------------------------------------
Go et al             |  1.620       1.590     1.660
Hamaguchi et al      |  1.670       1.250     2.220
Hillege et al        |  1.690       1.370     2.080
Kimura et al         |  1.870       1.300     2.600
Takagi et al         |  2.220       1.040     4.730
---------------------+-------------------------------------------------
D+L pooled ES        |  1.622       1.588     1.657
I-V pooled ES        |  1.622       1.588     1.657
---------------------+-------------------------------------------------
 Heterogeneity calculated by formula
  Q = SIGMA_i{ (1/variance_i)*(effect_i - effect_pooled)^2 }
where variance_i = ((upper limit - lower limit)/(2*z))^2

  Heterogeneity chi-squared =   1.51 (d.f. = 4) p = 0.825
  I-squared (variation in ES attributable to heterogeneity) =   0.0%
  Estimate of between-study variance Tau-squared =  0.0000

  Test of ES=1 : z=  44.48 p = 0.000
```

C14 Test of publication bias (combined adjusted all-cause mortality risk associated with comorbid COPD).

```
Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  7                                Root MSE      =   3.082
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.4714044	.0400606	11.77	0.000	.3684253	.5743836
bias	-.9391171	1.505771	-0.62	0.560	-4.809826	2.931591

```
Test of H0: no small-study effects          P = 0.560
```

C15 Correlation matrix for covariates for mortality outcome

	Age_c	gender	imd200~5	COPD_p~l	Diabet~l	Stag~D_2	egfr_M~1	egfr2	ACE_or~B	Beta_b~r	Diuretic	Systol~I	sys2	Diasto~I	BMI_I
Age_c	1.0000														
gender	0.2092	1.0000													
imd2007_5	-0.1010	0.0309	1.0000												
COPD_prese~l	-0.0285	-0.0573	0.0818	1.0000											
Diabetes_p~l	-0.1154	-0.0568	0.0655	-0.0119	1.0000										
Stage_MDRD_2	0.2908	0.1431	-0.0160	-0.0406	0.0576	1.0000									
egfr_MDRD_1	-0.3215	-0.1492	0.0234	0.0529	-0.0604	-0.7951	1.0000								
egfr2	-0.3234	-0.1476	0.0308	0.0570	-0.0429	-0.7616	0.9719	1.0000							
ACE_or_ARB	0.1703	0.0696	0.0013	0.0167	-0.0753	0.0283	-0.0549	-0.0353	1.0000						
Beta_blocker	0.1444	0.0696	0.0165	0.1562	-0.0565	-0.0068	0.0128	0.0120	0.1816	1.0000					
Diuretic	0.1226	0.0768	0.0118	0.0322	0.0645	0.1705	-0.1842	-0.1805	-0.1056	-0.0134	1.0000				
Systolic_I	0.0482	0.1092	-0.0039	-0.0500	0.0105	-0.0165	0.0131	0.0078	0.0234	0.0591	-0.0647	1.0000			
sys2	0.0489	0.1097	-0.0023	-0.0494	0.0089	-0.0103	0.0059	0.0020	0.0243	0.0587	-0.0589	0.9917	1.0000		
Diastolic_I	-0.1182	0.0507	-0.0066	-0.0453	-0.0736	-0.0985	0.1136	0.0999	0.0311	0.0454	-0.0843	0.5469	0.5319	1.0000	
BMI_I	-0.3217	-0.0196	0.0768	-0.0048	0.2289	-0.0398	0.0427	0.0411	-0.1196	-0.0697	0.0642	0.0802	0.0741	0.0975	1.0000
BMI2	-0.3163	0.0019	0.0800	0.0011	0.2221	-0.0412	0.0462	0.0463	-0.1070	-0.0575	0.0637	0.0741	0.0688	0.0931	0.9825
CH_mmol_L_I	0.0085	0.2479	-0.0286	-0.0044	-0.1937	0.0001	0.0051	-0.0026	0.0854	0.1391	-0.0226	0.1317	0.1317	0.1577	-0.0442
Hb_gdL_I	-0.2724	-0.2056	0.0002	0.0320	-0.0876	-0.2454	0.2890	0.2457	-0.0922	-0.0489	-0.0980	0.0325	0.0252	0.1893	0.0987
Smoking_~s_I	-0.2267	-0.2082	0.1169	0.2274	0.0306	-0.0883	0.1051	0.1137	-0.0130	0.0246	-0.0477	-0.0372	-0.0351	-0.0143	0.0023
ALC_status_I	-0.0637	-0.1644	-0.0633	0.0080	-0.0495	-0.0580	0.0616	0.0564	-0.0343	-0.0182	-0.0315	-0.0155	-0.0166	0.0097	-0.0112

	BMI2	CH_mmo~I	Hb_gdL_I	Smok~s_I	ALC_~s_I
BMI2	1.0000				
CH_mmol_L_I	-0.0389	1.0000			
Hb_gdL_I	0.0858	0.0924	1.0000		
Smoking_~s_I	0.0043	-0.0385	0.1186	1.0000	
ALC_status_I	-0.0158	-0.0015	0.0876	0.0781	1.0000

	egfr_M~1	egfr_c~3
egfr_MDRD_1	1.0000	
egfr_chang~3	0.2375	1.0000

	egfr_M~1	egfr_p~3
egfr_MDRD_1	1.0000	
egfr_p_cha~3	0.1997	1.0000

C16 Correlation matrix for centred covariates with quadratic extensions

	BMIC	bmiCsq	SysC	sysCsq	HbC	hbCsq	egfrC	egfrCsq
BMIC	1.0000							
bmiCsq	0.4352	1.0000						
SysC	0.0806	0.0159	1.0000					
sysCsq	-0.0228	0.0085	0.2353	1.0000				
HbC	0.0996	-0.0089	0.0276	-0.0459	1.0000			
hbCsq	0.0050	0.0149	-0.0241	0.0158	-0.2134	1.0000		
egfrC	0.0400	0.0391	0.0067	-0.0536	0.2904	-0.0520	1.0000	
egfrCsq	0.0084	0.0434	-0.0174	0.0235	-0.0766	0.0787	0.2286	1.0000

.

C17 Correlation matrix of variables in hospital admission linked HF cohort

	Age_c	gender	imd200~5	HAny_1~I	CH_mmo~I	BMI_I	Hb_gdL_I	Hbsq	Systol~I	syssq	Smok~s_I	ALC_~s_I	egfr_M~1	egfrsq	Beta_b~r	ACE_or~B	Diuretic	Diabet~1	COPD_p~1
Age_c	1.0000																		
gender	0.2068	1.0000																	
imd2007_5	-0.1071	0.0440	1.0000																
HAny_1yr_B~I	-0.0153	-0.0273	0.0199	1.0000															
CH_mmol_L_I	0.0203	0.2575	-0.0214	-0.0415	1.0000														
BMI_I	-0.3324	-0.0150	0.0948	-0.0258	-0.0583	1.0000													
Hb_gdL_I	-0.2957	-0.2689	-0.0112	-0.0733	0.0554	0.0875	1.0000												
Hbsq	-0.3036	-0.2785	-0.0088	-0.0724	0.0527	0.0906	0.9947	1.0000											
Systolic_I	0.0849	0.1153	-0.0085	-0.0434	0.1376	0.0625	-0.0222	-0.0240	1.0000										
syssq	0.0825	0.1146	-0.0058	-0.0392	0.1380	0.0573	-0.0252	-0.0266	0.9924	1.0000									
Smoking_~s_I	-0.2220	-0.2023	0.1000	0.0148	-0.0405	0.0221	0.1407	0.1461	-0.0502	-0.0468	1.0000								
ALC_status_I	-0.0749	-0.2092	-0.1041	-0.0107	-0.0214	-0.0175	0.1436	0.1439	-0.0187	-0.0199	0.0999	1.0000							
egfr_MDRD_1	-0.3471	-0.1752	0.0151	-0.0054	-0.0271	0.0617	0.2859	0.2825	-0.0166	-0.0225	0.0968	0.0865	1.0000						
egfrsq	-0.3427	-0.1680	0.0206	0.0005	-0.0300	0.0600	0.2481	0.2467	-0.0171	-0.0222	0.1007	0.0783	0.9762	1.0000					
Beta_blocker	0.1224	0.0611	0.0127	-0.0161	0.1548	-0.0676	-0.0440	-0.0406	0.0558	0.0546	0.0229	-0.0183	0.0017	0.0015	1.0000				
ACE_or_ARB	0.1384	0.0645	-0.0217	0.0035	0.0954	-0.1081	-0.0656	-0.0640	0.0378	0.0358	-0.0254	-0.0191	-0.0368	-0.0257	0.1415	1.0000			
Diuretic	0.1385	0.0706	0.0070	0.0029	-0.0037	0.0387	-0.0966	-0.0971	-0.0095	-0.0057	-0.0339	-0.0337	-0.1739	-0.1629	-0.0937	-0.0596	1.0000		
Diabetes_p~1	-0.1089	-0.0611	0.0642	0.0126	-0.1973	0.2228	-0.0730	-0.0674	0.0021	0.0008	0.0533	-0.0718	-0.0237	-0.0107	-0.0467	-0.0831	0.0357	1.0000	
COPD_prese~1	-0.0402	-0.0494	0.0842	0.0243	-0.0024	-0.0026	0.0380	0.0410	-0.0569	-0.0551	0.2172	-0.0060	0.0449	0.0453	0.1444	0.0029	0.0266	-0.0097	1.0000
Stage_MDRD_2	0.3102	0.1652	-0.0037	0.0017	0.0244	-0.0592	-0.2367	-0.2362	0.0142	0.0192	-0.0849	-0.0763	-0.7941	-0.7543	0.0026	0.0210	0.1571	0.0230	-0.0389

C18 Correlation matrix for centred covariates with quadratic extensions; hospital admission outcome

	AgeC	gender	imd200~5	HAny_1~I	CHC	BMIC	HbC	HbCsq	SysC	SysCsq	Smok~s_I	ALC_~s_I	egfrC	egfrCsq	Beta_b~r	ACE_or~B	Diuretic	Diabet~l	COPD_p~l
AgeC	1.0000																		
gender	0.2068	1.0000																	
imd2007_5	-0.1071	0.0440	1.0000																
HAny_1yr_B~I	-0.0153	-0.0273	0.0199	1.0000															
CHC	0.0203	0.2575	-0.0214	-0.0415	1.0000														
BMIC	-0.3324	-0.0150	0.0948	-0.0258	-0.0583	1.0000													
HbC	-0.2957	-0.2689	-0.0112	-0.0733	0.0554	0.0875	1.0000												
HbCsq	-0.0924	-0.1080	0.0229	0.0050	-0.0232	0.0349	0.0037	1.0000											
SysC	0.0849	0.1153	-0.0085	-0.0434	0.1376	0.0625	-0.0222	-0.0184	1.0000										
SysCsq	0.0052	0.0271	0.0194	0.0209	0.0426	-0.0235	-0.0302	0.0210	0.2234	1.0000									
Smoking_~s_I	-0.2220	-0.2023	0.1000	0.0148	-0.0405	0.0221	0.1407	0.0603	-0.0502	0.0122	1.0000								
ALC_status_I	-0.0749	-0.2092	-0.1041	-0.0107	-0.0214	-0.0175	0.1436	0.0112	-0.0187	-0.0147	0.0999	1.0000							
egfrC	-0.3471	-0.1752	0.0151	-0.0054	-0.0271	0.0617	0.2859	-0.0167	-0.0166	-0.0516	0.0968	0.0865	1.0000						
egfrCsq	-0.1085	-0.0325	0.0303	0.0244	-0.0230	0.0150	-0.0625	0.0687	-0.0084	0.0098	0.0530	-0.0043	0.2635	1.0000					
Beta_blocker	0.1224	0.0611	0.0127	-0.0161	0.1548	-0.0676	-0.0440	0.0305	0.0558	0.0067	0.0229	-0.0183	0.0017	-0.0003	1.0000				
ACE_or_ARB	0.1384	0.0645	-0.0217	0.0035	0.0954	-0.1081	-0.0656	0.0116	0.0378	-0.0056	-0.0254	-0.0191	-0.0368	0.0359	0.1415	1.0000			
Diuretic	0.1385	0.0706	0.0070	0.0029	-0.0037	0.0387	-0.0966	-0.0103	-0.0095	0.0273	-0.0339	-0.0337	-0.1739	-0.0152	-0.0937	-0.0596	1.0000		
Diabetes_p~l	-0.1089	-0.0611	0.0642	0.0126	-0.1973	0.2228	-0.0730	0.0501	0.0021	-0.0098	0.0533	-0.0718	-0.0237	0.0490	-0.0467	-0.0831	0.0357	1.0000	
COPD_prese~l	-0.0402	-0.0494	0.0842	0.0243	-0.0024	-0.0026	0.0380	0.0310	-0.0569	-0.0016	0.2172	-0.0060	0.0449	0.0186	0.1444	0.0029	0.0266	-0.0097	1.0000

E-Appendix D: Protocols

D1 Systematic review: PROSPERO protocol

PROSPERO International prospective register of systematic reviews

Comorbidity and prognosis in heart failure populations: a systematic review

Claire Rushton, Lucy Doos, Umesh Kadam, Peter Jones, Umesh Kadam

Citation

Claire Rushton, Lucy Doos, Umesh Kadam, Peter Jones. Comorbidity and prognosis in heart failure populations: a systematic review. PROSPERO 2013:CRD42013003605 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42013003605

Review question(s)

1. To determine which clinical comorbidities influence the HF-outcomes of patient reported measures, hospital admissions or mortality.

2. To investigate if and how ‘change' in comorbidity status has been used in HF prognosis studies.

3. To determine how comorbidity has been included in current HF prediction models, by chronic disease type, severity or status change.

Searches

The following electronic clinical bibliographic databases will be searched for citations between 1990 to present: MEDLINE (Medical Literature Analysis and Retrieval System Online), EMBASE (Excerpta Medica Database), CINAHL (Cumulative Index to Nursing and Allied Health Literature), DARE (Database of Abstract of Reviews of Effects), CDSR (Cochrane Database of systematic reviews) and The Cochrane Central Register of Controlled Trials (CENTRAL).

To reduce publication bias, online databases will be searched for unpublished studies such as HMIC (Health Management Information Consortium) and Index to Scientific and Technical proceedings. Zetoc and the Conference Papers Index will be used to search for conference abstracts. Where relevant conference abstracts exist, final reports will be requested, where available, for consideration for inclusion in the review. ETHOS, ProQuest and Networked Digital Library of Theses and Dissertations will be used to search for related theses.

The search strategy will include terms relating to the review objectives and prognosis methods. Validated search strategies for prognostic studies (factors and models) for EMBASE and MEDLINE and heart failure for MEDLINE will be used. The search strategies will be adapted for use with other bibliographic databases.

Medline - prognosis search string

Ref: Geersing G-J, et al. (2012) Search Filters for Finding Prognostic and Diagnostic Prediction Studies in Medline to Enhance Systematic Reviews. PLoS ONE 7(2):e32844. doi:10.1371/journal.pone.0032844

Embase – prognosis search string

Ref: Wilczynski N and Haynes R (2005) Optimal Search Strategies for Detecting Clinically Sound Prognostic Studies in EMBASE: An Analytic Survey. Journal of the American Medical Informatics Association 12(4):481-485

Medline – heart failure search string

Ref: Damarell et al. (2011) BMC Medical Research Methodology, 11:12

http://www.biomedcentral.com/1471-2288/11/12

Exclusions will be:

(i) Studies that focus on novel biomarkers or independent biochemical or electrophysiological indicators that are not clearly linked to a specific chronic disease

(ii) Studies that select populations e.g. clinical trials who exclude patients with comorbid disease

(iii) Prognostic factor studies that do not focus on the association between chronic disease and heart failure outcomes i.e. heart failure prognosis studies that only adjust for chronic disease

(iv) Non-English language papers (subject to assessment)

All database searches will be saved and rerun prior to the final analyses and further studies retrieved for inclusion. Database email alert facilities, where available, will be used to provide on-going feedback when a paper is added that matches the review search criteria.

Other sources will include:

- Reference lists from relevant studies.

- Contacting study authors where appropriate.

- Searching relevant internet resources such as Cochrane Prognostic Method's Group.

- Citation search.

Types of study to be included

We will include study designs that designs that focus on the association between a comorbidity factor and outcome in heart failure populations, including:

(i) Observational studies (cohort, case control, cross sectional).

(ii) Development, validation or impact assessment of a HF prediction model that includes comorbidity as an indicator/s.

(iii) RCTs will be included where appropriate using the usual arm cohort.

Condition or domain being studied

Chronic heart failure.

Comorbidity.

Prognosis - patient reported outcomes, hospital admission, mortality.

Participants/ population

Inclusion: Adults with a clinical diagnosis of chronic heart failure (with or without preserved ejection fraction) from general practice, specialist or hospital settings.

Context: The clinical diagnosis of heart failure will vary according to the study setting and time of investigation. Current European diagnosis recommendations include the combination of symptoms, signs and objective evidence of heart failure. However the use of echocardiogram to confirm diagnosis has only been widely recommended in the past 10 years (since 2003 in national evidence and introduced into the Quality Outcomes Framework for general practitioners since 2006 in the UK). Research definitions of heart failure are likely to vary within the time frame of the review and across settings and this factor will be acknowledged in the data synthesis.

Exclusion: Adults younger than 40years

Intervention(s), exposure(s)

Inclusion:

Comorbidity will be defined as any clinically defined diagnosis of chronic disease additional to heart failure. Chronic disease indicators that have been identified as independent and statistically significant prognostic factors will be included.

Comorbidity indicators may include

(i) chronic disease type e.g. diabetes, chronic obstructive pulmonary disease.

(ii) chronic diseases severity measure e.g. diabetes with target organ damage or chronic kidney dysfunction with a defined creatinine level.

(iii) Chronic disease severity change measure e.g.

a) changes to drug prescription or dose.

b) change in blood test indicator such as a reduction in estimated glomerular filtration rate (eGFR) in renal disease or increase in glycosylated haemoglobin (HbA1c) in diabetes.

c) frequency of healthcare episodes e.g. general practice consultations or hospital admissions.

Exclusion:

(i) Illnesses and symptoms that are not clearly linked to a specific chronic disease.

(ii) novel biomarkers or independent biochemical or electrophysiological indicators that are not clearly linked to a specific chronic disease.

Comparator(s)/ control

Not applicable.

Context

Studies in general practice or specialist settings such as hospitals.

Outcome(s)

Primary outcomes

A synthesis of evidence on the influence of clinical comorbidities on heart failure patient reported measures, hospital admissions and mortality.

Secondary outcomes

An analysis of current approaches to including ‘change' in comorbidity status in heart failure prognosis studies.

A synthesis of evidence on how comorbidity has been included in current heart failure prognostic models, by chronic disease type, severity or status change.

Data extraction, (selection and coding)

Title and abstract screening: Papers will be selected for initial inclusion based on the title (CR) then the abstract (CR and LD). The title review will be crosschecked using a sample of 50 titles (UK) and the abstracts list will be screened (UK). Any disagreement on papers for inclusion will be passed between the 2nd and 3rd reviewers (UK and LD) for a decision with CR as the final adjudicator.

Paper reviews: The 1st reviewer will review all the final papers. The papers will then be shared between the 2nd and 3rd (UK and LD) for final inclusion. All papers will then undergo a quality assessment by CR and LD.

The software package Refworks will be used to manage the references.

Using Excel to construct a data extraction form information will be collected on:

- Publication

- Study ID

- Report ID

- Review author

- Author(s), year

- Article title

- Citation

- Type (journal, conference abstract)

- Study characteristics

- Aims/objectives

- Study design (prospective or retrospective, case-control/cohort/cross sectional/RCT)

- Duration of follow-up

- Inclusion and exclusion criteria

- Participants

- Sample size, age, gender, ethnicity, country, clinical definition, setting

- Predictor Variables

- Comorbidity indicator/s included

- Unit of measurement (continuous, binary, categorical)

- Other variables included in multivariate analyses

- Outcome Variables

- Prognostic outcome/s and definition

- Unit of measurement (continuous, binary, categorical)

- Measurement tool

- Analysis

- method of analysis (univariate, multivariate, risk score)

- Statistical techniques used

- If multivariate analysis or risk score; statistical approach used

- Results

- Number participants included in the analysis

- Summary outcome (dichotomous: number of events/participants, continuous: mean and standard deviation, time-to-event: number of events, person years)

- Estimate of effect with confidence interval and p value (unadjusted and adjusted where available)

- Significance level of comorbidity effect within univariate or multivariate analysis

- Any subgroup analysis

- Other

- Key conclusions of the study authors

- References to other relevant studies

- Correspondence required.

- Miscellaneous comments by the review authors

The data extraction form will be piloted by CR and LD on a small sample of included studies prior to the review to ensure all the relevant data are captured and that there is consistency in data recording.

Data will then be extracted independently by CR and LD. Study data presented in a number of reports will be extracted directly into a single data collection form. The level of inter-rater agreement will be measured using a Kappa statistic.

Risk of bias (quality) assessment

The Quality In Prognosis Studies (QUIPS) assessment will be used for quality assessment. The QUIPS assessment tool assesses bias in relation to:

- Study participation: are the population, sampling frame, recruitment, diagnostic criteria and participants adequately described?

- Study attrition: was there an adequate response rate? Is loss to follow up adequately described?

- Bias related to prognostic factor development: are definitions, units of measurement and measurement approaches appropriate? Are imputation methods for missing data appropriate?

- Outcome measurement: are definitions, units of measurement and measurement approaches appropriate?

- Confounding measurement: are any important confounders taken into account? Are definitions, measurement and imputation methods appropriate?

- Analysis: are data sufficiently presented? Are the results representative or selected?

Ref: Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Annals Internal Medicine 2006; 144: 427-437

The QUIPS tool has domains that are relevant to the appraisal of both prognostic factor and prediction model studies. However there are some additional specific considerations for prognostic model studies that will be included:

- model building: are the assumptions of the modelling method (e.g. logistic or survival model) checked? How are the predictors for inclusion in multivariable analysis chosen? How are the predictors for the final model selected during multivariable modelling (e.g. backward elimination, forward selection, forced in model, added value of a particular predictor)? Were different models developed and/or compared?

- model performance: is calibration or discrimination assessed? are overall performance measures or clinical

usefulness measures assessed?

- model testing: are any internal (bootstrap, cross validation, random split-sample) or external (temporal, geographical, setting) used? If so was the model updated or recalibrated after (poor) external validation

Strategy for data synthesis

Due to potential heterogeneity in observational study designs, population and analyses, the narrative approach may be the primary synthesis. The comorbidity prognostic factors will be summarised using the following hierarchy (1) prognostic outcome category (1.1) setting (1.2) chronic disease type. Prognostic factors reported in different papers on the same cohort will be counted once. If there are a large variety of factors, only those factors found significant ($p<0.05$) in more than one study of moderate/high quality will be presented.

An additional summary of prediction models will be provided for each outcome category.

For specific chronic diseases; where sufficient studies of good quality (following QUIPs assessment), with an adequate sample size (>100 participants)(1) and of similar design (including common representation of variable data e.g. dichotomous or continuous and/or common effect size e.g. odds or hazard ratio, mean difference) and outcomes are available, meta-analysis methods will be employed as follows:

(i) An I-squared test of heterogeneity will be performed to quantify the degree of inconsistency across studies for each chronic disease comorbidity. The I-squared test will describe the percentage of variability in the effect estimates that can be attributed to the heterogeneity that is inherent across observational studies. An I-squared value of <50% will be deemed acceptable for meta-analysis. Where unacceptable heterogeneity is present, studies will be stratified by important study level characteristics. These are likely to be (a) study setting or (b) heart failure definition. An I-squared test will then be performed for each strata.

(ii) Forest plots will be used to display the effects of unadjusted and adjusted associations between comorbidity indicator and outcome.

(iii) Effect sizes will be combined into an overall estimate using the metan procedure in STATA . A random effects model which takes account of within and between study variance will be used to combine the results, with odds ratios for binary outcomes, hazard ratios for time-to-event outcomes and standardised mean differences for continuous outcomes. 95% confidence intervals with two sided P values will be calculated for each outcome. If the number of studies is small, due to the poor precision of tau-squared (between study variance), individual effects only, will be reported.

(iv) For time-to-event outcome studies, where a hazard ratio and variance are reported or a coefficient of the exposure effect and the variance from a Cox model are provided, these will be used in a meta-analysis directly. Where these are not available, other summary statistical data or survival curves will be used to estimate the Hazard ratio using a range of direct and indirect approaches(2).

(v) For each meta-analysis, sensitivity analyses will be performed where considered necessary. This will depend on the studies included but may be performed where:

a) studies have a heart failure or chronic disease measure that differs slightly from other studies but that were still deemed appropriate to include in the meta-analysis

b) studies that required effect sizes to be estimated using indirect methods

c) studies with the smallest sample sizes

Meta-analysis will be restricted to prognostic factor studies

(1) Centre for Reviews and Dissemination.

(2) Tierney J, Ghersi G, Burdett S, Sydes M. Practical methods for incorporating summary time-to-event data into

meta-analysis. Trials 2007;8:16.

Analysis of subgroups or subsets
None planned.

Dissemination plans
The systematic review will be one of the PhD thesis chapters.

The systematic review will be submitted as a paper in journal

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Anticipated or actual start date
21 January 2013

Anticipated completion date
30 April 2013

Funding sources/sponsors
The review forms part of a PhD study funded by a NIHR Doctoral research Fellowship (NIHR-DRF-2012-05-288)

Conflicts of interest
None known

Language
English

Country
England

Subject index terms status

Subject indexing assigned by CRD

Subject index terms
Comorbidity; Heart Failure; Humans; Prognosis

Stage of review
Ongoing

Date of registration in PROSPERO
04 February 2013

Date of publication of this revision
04 February 2013

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted	Chair 12_162A 15 Oct 2013	**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

1. Study Title

Comorbidity and changing prognosis in heart failure patients

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol)

Claire A Rushton, NIHR Doctoral Fellow, Keele University, c.a.rushton@keele.ac.uk

3. Affiliation (full address)

Health Services Research Unit, Innovation Centre 1, Keele University, Staffordshire, ST5 5BG

4. Protocol's Author (if different from the principal investigator)

5. Type of Institution (please tick one box below)

Academia	**x**	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

6. Financial Sponsor of study

Pharmaceutical Industry *(please specify)*	☐	Academia*(please specify)*	☐
Government / NHS *(please specify)*	☐	None	☐
Other *(please specify)*	☒	University Hospital Charities Board funding	

7. Data source *(please tick one box below)*

Sponsor has on-line access	☐	Purchase of ad hoc dataset	☒
Commissioned study	☐		
Other	☐	*(please specify)*	

8. Has this protocol been peer reviewed by another Committee?

Yes* ☒ No ☐

** Please state in your protocol the name of the reviewing Committee(s) and provide an outline of the review process and outcome.*

9. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety	☐	Drug Use	☐	Disease Epidemiology	☒
Drug Effectiveness	☐	Pharmacoeconomic	☐	Other	☐

10. This study is intended for:

Publication in peer reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☒	Other	

11. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ **No** ☐

12. If you are seeking access to data held under the CPRD Data Linkage Scheme, please select the source(s) of linked data being requested.

☒ **Hospital Episode Statistics**
☒ **ONS Mortality Data**
☐ **Mother Baby Link**
☐ **Cancer Registry Data***
☒ **Index of Multiple Deprivation/ Townsend Score**
☐ **Other: (please specify)**
☐ **MINAP**

Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email admin@cprd.com to discuss this requirement further.

13. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ **No*** ☐

Please contact the CPRD Research Team on +44 (20) 3080 6383 or email admin@cprd.com to discuss your requirements before submitting your application.

Please list below the name of the person/s at the CPRD with whom you have discussed your request.
Kendal Chidwick

14. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ **No** ☒

*** Please indicate what will be required:**
Completion of questionnaires by the GP[ψ] **Yes** ☐ **No** ☐
Provision of anonymised records (e.g. hospital discharge summaries) **Yes** ☐ **No** ☐
Other (please describe)

ψ Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

15. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ **No**** ☐

Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.
**** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.***

16. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ **No** ☒

17. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ **No** ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

18. Does this study require contact with patients in order to collect a sample?

Yes* ☐ **No** ☒

**** Please state what will be collected***

19.

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☒	☒
> 3	☐	☐

Is statistical expertise available within the research team? Yes ☒ No☐
If yes, please outline level of experience *Professor of Statistics*

Is experience of handling large data sets (>1 million records) available within the research team? Yes ☒ No☐
If yes, please outline level of experience *GP Epidemiologist, Senior Lecturer*

Is UK primary care experience available within the research team? Yes ☒ No☐
If yes, please outline level of experience GP *over 15 years clinical and research experience and using the CPRD database*

20. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

Braunstein J, Anderson G, Gerstenblith G, Weller W, Niefeld M, Herbert R, et al (2003) Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. *Journal of the American College of Cardiology*, 42(7):1226-1233.

Kadam UT, Schellevis F, van der Windt, DAWM et al (2008) Morbidity severity based on routine consultation data from English and Dutch general practice indicates physical function status. *Journal of Clinical Epidemiology*, 61:386-393.

Senni M, Santilli G, Parrella P, Renata De Maria S, Alari G, Berzuini C, et al (2006) A novel prognostic index to determine the Impact of cardiac conditions and co-morbidities on one-year outcome in patients with heart failure. *American Journal of Cardiology*, 98:1076-1082.

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	**Yes**	**No**	**If no, reason for omission**
Lay Summary (max.200 words)	**X**	☐	
Background	**X**	☐	
Objective, specific aims and rationale	**X**	☐	
Study Type ***Descriptive*** ***Hypothesis Generating*** ***Hypothesis Testing***	 **x** **x** **x**	 ☐ ☐ ☐	
Study Design	**X**	☐	
Sample size/power calculation (Please provide justification of sample size in the protocol)	**X**	☐	
Study population (including estimate of expected number of relevant patients in the CPRD)	**X**	☐	
Selection of comparison group(s) or controls	**X**	☐	
Exposures, outcomes and covariates ***Exposures are clearly described*** ***Outcomes are clearly described***	**x** **x** **x**	☐ ☐ ☐	
Data/ Statistical Analysis Plan ***There is plan for addressing confounding*** ***There is a plan for addressing missing data***	**x** **x** **x**	☐ ☐ ☐	
Patient/ user group involvement †	**X**	☐	
Limitations of the study design, data sources and analytic methods	**X**	☐	
Plans for disseminating and communicating study results	**X**	☐	

† ***It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.***

ISAC strongly recommends that researchers using CPRD consider registering as a NRR data provider in order that others engaged in research within the UK can be made aware of current works. The ***National Research Register (NRR)*** *is a register of ongoing and recently completed research projects funded by, or of interest to, the United Kingdom's National Health Service. Information on the NRR is available on www.nrr.nhs.uk .*

Please Note: Registration with the NRR is entirely voluntary and will not replace information on ISAC approved protocols that are published in summary minutes or in the ISAC annual report.

Project: Comorbidity and changing prognosis in heart failure (HF) patients – (2C-HF)

Lay summary

Heart Failure (HF) is an increasing burden in ageing populations and carries a poor prognosis and an uncertain disease trajectory. HF patients commonly experience other chronic diseases at the same time and these 'comorbidities' have been shown to influence the clinical course of disease. Yet many current clinical prediction models do

not take into account the importance of other diseases in determining health or healthcare outcomes. This project forms part of a PhD that will investigate patients with heart failure, and the influence of other diseases on their risk of death. Key questions addressed are (i) *which comorbidities are important in influencing mortality in HF general practice populations* and (ii) *how does change in comorbidity status influence the prediction of mortality*? The selection of comorbidities will be guided by systematic review of current evidence and clinical expertise to generate *a priori* hypothesises for testing. The Health Services Research Unit at Keele has access to previous CPRD data (protocol #07_104R) to investigate cardiovascular disease comorbidity, and this dataset had a HF sample (approximate N=6000). This study proposes to extend previous work to investigate HF comorbidity and prognosis. This prognostic evidence will provide a better basis for clinical decision making in HF and in improving patient outcomes by targeting the comorbidity.

Background

Heart failure (HF) carries a poor prognosis with 30% of people dying within 6 months of diagnosis and 38% within a year[1]. Whilst a diverse range of prognostic indicators exist[2], very little is known of how prognosis changes in HF populations over time. HF patients commonly experience other chronic diseases at the same time, partly due to age-association and partly due to cardiovascular complications[3]. Comorbidity has been shown to influence the clinical course of HF and there is growing evidence that comorbid conditions such as stroke, diabetes, atrial fibrillation or renal impairment influence outcomes such as mortality[4]. Each comorbid chronic disease will carry its own prognosis 'value' and one crucial question from patients' point of view is how these combine together to influence health and healthcare outcomes. However the full importance of comorbidity, as defined in this instance as 'other chronic diseases', in determining health or healthcare outcomes is seldom used in clinical practice or included in prognostic models[5-6].

Current prognostic approaches in HF commonly rely on complex and invasive clinical data and biometrics [7] and are often developed using selected hospital based and clinical trial patient populations, rather than in general settings[8-9]. Where comorbidity is included, they tend to focus on the absence or presence of a defined comorbid condition or disease state e.g. diabetes with target organ damage or chronic kidney dysfunction with a defined creatinine level[4,8-10]. This approach lacks sensitivity in determining prognosis change and may reduce the utility of such models for routine use in clinical practice.

Better approaches would include the range of common chronic diseases that patients experience, and incorporate comorbidity indicators that are sensitive to changing prognosis in an index condition such as HF. There is growing evidence that change in one disease is related to the change in another disease, for example the risk of mortality and readmission for HF has been found to increase for patients recently discharged for another condition, including stroke, diabetes, AF or renal dysfunction[13]. Current interest in 'cardiorenal' syndrome has demonstrated a close link between worsening renal function and reduced survival in patients with HF[14-15]. This evidence has not yet been translated effectively into prognostic assessment in HF. This study will use routinely available clinical data and incorporate time-dependent markers of general comorbidity status from general practice data, to identify and develop prognostic models for mortality. This CPRD study is the second phase of the PhD. The first phase of the PhD is on systematic review which will identify the key and common comorbidities

for the CPRD investigation. The CPRD investigation then links to third PhD phase, in which I will investigate other outcomes including hospital admissions and patient reported outcomes in other datasets.

OBJECTIVES

Aim:

To identify prognostic comorbidity factors in heart failure and to construct comorbidity prognostic models for the outcome mortality in the general practice population.

Primary objective:

To investigate the association between comorbidity factors in heart failure and all-cause mortality in general practice populations.

Secondary objective:

To develop comorbidity 'change' measures from general practice data and construct comorbidity prognostic models to predict mortality in HF populations.

Study Type

Observational study incorporating nested case-control design.

Study Design

A nested case-control design will be used to identify comorbidity prognostic indicators for mortality within a national population of heart failure patients. The HF sample from the current CPRD dataset will be used to construct cases and controls aged 40 years and over. The HF sample has twelve continuous years (1995-2006) of observation to assess all-cause mortality. Since the HF patients may be at different stages of severity, a nested case-control design will be used to develop the prognostic model.

Study population

A previously extracted cohort of patients diagnosed with heart failure within the Clinical Practice Research Datalink (CPRD) population (Protocol #07_104R) will be used. This cohort consists of 6000 patients with a recorded medical diagnosis of HF (incident or prevalent) (Read code CG58 and daughter codes and associated OXMIS codes) in their clinical or referral record in a 2-year time period (1st January 1995 to 31st December 1996). All patients had at least two years of up-to-standard follow-up prior to the date of the first recorded HF diagnosis during this time window.

(i) Cases: Within the HF population, cases will be defined as those with a record of death (all-cause mortality) within 12-month windows in the 10 year follow-up time-period (1st January 1996 to 31st December 2006).

(ii) Controls: Within the HF population, controls will be defined as those without a record of death within corresponding 12 month time-windows in the 10 year follow-up time-period (1st January 1996 to 31st December 2006).

Sample Size

For the development of prognostic models it is recommended that sample sizes are calculated based on a requirement of at least 10 observations for each parameter to be estimated in regression models[16-17]. The available CPRD dataset has a total of 6000

patients with HF. Based on this number, and a HF general population mortality risk of 9%[18] there is likely to be around 3600 cases over the 10 years. This will allow for the exploration of a large number of parameters (prognostic factors and interactions) to be included in the logistic regression models.

Exposures, Outcomes, and Covariates
Ascertainment window study population: 1st January 1995 to 31st December 1996
Outcome window: 1st January 1996 to 31st December 2006

Objective 1: To investigate the association between comorbidity factors and all-cause mortality in HF general practice populations

Adults aged 40 years and over who consulted for HF (incident or prevalent HF consultations) within the ascertainment time window and who have an all-cause mortality code within the outcome time window will be compared to living HF controls for comorbidity measures, with 12-month windows in the follow-up time-period used to construct nested case and control groups.

Exposure measurement:
The comorbidity measures will be based on chronic disease type which will be selected *a priori* based on (i) evidence of their prevalence in HF (prior systematic review), (ii) evidence of their prior association with mortality risk (prior systematic review) and (iii) using the Kadam morbidity index which provides a defined code list of common illness and chronic disease based on routine GP consultations(RW.ERROR - Unable to find reference:947). A clinical expert panel group will use the findings of systematic review to provide guidance on the approach to identifying comorbidity measures to be tested in the CPRD case-control study. It is likely that the systematic review will reveal a broad range of factors that are associated with heart failure outcomes and the expert panel will bring focus and feasibility to the possible factors in terms of their; importance in predicting the outcomes of interest, prevalence in the general population, ease of measurement in routine practice and availability of routine data collection.

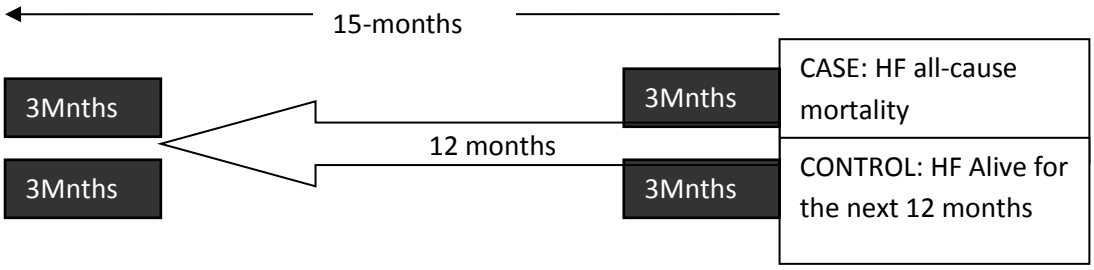
Within the CPRD dataset the *selected* comorbid chronic diseases will be identified by their Read codes applied during the 2-year time windows before death for the cases and controls. Each 2-year time-period will allow for the measurement of chronic disease recording either as new events or as monitoring review events. This also means there will be five 2-year time-windows in the 10 year follow-up period, which can be used to nest case and control groups..

Objective 2: To develop comorbidity 'change' measures from general practice data and construct comorbidity prognostic models to predict mortality in HF populations

Two 3-month time windows for each case and control will be constructed to allow for the assessment of change.

a. First time window: for the cases this time window will cover the 3-months immediately prior to the date of death and for the controls this will cover the 3-months prior to the date of control selection.

b. Second time window: 3-month period leading up-to the 12-months prior to the case event and control selection. This will allow the measurement of comorbidity change in the year immediately prior to death.



Exposure measurement:
This time the comorbidity exposures will focus on chronic disease *type* measures, *severity* measures and *healthcare use* measures of chronic disease to allow us to assess change.

(i) Chronic disease type

a. New diagnosis: This refers to a new chronic disease diagnostic code applied in the first time window that was not applied in the second time window or the year preceding this. This new diagnosis code will be defined at the biological system level (Read code chapters) e.g. cardiovascular, respiratory, gastro-intestinal and identified using the Kadam severity index. This prevents the complication of distinguishing between clinical presentations that are part of the same disease spectrum. The aim of this approach is to capture patients who have developed a new disease *or* who have developed a change to an existing previously stable disease or disease state that requires consultation prior to death.
b. New drug prescription: Prescriptions can be used as a proxy indication of disease and will allow us to capture patients who have developed a new disease (the drug was not prescribed in the second time window but is prescribed in the first time window) but who may not have consulted for this disease during the first time window. Again the new drug definition will be applied at the main body system level. The BNF which is routinely used to code prescriptions in general practice has 15 chapters which each relate to a different body systems[20] and observing prescriptions from different BNF chapters provides a proxy measure of the range and scope of a patient's comorbidity.

(ii) Chronic disease severity

a. Drug prescription change: For each of the limited number of comorbid diseases identified for investigation in objective 1, the mean number of disease specific drug changes between the two time windows will be calculated. Changes will include discontinued drugs and new prescriptions but *not* dose changes for the same drug. This will allow for the comparison of disease instability between the cases and controls.
b. Drug dose change. For each of the selected comorbid diseases *one* common drug that is expected to increase or change in dose as the condition

progresses will be identified. The mean dose of this drug will be calculated in the two 3-month time windows. Different drugs for one indication will be standardised using WHO defined daily doses based on average daily maintenance doses e.g. within proton pump inhibitors Omeprazole 20mg is equivalent to 30mg of Lansoprazole and within ace inhibitors Captopril 50mg, Enalopril 10mg and Lisinopril 10mg are equivalent doses[21].

(iii) Healthcare use indicators

a. The frequency of consultations in general practice can be used as a proxy indication of patient change (i.e. the hypothesis that more frequent consultation means health status is changing). For the comorbid diseases identified in objective 1, the frequency of consultations between the two 3-month time windows will be counted. Increasing frequency will be calculated by the difference between the mean numbers of consultations between the two time-windows. In addition the purpose of consultations as Read coded by HF, other CVD and non-CVD comorbidity will be identified and then compared between cases and controls.

The 3-month time windows allow for construction of the 'change' concept which are admittedly fixed to allow the investigation of prognostic factors in the immediate time-period before death, but this analysis is set against the overall 2-year time window in objective 1, to ensure 'change' measurement is real and not due to time gaps.

Covariate measurement:

Known predictive factors will be added to the comorbidity model. These factors, again guided by systematic review, will include socio-demographic factors including age, gender and social deprivation[22-23], health factors including smoking history in the two year prior to event and BMI[24] (latest recording prior to event will be used), and index disease factors including co-drug treatments and severity factors. Patients who are not prescribed mainline treatment in HF (beta blocker and ace-inhibitors) are known to have a higher mortality risk and comorbid disease is known to influence treatment prescription[25]. Duration of HF disease will be estimated by the time since date of diagnosis will also be included as proxy measure of HF severity.

Statistical Analysis

Statistical analysis will be performed in three stages:

(i) Descriptive analyses - First, the prevalence of chronic disease comorbidity in the case and control groups will be presented in the 2-years prior to the date of death or control selection.

(ii) Prognostic model building

a. Unadjusted associations using odds ratios will be calculated to compare cases with controls for each chronic disease to be tested and the results will be stratified by important covariates such as age, gender and deprivation.

b. Multiple binary logistic regression methods will be used to compare cases with controls in relation to mortality. Comorbidity factors and covariates will be fitted into a logistic model. A stepwise approach will be used to obtain a subset of predictors including interactions out of the many identified. Categorical and continuous variables where possible will be

compared to test for model fit and likelihood-ratio tests will be used to identify any interactions to be included in the model.

(iii) Modelling prognostic change

a. Unadjusted associations using odds ratios will be calculated to compare cases with controls for each change measure and the results will be stratified by important covariates as above.
b. Multiple binary logistic regression methods will be used to model comorbid prognostic 'change' measures for mortality. Disease type, severity and healthcare use measures will be fitted into the logistic regression model along with the defined chronic diseases and covariates and a stepwise approach used to reduce the model. The influence of the comorbidity *change* measure in addition to the chronic disease *type* on mortality will be investigated. Missing data: Methods of multiple imputation will be considered using the procedure ICE in Stata (this may for example be required for BMI or smoking). The comorbidity prognostic model for HF that is built as a part of this process will be further tested and calibrated in other GP datasets, and in longitudinal survival analyses.

Patient or user group involvement

Patients and service users were involved in the development of potential measures. A prior study on HF multi-drug therapy has helped to develop the project ideas around comorbidity measures (draft paper in submission). This had active engagement with Stoke-on-Trent Community Health and discussions, particularly in terms of the complexity of drug regimes that HF patients are exposed to, guided the measures that were used in the multi-drug study and will be used in this study.

Limitations of study design, data sources, and analytic methods

The case and control definitions are based on a consultation for HF in a 2-year time period, constructing an ascertainment group to follow-up for the outcome of mortality. Consultation sources such as the GPRD are based on routinely collected data, and as such rely on both the patient's decision to consult and the GP's precision in recording. This could lead to mis-classification of some morbidity data including the HF label and this may affect some morbidities more than others particular in the context of patients will multiple diagnosis. However given that the study population and the exposures to be measured relate to chronic disease it is likely that patients will have on-going chronic disease management plans requiring consultation and further investigation. Any mis-coding or classification of morbidity whilst potentially disproportionate across different morbidities is likely to be proportionate across cases and controls and does not detract from *a priori* hypothesis testing. The GPRD does have clear framework for ensuring the quality of data.

The other issue in terms of using a dataset to build a prognostic model is the application of the model to an individual patient. Whilst the GPRD will provide a rich data source in terms of chronic disease within a large general population, a linked cohort study will provide the mechanism to further refine and test the model in HF patients.

Finally, given the length of follow-up (12 years) there is likely to be patients who were lost to follow-up in the observation window. It will be important to compare these

patients to the study groups in terms of factors that might influence the exposures or the outcomes (e.g. socio-demographic data).

Dissemination

This study forms part of a three phase PhD that will be delivered over three years and is supported by an NIHR Doctoral Research Fellowship. Dissemination will be through peer-reviewed general practice, cardiology, epidemiological and statistical journals and through presentations at relevant conferences, for example the British Society of Heart Failure Annual Autumn Meeting, RCN Annual International Nursing Research Conference and the American College of Epidemiology Conference. We also have links with local practices, health professionals and patient groups, as well as collaborative links with research professors in Sweden who have an international programme of HF research, so that key messages can be communicated widely. There is no restriction on extent and timing of publications.

This protocol has been previously reviewed by the NIHR and is supported by a full time doctoral Fellowship.

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Amendments

Using the same methods and statistical approach we would like to amend this protocol to include hospital admission outcome using incident heart failure cases over a ten year period (1st March 2002 – 31st March 2012). We would like to investigate patients with heart failure, and the influence of other diseases on their risk of hospital admission and death.
The aims and objectives remain the same with the addition of hospital admission outcome.
With a new CPRD data set the population will now consist of patients aged 40 years and over with a recorded medical diagnosis of HF (incident cases) (Read code CG58 and daughter codes) in their clinical or referral record over the 10 year time period. As before, all patients will have at least two years of up-to-standard follow-up prior to the date of the first recorded HF diagnosis during this time window.

Exposures, Outcomes, and Covariates

The exposures and covariates remain the same. The objectives have been rewritten here to reflect the hospital admission outcome:

Objective 1: To investigate the association between comorbidity factors *and hospital admission* and all-cause mortality in HF general practice populations

Adults aged 40 years and over who consulted for HF (incident HF consultations) within the 10 year ascertainment time window and who have *(i) a hospital admission* or (ii) an all-cause mortality code during follow-up (minimum 1 year) will be compared to HF

controls for comorbidity measures. 12-month windows in the 10 year time-period will be used to construct nested case and control groups.

For hospital admissions:

(iii) Cases: Within the HF population, cases will be defined as those with a record of a hospital admission within 12-month windows in the 10 year time-period

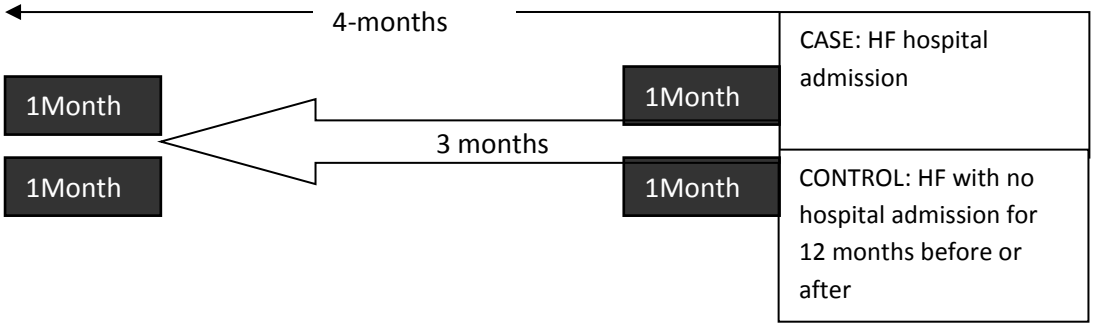
(iv) Controls: Within the HF population, controls will be defined as those without a record of a hospital admission for 12 months prior to and after the control selection date, within corresponding 12 month time-windows in the 10 year time-period

Objective 2 (same as in the previous protocol): To develop comorbidity 'change' measures from general practice data and construct comorbidity prognostic models to predict mortality and hospital admission in HF populations

Hospital admission:

Two 1-month time windows for each case and control will be constructed to allow for the assessment of change.

c. First time window: for the cases this time window will cover the month immediately prior to the date of hospital admission and for the controls this will cover the month prior to the date of control selection.
d. Second time window: 1-month period leading up-to the 3-months prior to the case event and control selection. This will allow the measurement of comorbidity change in the 3 months immediately prior to hospital admission.



Statistical Analysis:

The analysis plan remains the same with the addition of hospital admission outcome. Where multiple hospital admissions occur in a 12-month analysis time window the first hospital admission during that time-period will be used.

Sample Size

We intend to perform the study in a new CPRD data set with linkage to HES. Previous enquiries to CPRD have indicated approximately 20,000 incident HF cases with HES linkage in the 10 year time period and this would allow for:

- A larger set of prognostic factors and some clinically relevant higher order interaction terms to be tested
- An adjustment of significance levels to incorporate multiple analyses with different outcome measures
- An ability to internally validate the models produced from a "training set" on an independent "test set" of data

E-Appendix E: Miscellaneous

E1 Cochrane prognosis methods group letter

Keele University

Claire Rushton <c.a.rushton@keele.ac.uk>

(no subject)
2 messages

Moons, K.G.M. <K.G.M.Moons@umcutrecht.nl> 3 April 2013 20:06
To: Claire Rushton <c.a.rushton@keele.ac.uk>
Cc: Richard Riley <r.d.riley@bham.ac.uk>, "jill.hayden@cdha.nshealth.ca" <jill.hayden@cdha.nshealth.ca>

Dear Claire,

I have read it and in principle it looks fine to me.

Your review clealry focuses not on models but on a prognostic factor - and Jil Haydn and Richrad Riley are the experts on this. I cc them in, both convenors of the cochrane PMG. a few notes for starters: Quips is just updated and see also the recent PRogress paper 2 in BMJ 2013, by Riley et al, which also addresses this topic.

Jill and Richard would one of you please have a short feed back perhaps for Claire, who apporached the PMG for feed back on her protocol.

BW,

Carl

E2 Medline HF filter(9)

#	Searches
1	HF.mp.
2	ventricular dysfunction, left.sh.
3	cardiomyopathy.mp.
4	left ventricular ejection fraction.mp.
5	Or/1-4

E3 Heart failure string(9): database search results

No.	Search [Date of search]	MEDLINE	EMBASE	CINAHL	MEDLINE 22/1/13	Embase 22/1/13	CINAHL 22/1/13
	POPULATION						
1.	heart failure	[tw] OR [mh]	.tw OR exp	.tx OR exp	126808	218293	60176
2.	ventricular dysfunction, left (heart left ventricle function for Embase exp)	[mh]	exp	exp	19559	0	3400
3.	cardiomyopathy	[tw] OR [mh]	.tw OR .exp	.af	83613	88408	9656
4.	left ventricular ejection fraction (heart left ventricle ejection fraction for Embase exp) (ventricular ejection fraction for Cinahl exp)	[tw] OR [mh]	.tw OR .exp	.tx OR exp	14913	21866	8856
5.	**1–4 combined using OR**				**211089**	**291188**	**68180**
	OUTCOMES	[tiab]	.ti,ab	.ti,ab			
6	Mortalit*				420960	552820	50117
7	Death*				494095	634892	52962
8	Survival				531260	693740	32464
9	Admission*				124353	176330	23547
10	Readmission*				8527	12405	2456
11	“quality of life”				125986	184775	34942
12	health				978950	1210425	341800
13	“Kansas City Cardiomyopathy Questionnaire”				114	190	44
14	KCCQ				81	166	26
15	“Minnesota Living with Heart Failure Questionnaire”				0	519	99
16	“Short form”				14920	18532	4297
17	Sf-36				11445	16146	3192
18	Sf36				659	1332	3192
19	Sf12				120	289	533
20	Sf-12				1762	2629	533
21	EuroQol				1825	2557	398
22	EQ-5D				2303	3787	550
23	“Heart Failure Symptom Scale”				0	3	1
24	**6-23 combined using OR**				**2242958**	**2863960**	**467281**

No.	Medline Search Date of search	Hits 22/1/13	EMBASE Search	Hits 22/1/13	CINAHL Search	Hits 22/1/13
	PROGNOSIS		PROGNOSIS		PROGNOSIS	
25.	Predict[tiab]	176976	Exp DISEASE COURSE/	1832649	“Disease course”.af	1420
26.	predictive value of tests[mh]	125438	risk*.tw OR exp	2030149	risk*.af	480890
27.	scor*[tiab]	467190	diagnos*.tw OR exp DIAGNOSIS/	3259540	diagnos*.af	508960
28.	observ*[mh]	2259239	follow-up.tw OR exp FOLLOW UP/	1007458	follow-up.af	143818
29.	observer variation	28527	ep.fs	894954	exp EPIDEMIOLOGY/	251693
30.	"Stratification"[mh]	26264	outcome.tw	714375	outcome.tx	196555
31.	"Roc curve"	241187				
32.	"Discrimination"	94487				
33.	"Discriminate"	36646				
34.	"c-statistic"	1282				
35.	"c statistic"	1282				
36.	"Area under the curve"	17455				
37.	"AUC"	30265				
38.	"Calibration"	55958				
39.	"Indices"	104597				
40	“Algorithm"	88075				
41	"Multivariable"	24450				
42	25–41 combined (OR)	3209003	25-30 combined (OR)	7103036	25-30 combined (OR)	1018837

COMBINED SEARCHES	MEDLINE	EMBASE	CINAHL
4 AND 24 AND 42	16955	69266	15791
LIMITED SEARCHES*	**10976**	**23343**	**7775**

*Medline: Human, Age>19, 1990> *Embase: Human, Age>18, 1990> *Cinahl: Adults, 1990>

E4 Heart failure search string

Controlled vocabulary terms	Condensed Unique list
Medline	
MeSH:	Heart failure
Heart failure	Ventricular dysfunction
Ventricular dysfunction, left	Cardiac edema
Edema, cardiac	Cardiomyopathy
Heart failure, systolic	Cardiac failure
Heart failure, diastolic	Myocardial failure
Cardiomyopathy, dilated	Heart decompensation
Entry terms:	Ventricular failure
Cardiac Failure	Ventricular ejection fraction
Congestive Heart Failure	Cor Pulmonale
Heart Decompensation	
Heart Failure, Congestive	
Heart Failure, Left-Sided	
Heart Failure, Right-Sided	
Left-Sided Heart Failure	
Myocardial Failure	
Right-Sided Heart Failure	
Cor Pulmonale	
ventricular ejection fraction	
EMBASE	
EMTREE:	Heart failure
heart failure	Ventricular dysfunction
congestive heart failure	Heart edema
diastolic dysfunction	cardiac failure
forward heart failure	diastolic dysfunction
heart ventricle failure	systolic dysfunction
high output heart failure	cor pulmonale
systolic dysfunction	congestive cardiomyopathy
heart failure, congestive	congestive heart disease
heart failure, diastolic	ventricular ejection fraction
heart failure, systolic	ventricle failure
congestive cardiac failure	
cor pulmonale	
heart edema	
congestive cardiomyopathy	
congestive heart disease	
left ventricular systolic dysfunction	
ventricular ejection fraction	
CINAHL	
Heart failure	Heart failure
Combined list of unique terms	
Heart failure	Myocardial failure”
“Ventricular dysfunction”	“Heart decompensation”
“Cardiac edema”	“Ventric* failure”
“Heart edema”	“Ventricular ejection fraction”
Cardiomyopathy	“Cor Pulmonale”
“Cardiac failure”	“diastolic dysfunction”
“congestive heart disease”	“systolic dysfunction”

E5a Updated Haynes filter for MEDLINE(10)

Predict*[tiab]
OR Predictive value of tests[mh]
OR Scor*[tiab]
OR Observ*[tiab]
OR Observer
OR variation[mh]
OR ‘‘Stratification’’
OR ‘‘ROC Curve’’[Mesh]
OR ‘‘Discrimination’’
OR ‘‘Discriminate’’
OR ‘‘c-statistic’’
OR ‘‘c statistic’’
OR ‘‘Area under the curve’’
OR ‘‘AUC’’
OR ‘‘Calibration’’
OR ‘‘Indices’’
OR ‘‘Algorithm’’
OR ‘‘Multivariable’’

E5b Prognosis search filter for EMBASE(11)

exp disease course/
OR risk*.mp.
OR diagnos*.mp.
OR follow-up.mp.
OR ep.fs.
OR outcome.tw.

E5c Prognosis search filter for CINAHL

“Disease course”.af
OR risk*.af
OR diagnos*.af
OR follow-up.af
OR exp EPIDEMIOLOGY/
OR outcome.tx

E6 Outcomes search string

"mortalit*".ti,ab.
OR survival.ti,ab.
OR "Admission*".ti,ab.
OR "Readmission*".ti,ab.
OR "rehospitalization*".ti,ab.
OR "hospitalization*".ti,ab.
OR 20 or 21
OR "death*".ti,ab.
OR "quality of life".ti,ab.
OR health.ti,ab.
OR "Kansas City Cardiomyopathy Questionnaire".ti,ab.
OR KCCQ.ti,ab.
OR "Minnesota Living with Heart Failure Questionnaire".ti,ab.
OR "Short form".ti,ab.
OR sf-36.ti,ab.
OR sf36.ti,ab.
OR sf12.ti,ab.
OR sf-12.ti,ab.
OR euroqol.ti,ab.
OR eq-5d.ti,ab.
OR "Heart Failure Symptom Scale".ti,ab.

E7 Inter-rater reliability assessment using Cohen's kappa(6)

	Screener 2		
Screener 1	Moderate score	Other score	Total
Moderate score	39	2	41
Other score	3	24	27
Total	**42**	**26**	**68**

Crude agreement

'Other' indicates where a score other than moderate was allocated (i.e high or low). Any disagreements between the two reviewers in this study were where one reviewer had allocated a moderate score and the other a high or low score. Two 'other' scores therefore in this case were always agreement (either high or low).

Crude agreements = 39 +24/68 = 0.93%

Taking account of chance agreement

Include = 42 x 41/68 = 25.32

Exclude 27x24/68 = 9.53

Total = 34.85 agreed articles expected by chance

Proportion expected by chance = 34.68/68 = 0.513

Maximum agreement is 1.0 therefore the inter-rater reliability agreement (Kappa) =

$$\frac{\text{Crude agreement} - \text{chance agreement}}{1 - \text{chance agreement}}$$

$$= 0.93\text{-}0.513 \,/\, 1\text{-}0.513 = \mathbf{86\%}$$

E8 Frequency of subject use in case control analyses

MORTALITY

Frequency of same subject use in matched set (N)	Frequency	%	Cumulative %
1	14005	29.9	29.9
2	11225	23.9	53.8
3	7995	17.0	70.8
4	5512	11.7	82.6
5	3377	7.2	89.8
6	2122	4.5	94.3
7	1245	2.7	97.0
8	680	1.4	98.4
9	390	.8	99.2
10	199	.4	99.7
11	95	.2	99.9
12	37	.1	99.9
13	16	.0	100.0
14	8	.0	100.0
15	4	.0	100.0
16	1	.0	100.0
Total	46911	100.0	

HOSPITAL ADMISSION

Frequency of same subject use in matched set (N)	Frequency	%	Cumulative %
1	16055	57.4	57.4
2	1118	4.0	61.4
3	1164	4.2	65.5
4	1310	4.7	70.2
5	1282	4.6	74.8
6	1101	3.9	78.7
7	1034	3.7	82.4
8	868	3.1	85.5
9	674	2.4	88.0
10	545	1.9	89.9
11	489	1.7	91.6
12	381	1.4	93.0
13	307	1.1	94.1
14	270	1.0	95.1
15	234	.8	95.9
16	168	.6	96.5
17	131	.5	97.0
18	146	.5	97.5
19	134	.5	98.0
20	87	.3	98.3
21	76	.3	98.6
22	63	.2	98.8
23	61	.2	99.0
24	54	.2	99.2
25	46	.2	99.4
26	37	.1	99.5
27	45	.2	99.7
28	19	.1	99.7
29	16	.1	99.8
30	14	.1	99.8
31	12	.0	99.9
32	9	.0	99.9
33	11	.0	99.9
34	5	.0	100.0
35	1	.0	100.0
36	2	.0	100.0
37	4	.0	100.0
38	2	.0	100.0
43	1	.0	100.0
Total	27976	100.0	

E9a Chronic obstructive pulmonary disease search strategy

Read Code,h3*

Read Term,*COPD*

Read Term,*emphysem*

Read Term,*bronchiectas*

Read Term,*bronchitis*

Read Term,*chronic air*

Read Term,*chronic obstruct*

E9b Diabetes mellitus search strategy

Read Code c10*

Read Term *diabet*

E9c Chronic kidney disease search strategy

Read Term,*renal*

Read Term,*nephro*

Read Term,*nephri*

Read Term,*medullary*

Read Term,*kidney*

Read Code,k0*

Read Code,k1*

Read Code,g2*

Read Code,1z*

Read Code,14d*

Read Code,pd1*

Read Code,9h*

E10 Chronic Obstructive Pulmonary Disease Code set

CPRD Medcode	Read code	Read Term	Previous validation	QoF listed	Read code type	Study code type
1001	H3...00	Chronic obstructive pulmonary disease	√	√	Diagnostic	Index
998	H3...11	Chronic obstructive airways disease	√	√	Diagnostic	Index
10863	H36..00	Mild chronic obstructive pulmonary disease	√	√	Diagnostic	Index
5710	H3z..00	Chronic obstructive airways disease NOS	√	√	Diagnostic	Index
10802	H37..00	Moderate chronic obstructive pulmonary disease	√	√	Diagnostic	Index
794	H32..00	Emphysema	√	√	Diagnostic	Index
9876	H38..00	Severe chronic obstructive pulmonary disease	√	√	Diagnostic	Index
93568	H39..00	Very severe chronic obstructive pulmonary disease	√	√	Diagnostic	Index
14798	H312100	Emphysematous bronchitis	√	√	Diagnostic	Index
12166	H3y..00	Other specified chronic obstructive airways disease	√	√	Diagnostic	Index
33450	H32z.00	Emphysema NOS	√	√	Diagnostic	Index
37247	H3z..11	Chronic obstructive pulmonary disease NOS	√	√	Diagnostic	Index
26306	H320.00	Chronic bullous emphysema	√	√	Diagnostic	Index
10980	H322.00	Centrilobular emphysema	√	√	Diagnostic	Index
23492	H320z00	Chronic bullous emphysema NOS	√	√	Diagnostic	Index
44525	H312z00	Obstructive chronic bronchitis NOS	√	√	Diagnostic	Index
11287	66YM.00	Chronic obstructive pulmonary disease annual review	√		Process	Prevalence
9520	66YB.00	Chronic obstructive pulmonary disease monitoring	√		Process	Prevalence
28755	9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter	√		Process	Prevalence
18621	66YL.00	Chronic obstructive pulmonary disease follow-up	√		Process	Prevalence
34202	9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter	√		Process	Prevalence
18476	66YL.11	COPD follow-up	√		Process	Prevalence
34215	9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter	√		Process	Prevalence
18792	9Oi..00	Chronic obstructive pulmonary disease monitoring admin	√		Process	Prevalence
37371	66YD.00	Chronic obstructive pulmonary disease monitoring due	√		Process	Prevalence

26018	66YS.00	Chronic obstructive pulmonary disease monitoring by nurse	√		Process	Prevalence
45771	66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep	√		Process	Prevalence
45998	66YT.00	Chronic obstructive pulmonary disease monitoring by doctor	√		Process	Prevalence
3243	H31..00	Chronic bronchitis		√	Diagnostic	Index
15157	H31z.00	Chronic bronchitis NOS		√	Diagnostic	Index
15626	H310000	Chronic catarrhal bronchitis		√	Diagnostic	Index
5798	H312000	Chronic asthmatic bronchitis		√	Diagnostic	Index
27819	H312.00	Obstructive chronic bronchitis		√	Diagnostic	Index
25603	H310.00	Simple chronic bronchitis		√	Diagnostic	Index
5909	H312011	Chronic wheezy bronchitis		√	Diagnostic	Index
11150	H311.00	Mucopurulent chronic bronchitis		√	Diagnostic	Index
26125	H312300	Bronchiolitis obliterans		√	Diagnostic	Index
45089	H31y100	Chronic tracheobronchitis		√	Diagnostic	Index
16410	H32yz00	Other emphysema NOS		√	Diagnostic	Index
40788	H32y.00	Other emphysema		√	Diagnostic	Index
40159	H311000	Purulent chronic bronchitis		√	Diagnostic	Index
61118	H310z00	Simple chronic bronchitis NOS		√	Diagnostic	Index
104608	H3A..00	End stage chronic obstructive airways disease		√	Diagnostic	Index
24248	H313.00	Mixed simple and mucopurulent chronic bronchitis		√	Diagnostic	Index
61513	H311z00	Mucopurulent chronic bronchitis NOS		√	Diagnostic	Index
63479	H32y200	MacLeod's unilateral emphysema		√	Diagnostic	Index
66043	H31y.00	Other chronic bronchitis		√	Diagnostic	Index
68066	H31yz00	Other chronic bronchitis NOS		√	Diagnostic	Index
46578	H321.00	Panlobular emphysema		√	Diagnostic	Index
60188	H320200	Giant bullous emphysema		√	Diagnostic	Index
56860	H320000	Segmental bullous emphysema		√	Diagnostic	Index
68662	H320100	Zonal bullous emphysema		√	Diagnostic	Index
99536	H320300	Bullous emphysema with collapse		√	Diagnostic	Index
67040	H3y..11	Other specified chronic obstructive pulmonary disease		√	Diagnostic	Index

37959	H311100	Fetid chronic bronchitis	√	Diagnostic	Index
70787	H32y100	Atrophic (senile) emphysema	√	Diagnostic	Index
59263	H32y111	Acute interstitial emphysema	√	Diagnostic	Index
103733	H320311	Tension pneumatocoele	√	Diagnostic	Index
92955	H32y000	Acute vesicular emphysema	√	Diagnostic	Index
1446	H312200	Acute exacerbation of chronic obstructive airways disease		Diagnostic	Index
28743	66Yf.00	Number of COPD exacerbations in past year		Process	Prevalence
18501	66YI.00	COPD self-management plan given		Process	Prevalence
7884	H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec		Diagnostic	Index
11019	8H2R.00	Admit COPD emergency		Process	Index
42313	679V.00	Health education - chronic obstructive pulmonary disease		Process	Prevalence
101042	8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack		Process	Prevalence
38074	9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite		Process	Prevalence
45777	8CR1.00	Chronic obstructive pulmonary disease clini management plan		Process	Prevalence
19106	66Yd.00	COPD accident and emergency attendance since last visit		Process	Prevalence
19003	66Ye.00	Emergency COPD admission since last appointment		Process	Prevalence
42258	9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite		Process	Prevalence
21061	H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn		Diagnostic	Index
7092	H30..12	Recurrent wheezy bronchitis		Diagnostic	Index
103007	66YB100	Chronic obstructive pulmonary disease 6 monthly review		Process	Prevalence
102685	66YB000	Chronic obstructive pulmonary disease 3 monthly review		Process	Prevalence
19721	8CE6.00	Chronic obstructive pulmonary disease leaflet given		Process	Prevalence
99948	9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin		Process	Prevalence
104117	661M300	COPD self-management plan agreed		Process	Prevalence
104169	661N300	COPD self-management plan review		Process	Prevalence
46036	66Yi.00	Multiple COPD emergency hospital admissions		Process	Prevalence
103494	14B3.12	History of chronic obstructive pulmonary disease		Process	Prevalence
104265	9e03.00	GP OOH service notified of COPD care plan		Process	Prevalence
103758	8Hkw.00	Referral to COPD community nursing team		Process	Prevalence

103678	8BMa000	Chronic obstructiv pulmonary disease medication optimisation	Process	Prevalence
45770	66Yg.00	Chronic obstructive pulmonary disease disturbs sleep	Process	Prevalence
105457	8CMW500	Chronic obstructive pulmonary disease care pathway	Process	Prevalence
97800	9kf..00	COPD - enhanced services administration	Process	Prevalence
22905	H581.00	Interstitial emphysema	Diagnostic	Index
103558	8CeD.00	Preferred place of care for next exacerbation of COPD	Process	Prevalence
104481	8CMV.00	Has chronic obstructive pulmonary disease care plan	Process	Prevalence
98284	9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin	Process	Prevalence
65733	Hyu3100	[X]Other specified chronic obstructive pulmonary disease	Diagnostic	Index
98283	9kf2.00	COPD structured smoking assessment declined - enh serv admin	Process	Prevalence
104985	9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway	Process	Prevalence
103760	9kf2.11	COPD structured smoking assessment declined	Process	Prevalence
103864	9kf0.11	COPD patient unsuitable for pulmonary rehabilitation	Process	Prevalence
103400	9kf1.11	Referred for COPD structured smoking assessment	Process	Prevalence
104710	9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway	Process	Prevalence

E11 Diabetes Mellitus Code set

			Validation		Code type	
CPRD Medcode	**Read code**	**Read term**	**Previous studies**	**Qof listed**	**Read code type**	**Study code type**
711	C10..00	Diabetes mellitus	√	√	Diagnostic	Index
18278	C109J00	Insulin treated Type 2 diabetes mellitus	√	√	Diagnostic	Index
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus	√	√	Diagnostic	Index
18264	C109J12	Insulin treated Type II diabetes mellitus	√	√	Diagnostic	Index
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	√	√	Diagnostic	Index
43453	C10C.00	Diabetes mellitus autosomal dominant	√	√	Diagnostic	Index
46624	C10C.11	Maturity onset diabetes in youth	√	√	Diagnostic	Index
98392	C10C.12	Maturity onset diabetes in youth type 1	√	√	Diagnostic	Index
36695	C10D.00	Diabetes mellitus autosomal dominant type 2	√	√	Diagnostic	Index
59991	C10D.11	Maturity onset diabetes in youth type 2	√	√	Diagnostic	Index
1549	C10E.00	Type 1 diabetes mellitus	√	√	Diagnostic	Index
12455	C10E.11	Type I diabetes mellitus	√	√	Diagnostic	Index
51261	C10E.12	Insulin dependent diabetes mellitus	√	√	Diagnostic	Index
47582	C10E000	Type 1 diabetes mellitus with renal complications	√	√	Diagnostic	Index
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications	√	√	Diagnostic	Index
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications	√	√	Diagnostic	Index
99311	C10E111	Type I diabetes mellitus with ophthalmic complications	√	√	Diagnostic	Index
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps	√	√	Diagnostic	Index
42831	C10E200	Type 1 diabetes mellitus with neurological complications	√	√	Diagnostic	Index
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps	√	√	Diagnostic	Index
47650	C10E300	Type 1 diabetes mellitus with multiple complications	√	√	Diagnostic	Index
91942	C10E311	Type I diabetes mellitus with multiple complications	√	√	Diagnostic	Index
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat	√	√	Diagnostic	Index
43921	C10E400	Unstable type 1 diabetes mellitus	√	√	Diagnostic	Index
49949	C10E411	Unstable type I diabetes mellitus	√	√	Diagnostic	Index

54600	C10E412	Unstable insulin dependent diabetes mellitus	√	√	Diagnostic	Index
18683	C10E500	Type 1 diabetes mellitus with ulcer	√	√	Diagnostic	Index
93878	C10E511	Type I diabetes mellitus with ulcer	√	√	Diagnostic	Index
98704	C10E512	Insulin dependent diabetes mellitus with ulcer	√	√	Diagnostic	Index
69993	C10E600	Type 1 diabetes mellitus with gangrene	√	√	Diagnostic	Index
102112	C10E611	Type I diabetes mellitus with gangrene	√	√	Diagnostic	Index
18387	C10E700	Type 1 diabetes mellitus with retinopathy	√	√	Diagnostic	Index
95343	C10E711	Type I diabetes mellitus with retinopathy	√	√	Diagnostic	Index
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy	√	√	Diagnostic	Index
35288	C10E800	Type 1 diabetes mellitus - poor control	√	√	Diagnostic	Index
105337	C10E811	Type I diabetes mellitus - poor control	√	√	Diagnostic	Index
72702	C10E812	Insulin dependent diabetes mellitus - poor control	√	√	Diagnostic	Index
40682	C10E900	Type 1 diabetes mellitus maturity onset	√	√	Diagnostic	Index
96235	C10E911	Type I diabetes mellitus maturity onset	√	√	Diagnostic	Index
97849	C10E912	Insulin dependent diabetes maturity onset	√	√	Diagnostic	Index
69676	C10EA00	Type 1 diabetes mellitus without complication	√	√	Diagnostic	Index
62613	C10EA11	Type I diabetes mellitus without complication	√	√	Diagnostic	Index
99719	C10EA12	Insulin-dependent diabetes without complication	√	√	Diagnostic	Index
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy	√	√	Diagnostic	Index
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy	√	√	Diagnostic	Index
91943	C10EC11	Type I diabetes mellitus with polyneuropathy	√	√	Diagnostic	Index
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy	√	√	Diagnostic	Index
10418	C10ED00	Type 1 diabetes mellitus with nephropathy	√	√	Diagnostic	Index
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy	√	√	Diagnostic	Index
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma	√	√	Diagnostic	Index
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma	√	√	Diagnostic	Index
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract	√	√	Diagnostic	Index
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract	√	√	Diagnostic	Index
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy	√	√	Diagnostic	Index

18642	C10EH00	Type 1 diabetes mellitus with arthropathy	√	√	Diagnostic	Index
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy	√	√	Diagnostic	Index
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria	√	√	Diagnostic	Index
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria	√	√	Diagnostic	Index
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria	√	√	Diagnostic	Index
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis	√	√	Diagnostic	Index
62209	C10EM11	Type I diabetes mellitus with ketoacidosis	√	√	Diagnostic	Index
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma	√	√	Diagnostic	Index
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma	√	√	Diagnostic	Index
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy	√	√	Diagnostic	Index
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy	√	√	Diagnostic	Index
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis	√	√	Diagnostic	Index
95636	C10ER00	Latent autoimmune diabetes mellitus in adult	√	√	Diagnostic	Index
758	C10F.00	Type 2 diabetes mellitus	√	√	Diagnostic	Index
22884	C10F.11	Type II diabetes mellitus	√	√	Diagnostic	Index
18777	C10F000	Type 2 diabetes mellitus with renal complications	√	√	Diagnostic	Index
57278	C10F011	Type II diabetes mellitus with renal complications	√	√	Diagnostic	Index
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications	√	√	Diagnostic	Index
100964	C10F111	Type II diabetes mellitus with ophthalmic complications	√	√	Diagnostic	Index
34268	C10F200	Type 2 diabetes mellitus with neurological complications	√	√	Diagnostic	Index
98616	C10F211	Type II diabetes mellitus with neurological complications	√	√	Diagnostic	Index
65267	C10F300	Type 2 diabetes mellitus with multiple complications	√	√	Diagnostic	Index
43227	C10F311	Type II diabetes mellitus with multiple complications	√	√	Diagnostic	Index
49074	C10F400	Type 2 diabetes mellitus with ulcer	√	√	Diagnostic	Index
91646	C10F411	Type II diabetes mellitus with ulcer	√	√	Diagnostic	Index
12736	C10F500	Type 2 diabetes mellitus with gangrene	√	√	Diagnostic	Index
104323	C10F511	Type II diabetes mellitus with gangrene	√	√	Diagnostic	Index
18496	C10F600	Type 2 diabetes mellitus with retinopathy	√	√	Diagnostic	Index
49655	C10F611	Type II diabetes mellitus with retinopathy	√	√	Diagnostic	Index

25627	C10F700	Type 2 diabetes mellitus - poor control	√	√	Diagnostic	Index
47315	C10F711	Type II diabetes mellitus - poor control	√	√	Diagnostic	Index
47954	C10F900	Type 2 diabetes mellitus without complication	√	√	Diagnostic	Index
53392	C10F911	Type II diabetes mellitus without complication	√	√	Diagnostic	Index
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy	√	√	Diagnostic	Index
95351	C10FA11	Type II diabetes mellitus with mononeuropathy	√	√	Diagnostic	Index
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy	√	√	Diagnostic	Index
50527	C10FB11	Type II diabetes mellitus with polyneuropathy	√	√	Diagnostic	Index
12640	C10FC00	Type 2 diabetes mellitus with nephropathy	√	√	Diagnostic	Index
102201	C10FC11	Type II diabetes mellitus with nephropathy	√	√	Diagnostic	Index
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma	√	√	Diagnostic	Index
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma	√	√	Diagnostic	Index
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract	√	√	Diagnostic	Index
93727	C10FE11	Type II diabetes mellitus with diabetic cataract	√	√	Diagnostic	Index
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy	√	√	Diagnostic	Index
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy	√	√	Diagnostic	Index
59253	C10FG00	Type 2 diabetes mellitus with arthropathy	√	√	Diagnostic	Index
103902	C10FG11	Type II diabetes mellitus with arthropathy	√	√	Diagnostic	Index
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy	√	√	Diagnostic	Index
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus	√	√	Diagnostic	Index
64668	C10FJ11	Insulin treated Type II diabetes mellitus	√	√	Diagnostic	Index
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus	√	√	Diagnostic	Index
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria	√	√	Diagnostic	Index
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria	√	√	Diagnostic	Index
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria	√	√	Diagnostic	Index
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria	√	√	Diagnostic	Index
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis	√	√	Diagnostic	Index
106528	C10FN11	Type II diabetes mellitus with ketoacidosis	√	√	Diagnostic	Index
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma	√	√	Diagnostic	Index

106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma	√	√	Diagnostic	Index
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy	√	√	Diagnostic	Index
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis	√	√	Diagnostic	Index
95539	C10FS00	Maternally inherited diabetes mellitus	√	√	Diagnostic	Index
51697	C10G.00	Secondary pancreatic diabetes mellitus	√	√	Diagnostic	Index
96506	C10G000	Secondary pancreatic diabetes mellitus without complication	√	√	Diagnostic	Index
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs	√	√	Diagnostic	Index
67212	C10H000	DM induced by non-steroid drugs without complication	√	√	Diagnostic	Index
43857	C10M.00	Lipoatrophic diabetes mellitus	√	√	Diagnostic	Index
22487	C10N.00	Secondary diabetes mellitus	√	√	Diagnostic	Index
94383	C10N000	Secondary diabetes mellitus without complication	√	√	Diagnostic	Index
93380	C10N100	Cystic fibrosis related diabetes mellitus	√	√	Diagnostic	Index
34528	3882	Diabetes well being questionnaire	√		Process	Prevalence only
98954	3883	Diabetes treatment satisfaction questionnaire	√		Process	Prevalence only
49884	6761	Diabetic pre-pregnancy counselling	√		Process	Prevalence only
21689	13AB.00	Diabetic lipid lowering diet	√		Process	Prevalence only
13078	13AC.00	Diabetic weight reducing diet	√		Process	Prevalence only
13074	13B1.00	Diabetic diet	√		Process	Prevalence only
107423	661N400	Diabetes self-management plan review	√		Process	Prevalence only
3550	66A..00	Diabetic monitoring	√		Process	Prevalence only
7563	66A3.00	Diabetic on diet only	√		Process	Prevalence only
1684	66A4.00	Diabetic on oral treatment	√		Process	Prevalence only
8842	66A5.00	Diabetic on insulin	√		Process	Prevalence only
25636	66Aa.00	Diabetic diet - poor compliance	√		Process	Prevalence only
22823	66Ab.00	Diabetic foot examination	√		Process	Prevalence only
10977	66Ac.00	Diabetic peripheral neuropathy screening	√		Process	Prevalence only
53238	66AG.00	Diabetic drug side effects	√		Process	Prevalence only
16490	66AH.00	Diabetic treatment changed	√		Process	Index
28873	66Ai.00	Diabetic 6 month review	√		Process	Prevalence only

13071	66AI.00	Diabetic - good control	√	Process	Prevalence only
2378	66AJ.00	Diabetic - poor control	√	Process	Prevalence only
22023	66AJz00	Diabetic - poor control NOS	√	Process	Prevalence only
43951	66AK.00	Diabetic - cooperative patient	√	Process	Prevalence only
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion	√	Process	Prevalence only
17869	66AL.00	Diabetic-uncooperative patient	√	Process	Prevalence only
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion	√	Process	Prevalence only
17886	66AM.00	Diabetic - follow-up default	√	Process	Prevalence only
85660	66An.00	Diabetes type 1 review	√	Process	Prevalence only
83532	66Ao.00	Diabetes type 2 review	√	Process	Prevalence only
12506	66AP.00	Diabetes: practice programme	√	Process	Prevalence only
95994	66Aq.00	Diabetic foot screen	√	Process	Prevalence only
12675	66AQ.00	Diabetes: shared care programme	√	Process	Prevalence only
8836	66AR.00	Diabetes management plan given	√	Process	Prevalence only
6125	66AS.00	Diabetic annual review	√	Process	Prevalence only
101728	66As.00	Diabetic on subcutaneous treatment	√	Process	Prevalence only
101177	66At.00	Diabetic dietary review	√	Process	Prevalence only
12307	66AU.00	Diabetes care by hospital only	√	Process	Prevalence only
102434	66Au.00	Diabetic erectile dysfunction review	√	Process	Prevalence only
102490	66Av.00	Diabetic assessment of erectile dysfunction	√	Process	Prevalence only
28769	66AV.00	Diabetic on insulin and oral treatment	√	Process	Prevalence only
50175	66AW.00	Diabetic foot risk assessment	√	Process	Prevalence only
46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet	√	Process	Prevalence only
26604	66AY.00	Diabetic diet - good compliance	√	Process	Prevalence only
13067	66AZ.00	Diabetic monitoring NOS	√	Process	Prevalence only
18311	68A7.00	Diabetic retinopathy screening	√	Process	Prevalence only
19739	68A9.00	Diabetic retinopathy screening offered	√	Process	Prevalence only
61021	68AB.00	Diabetic digital retinopathy screening offered	√	Process	Prevalence only
47341	8A12.00	Diabetic crisis monitoring	√	Process	Prevalence only

24363	8A13.00	Diabetic stabilisation	√	Process	Prevalence only
11471	8B3l.00	Diabetes medication review	√	Process	Prevalence only
18066	8CE0.00	Diabetic leaflet given	√	Process	Prevalence only
105585	8CMW700	Diabetes clinical pathway	√	Process	Prevalence only
63412	8CR2.00	Diabetes clinical management plan	√	Process	Prevalence only
47032	8CS0.00	Diabetes care plan agreed	√	Process	Prevalence only
11018	8HBG.00	Diabetic retinopathy 12 month review	√	Process	Prevalence only
18662	8HBH.00	Diabetic retinopathy 6 month review	√	Process	Prevalence only
61557	8HKE.00	Diabetology D.V. requested	√	Process	Prevalence only
47370	8HLE.00	Diabetology D.V. done	√	Process	Prevalence only
18824	8I3W.00	Diabetic foot examination declined	√	Process	Prevalence only
12262	8I3X.00	Diabetic retinopathy screening refused	√	Process	Prevalence only
101456	8IAs.00	Diabetic dietary review declined	√	Process	Prevalence only
103743	8IE2.00	Diabetes care plan declined	√	Process	Prevalence only
103798	9b92000	Diabetic medicine	√	Process	Prevalence only
106269	9m0..00	Diabetic retinopathy screening administrative status	√	Process	Prevalence only
9897	9OL..00	Diabetes monitoring admin.	√	Process	Prevalence only
13191	9OL..11	Diabetes clinic administration	√	Process	Prevalence only
22130	9OL3.00	Diabetes monitoring default	√	Process	Prevalence only
13194	9OL4.00	Diabetes monitoring 1st letter	√	Process	Prevalence only
13195	9OL5.00	Diabetes monitoring 2nd letter	√	Process	Prevalence only
12030	9OL6.00	Diabetes monitoring 3rd letter	√	Process	Prevalence only
31240	9OL7.00	Diabetes monitor.verbal invite	√	Process	Prevalence only
31141	9OL8.00	Diabetes monitor.phone invite	√	Process	Prevalence only
20900	9OLA.11	Diabetes monitored	√	Process	Prevalence only
35383	9OLD.00	Diabetic patient unsuitable for digital retinal photography	√	Process	Prevalence only
94186	9OLF.00	Diabetes structured education programme completed	√	Process	Prevalence only
93854	9OLM.00	Diabetes structured education programme declined	√	Process	Prevalence only
101455	9OLN.00	Diabetes monitor invitation by SMS (short message service)	√	Process	Prevalence only

31241	9OLZ.00	Diabetes monitoring admin.NOS	√	Process	Prevalence only
94647	9Oy..00	Diabetes screening administration	√	Process	Prevalence only
95124	9Oy0.00	Diabetes screening invitation	√	Process	Prevalence only
38986	C100.00	Diabetes mellitus with no mention of complication	√	Diagnostic	Index
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication	√	Diagnostic	Index
1038	C100011	Insulin dependent diabetes mellitus	√	Diagnostic	Index
14803	C100100	Diabetes mellitus, adult onset, no mention of complication	√	Diagnostic	Index
14889	C100111	Maturity onset diabetes	√	Diagnostic	Index
506	C100112	Non-insulin dependent diabetes mellitus	√	Diagnostic	Index
50972	C100z00	Diabetes mellitus NOS with no mention of complication	√	Diagnostic	Index
1682	C101.00	Diabetes mellitus with ketoacidosis	√	Diagnostic	Index
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis	√	Diagnostic	Index
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis	√	Diagnostic	Index
38617	C101y00	Other specified diabetes mellitus with ketoacidosis	√	Diagnostic	Index
42505	C101z00	Diabetes mellitus NOS with ketoacidosis	√	Diagnostic	Index
21482	C102.00	Diabetes mellitus with hyperosmolar coma	√	Diagnostic	Index
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma	√	Diagnostic	Index
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma	√	Diagnostic	Index
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma	√	Diagnostic	Index
15690	C103.00	Diabetes mellitus with ketoacidotic coma	√	Diagnostic	Index
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma	√	Diagnostic	Index
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma	√	Diagnostic	Index
59288	C103y00	Other specified diabetes mellitus with coma	√	Diagnostic	Index
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma	√	Diagnostic	Index
16502	C104.00	Diabetes mellitus with renal manifestation	√	Diagnostic	Index
2475	C104.11	Diabetic nephropathy	√	Diagnostic	Index
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation	√	Diagnostic	Index
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation	√	Diagnostic	Index
13279	C104y00	Other specified diabetes mellitus with renal complications	√	Diagnostic	Index

35107	C104z00	Diabetes mellitus with nephropathy NOS	√	Diagnostic	Index
33254	C105.00	Diabetes mellitus with ophthalmic manifestation	√	Diagnostic	Index
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation	√	Diagnostic	Index
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation	√	Diagnostic	Index
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn	√	Diagnostic	Index
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation	√	Diagnostic	Index
16230	C106.00	Diabetes mellitus with neurological manifestation	√	Diagnostic	Index
59903	C106.11	Diabetic amyotrophy	√	Diagnostic	Index
7795	C106.12	Diabetes mellitus with neuropathy	√	Diagnostic	Index
16491	C106.13	Diabetes mellitus with polyneuropathy	√	Diagnostic	Index
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation	√	Diagnostic	Index
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation	√	Diagnostic	Index
61523	C106y00	Other specified diabetes mellitus with neurological comps	√	Diagnostic	Index
22573	C106z00	Diabetes mellitus NOS with neurological manifestation	√	Diagnostic	Index
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder	√	Diagnostic	Index
32403	C107.11	Diabetes mellitus with gangrene	√	Diagnostic	Index
32556	C107.12	Diabetes with gangrene	√	Diagnostic	Index
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder	√	Diagnostic	Index
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder	√	Diagnostic	Index
33807	C107200	Diabetes mellitus, adult with gangrene	√	Diagnostic	Index
69124	C107300	IDDM with peripheral circulatory disorder	√	Diagnostic	Index
56803	C107400	NIDDM with peripheral circulatory disorder	√	Diagnostic	Index
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder	√	Diagnostic	Index
1647	C108.00	Insulin dependent diabetes mellitus	√	Diagnostic	Index
18505	C108.11	IDDM-Insulin dependent diabetes mellitus	√	Diagnostic	Index
17858	C108.12	Type 1 diabetes mellitus	√	Diagnostic	Index
24423	C108.13	Type I diabetes mellitus	√	Diagnostic	Index
46963	C108000	Insulin-dependent diabetes mellitus with renal complications	√	Diagnostic	Index
61344	C108011	Type I diabetes mellitus with renal complications	√	Diagnostic	Index

21983	C108012	Type 1 diabetes mellitus with renal complications	√	Diagnostic	Index
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps	√	Diagnostic	Index
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications	√	Diagnostic	Index
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps	√	Diagnostic	Index
49146	C108211	Type I diabetes mellitus with neurological complications	√	Diagnostic	Index
61829	C108212	Type 1 diabetes mellitus with neurological complications	√	Diagnostic	Index
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn	√	Diagnostic	Index
26855	C108400	Unstable insulin dependent diabetes mellitus	√	Diagnostic	Index
60107	C108411	Unstable type I diabetes mellitus	√	Diagnostic	Index
97474	C108412	Unstable type 1 diabetes mellitus	√	Diagnostic	Index
44443	C108500	Insulin dependent diabetes mellitus with ulcer	√	Diagnostic	Index
51957	C108511	Type I diabetes mellitus with ulcer	√	Diagnostic	Index
68390	C108512	Type 1 diabetes mellitus with ulcer	√	Diagnostic	Index
60499	C108600	Insulin dependent diabetes mellitus with gangrene	√	Diagnostic	Index
6509	C108700	Insulin dependent diabetes mellitus with retinopathy	√	Diagnostic	Index
38161	C108711	Type I diabetes mellitus with retinopathy	√	Diagnostic	Index
41049	C108712	Type 1 diabetes mellitus with retinopathy	√	Diagnostic	Index
6791	C108800	Insulin dependent diabetes mellitus - poor control	√	Diagnostic	Index
46850	C108811	Type I diabetes mellitus - poor control	√	Diagnostic	Index
45914	C108812	Type 1 diabetes mellitus - poor control	√	Diagnostic	Index
31310	C108900	Insulin dependent diabetes maturity onset	√	Diagnostic	Index
63017	C108911	Type I diabetes mellitus maturity onset	√	Diagnostic	Index
97446	C108912	Type 1 diabetes mellitus maturity onset	√	Diagnostic	Index
56448	C108A00	Insulin-dependent diabetes without complication	√	Diagnostic	Index
95992	C108A11	Type I diabetes mellitus without complication	√	Diagnostic	Index
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy	√	Diagnostic	Index
99231	C108B11	Type I diabetes mellitus with mononeuropathy	√	Diagnostic	Index
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy	√	Diagnostic	Index
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy	√	Diagnostic	Index

66872	C108D11	Type I diabetes mellitus with nephropathy	√	Diagnostic	Index
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma	√	Diagnostic	Index
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma	√	Diagnostic	Index
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma	√	Diagnostic	Index
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract	√	Diagnostic	Index
17545	C108F11	Type I diabetes mellitus with diabetic cataract	√	Diagnostic	Index
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy	√	Diagnostic	Index
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy	√	Diagnostic	Index
62352	C108H11	Type I diabetes mellitus with arthropathy	√	Diagnostic	Index
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy	√	Diagnostic	Index
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy	√	Diagnostic	Index
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy	√	Diagnostic	Index
46290	C108y00	Other specified diabetes mellitus with multiple comps	√	Diagnostic	Index
64449	C108z00	Unspecified diabetes mellitus with multiple complications	√	Diagnostic	Index
4513	C109.00	Non-insulin dependent diabetes mellitus	√	Diagnostic	Index
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus	√	Diagnostic	Index
17859	C109.12	Type 2 diabetes mellitus	√	Diagnostic	Index
18219	C109.13	Type II diabetes mellitus	√	Diagnostic	Index
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps	√	Diagnostic	Index
50225	C109011	Type II diabetes mellitus with renal complications	√	Diagnostic	Index
18209	C109012	Type 2 diabetes mellitus with renal complications	√	Diagnostic	Index
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps	√	Diagnostic	Index
59725	C109111	Type II diabetes mellitus with ophthalmic complications	√	Diagnostic	Index
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications	√	Diagnostic	Index
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps	√	Diagnostic	Index
67905	C109211	Type II diabetes mellitus with neurological complications	√	Diagnostic	Index
45919	C109212	Type 2 diabetes mellitus with neurological complications	√	Diagnostic	Index
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps	√	Diagnostic	Index
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer	√	Diagnostic	Index

55075	C109411	Type II diabetes mellitus with ulcer	√	Diagnostic	Index
65704	C109412	Type 2 diabetes mellitus with ulcer	√	Diagnostic	Index
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene	√	Diagnostic	Index
62107	C109511	Type II diabetes mellitus with gangrene	√	Diagnostic	Index
46150	C109512	Type 2 diabetes mellitus with gangrene	√	Diagnostic	Index
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy	√	Diagnostic	Index
58604	C109611	Type II diabetes mellitus with retinopathy	√	Diagnostic	Index
42762	C109612	Type 2 diabetes mellitus with retinopathy	√	Diagnostic	Index
8403	C109700	Non-insulin dependent diabetes mellitus - poor control	√	Diagnostic	Index
24458	C109711	Type II diabetes mellitus - poor control	√	Diagnostic	Index
45913	C109712	Type 2 diabetes mellitus - poor control	√	Diagnostic	Index
29979	C109900	Non-insulin-dependent diabetes mellitus without complication	√	Diagnostic	Index
105784	C109912	Type 2 diabetes mellitus without complication	√	Diagnostic	Index
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy	√	Diagnostic	Index
50813	C109A11	Type II diabetes mellitus with mononeuropathy	√	Diagnostic	Index
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy	√	Diagnostic	Index
47409	C109B11	Type II diabetes mellitus with polyneuropathy	√	Diagnostic	Index
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy	√	Diagnostic	Index
64571	C109C11	Type II diabetes mellitus with nephropathy	√	Diagnostic	Index
24836	C109C12	Type 2 diabetes mellitus with nephropathy	√	Diagnostic	Index
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma	√	Diagnostic	Index
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma	√	Diagnostic	Index
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma	√	Diagnostic	Index
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract	√	Diagnostic	Index
48192	C109E11	Type II diabetes mellitus with diabetic cataract	√	Diagnostic	Index
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract	√	Diagnostic	Index
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath	√	Diagnostic	Index
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy	√	Diagnostic	Index
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy	√	Diagnostic	Index

24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy	√	Diagnostic	Index
18143	C109G11	Type II diabetes mellitus with arthropathy	√	Diagnostic	Index
49869	C109G12	Type 2 diabetes mellitus with arthropathy	√	Diagnostic	Index
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy	√	Diagnostic	Index
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy	√	Diagnostic	Index
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy	√	Diagnostic	Index
52236	C10A.00	Malnutrition-related diabetes mellitus	√	Diagnostic	Index
66675	C10A000	Malnutrition-related diabetes mellitus with coma	√	Diagnostic	Index
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis	√	Diagnostic	Index
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn	√	Diagnostic	Index
11551	C10B.00	Diabetes mellitus induced by steroids	√	Diagnostic	Index
26108	C10B000	Steroid induced diabetes mellitus without complication	√	Diagnostic	Index
37957	C10K.00	Type A insulin resistance	√	Diagnostic	Index
56885	C10K000	Type A insulin resistance without complication	√	Diagnostic	Index
107603	C10P.00		√	Diagnostic	Index
33343	C10y.00	Diabetes mellitus with other specified manifestation	√	Diagnostic	Index
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation	√	Diagnostic	Index
10098	C10yy00	Other specified diabetes mellitus with other spec comps	√	Diagnostic	Index
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation	√	Diagnostic	Index
45491	C10z.00	Diabetes mellitus with unspecified complication	√	Diagnostic	Index
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication	√	Diagnostic	Index
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication	√	Diagnostic	Index
64283	C10zy00	Other specified diabetes mellitus with unspecified comps	√	Diagnostic	Index
64357	C10zz00	Diabetes mellitus NOS with unspecified complication	√	Diagnostic	Index
44033	F345000	Diabetic mononeuritis multiplex	√	Diagnostic	Index
17247	F35z000	Diabetic mononeuritis NOS	√	Diagnostic	Index
5002	F372.11	Diabetic polyneuropathy	√	Diagnostic	Index
2342	F372.12	Diabetic neuropathy	√	Diagnostic	Index
2340	F381311	Diabetic amyotrophy	√	Diagnostic	Index

37315	F3y0.00	Diabetic mononeuropathy	√	Diagnostic	Index
1323	F420.00	Diabetic retinopathy	√	Diagnostic	Index
3837	F420400	Diabetic maculopathy	√	Diagnostic	Index
11626	F420z00	Diabetic retinopathy NOS	√	Diagnostic	Index
17313	F440700	Diabetic iritis	√	Diagnostic	Index
10659	F464000	Diabetic cataract	√	Diagnostic	Index
34152	G73y000	Diabetic peripheral angiopathy	√	Diagnostic	Index
18142	N030000	Diabetic cheiroarthropathy	√	Diagnostic	Index
57333	N030011	Diabetic cheiropathy	√	Diagnostic	Index
27891	N030100	Diabetic Charcot arthropathy	√	Diagnostic	Index
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire	√		Prevalence only
94699	ZRB5.00	Diabetes treatment satisfaction questionnaire	√		Prevalence only
38130	ZRB6.00	Diabetes wellbeing questionnaire	√		Prevalence only
608.00	66A2.00	Follow-up diabetic assessment	√	PROCESS	Prevalence only
2379.00	9N1Q.00	Seen in diabetic clinic	√	PROCESS	Prevalence only
2471.00	K01x100	Nephrotic syndrome in diabetes mellitus	√	Diagnostic	Index
2478.00	66AJ100	Brittle diabetes	√	PROCESS	Prevalence only
2986.00	F420200	Preproliferative diabetic retinopathy	√	Diagnostic	Index
3286.00	F420100	Proliferative diabetic retinopathy	√	Diagnostic	Index
6430.00	9NM0.00	Attending diabetes clinic	√	PROCESS	Prevalence only
6813.00	1434.00	H/O: diabetes mellitus	√	PROCESS	Prevalence only
7045.00	14F4.00	H/O: Admission in last year for diabetes foot problem	√	PROCESS	Prevalence only
7059.00	8H2J.00	Admit diabetic emergency	√	PROCESS	Index
7069.00	F420000	Background diabetic retinopathy	√	Diagnostic	Index
7328.00	M037200	Cellulitis in diabetic foot	√	Diagnostic	Index
7777.00	8H4F.00	Referral to diabetologist	√	PROCESS	Prevalence only
8306.00	8H7f.00	Referral to diabetes nurse	√	PROCESS	Prevalence only
8414.00	8CA4100	Pt advised re diabetic diet	√	PROCESS	Prevalence only
8618.00	ZLA2500	Seen by diabetic liaison nurse	√	Diagnostic	Prevalence only

9013.00	66AJ.11	Unstable diabetes	√	PROCESS	Prevalence only
9145.00	9N4I.00	DNA - Did not attend diabetic clinic	√	PROCESS	Prevalence only
9835.00	2BBL.00	O/E - diabetic maculopathy present both eyes	√	PROCESS	Prevalence only
9881.00	M271200	Mixed diabetic ulcer - foot	√	Diagnostic	Index
9958.00	42W..00	Hb. A1C - diabetic control	√	PROCESS	Prevalence only
9974.00	9N1v.00	Seen in diabetic eye clinic	√	PROCESS	Prevalence only
10099.00	F420300	Advanced diabetic maculopathy	√	Diagnostic	Index
10642.00	ZC2C800	Dietary advice for diabetes mellitus	√	Diagnostic	Prevalence only
10755.00	F420600	Non proliferative diabetic retinopathy	√	Diagnostic	Index
10824.00	9N1i.00	Seen in diabetic foot clinic	√	PROCESS	Prevalence only
11094.00	9NND.00	Under care of diabetic foot screener	√	PROCESS	Prevalence only
11129.00	2BBQ.00	O/E - left eye background diabetic retinopathy	√	PROCESS	Prevalence only
11433.00	2BBP.00	O/E - right eye background diabetic retinopathy	√	PROCESS	Prevalence only
11599.00	7276.00	Pan retinal photocoagulation for diabetes	√	PROCESS	Index
11663.00	M271100	Neuropathic diabetic ulcer - foot	√	Diagnostic	Index
11677.00	8H7r.00	Refer to diabetic foot screener	√	PROCESS	Prevalence only
11930.00	9NN9.00	Under care of diabetes specialist nurse	√	PROCESS	Prevalence only
11977.00	ZL62500	Referral to diabetes nurse	√	Diagnostic	Prevalence only
12213.00	8BL2.00	Patient on maximal tolerated therapy for diabetes	√	PROCESS	Prevalence only
12225.00	8H7C.00	Refer, diabetic liaison nurse	√	PROCESS	Prevalence only
12507.00	9N2i.00	Seen by diabetic liaison nurse	√	PROCESS	Prevalence only
12682.00	679R.00	Patient offered diabetes structured education programme	√	PROCESS	Prevalence only
12703.00	3881.00	Education score - diabetes	√	PROCESS	Prevalence only
13057.00	679L.00	Health education - diabetes	√	PROCESS	Prevalence only
13069.00	66A8.00	Has seen dietician - diabetes	√	PROCESS	Prevalence only
13097.00	2BBT.00	O/E - right eye proliferative diabetic retinopathy	√	PROCESS	Prevalence only
13099.00	2BBR.00	O/E - right eye preproliferative diabetic retinopathy	√	PROCESS	Prevalence only
13101.00	2BBV.00	O/E - left eye proliferative diabetic retinopathy	√	PROCESS	Prevalence only
13102.00	2BBW.00	O/E - right eye diabetic maculopathy	√	PROCESS	Prevalence only

13103.00	2BBS.00	O/E - left eye preproliferative diabetic retinopathy	√	PROCESS	Prevalence only
13108.00	2BBX.00	O/E - left eye diabetic maculopathy	√	PROCESS	Prevalence only
13197.00	9OL1.00	Attends diabetes monitoring	√	PROCESS	Prevalence only
13678.00	ZL62600	Referral to diabetic liaison nurse	√	Diagnostic	Prevalence only
16881.00	ZV65312	[V]Dietary counselling in diabetes mellitus	√	Diagnostic	Prevalence only
17067.00	F171100	Autonomic neuropathy due to diabetes	√	Diagnostic	Index
17095.00	2G5A.00	O/E - Right diabetic foot at risk	√	PROCESS	Prevalence only
18056.00	2G5C.00	Foot abnormality - diabetes related	√	PROCESS	Prevalence only
19381.00	8HTk.00	Referral to diabetic eye clinic	√	PROCESS	Prevalence only
20696.00	66AA.11	Injection sites - diabetic	√	PROCESS	Prevalence only
22967.00	2BBF.00	Retinal abnormality - diabetes related	√	PROCESS	Prevalence only
23479.00	C350011	Bronzed diabetes	√	Diagnostic	Index
24327.00	M271000	Ischaemic ulcer diabetic foot	√	Diagnostic	Index
24571.00	F372200	Asymptomatic diabetic neuropathy	√	Diagnostic	Index
25041.00	ZC2CA00	Dietary advice for type II diabetes	√	Diagnostic	Prevalence only
26605.00	9OLB.00	Attended diabetes structured education programme	√	PROCESS	Prevalence only
26664.00	2G5B.00	O/E - Left diabetic foot at risk	√	PROCESS	Prevalence only
26666.00	2G5E.00	O/E - Right diabetic foot at low risk	√	PROCESS	Prevalence only
26667.00	2G5I.00	O/E - Left diabetic foot at low risk	√	PROCESS	Prevalence only
27921.00	2G51000	Foot abnormality - diabetes related	√	PROCESS	Prevalence only
28856.00	8CP2.00	Transition of diabetes care options discussed	√	PROCESS	Prevalence only
29041.00	66AN.00	Date diabetic treatment start	√	PROCESS	Prevalence only
30477.00	F420700	High risk proliferative diabetic retinopathy	√	Diagnostic	Index
30648.00	9N4p.00	Did not attend diabetic retinopathy clinic	√	PROCESS	Prevalence only
31053.00	R054300	[D]Widespread diabetic foot gangrene	√	Diagnostic	Index
31156.00	2G5J.00	O/E - Left diabetic foot at moderate risk	√	PROCESS	Prevalence only
31157.00	2G5F.00	O/E - Right diabetic foot at moderate risk	√	PROCESS	Prevalence only
31171.00	2G5G.00	O/E - Right diabetic foot at high risk	√	PROCESS	Prevalence only
31172.00	2G5K.00	O/E - Left diabetic foot at high risk	√	PROCESS	Prevalence only

31790.00	F372.00	Polyneuropathy in diabetes	√	Diagnostic	Index
32359.00	ZRbH.00	Perceived control of insulin-dependent diabetes	√	Diagnostic	Index
32619.00	66Af.00	Patient diabetes education review	√	PROCESS	Prevalence only
32739.00	9N0n.00	Seen in community diabetes specialist clinic	√	PROCESS	Prevalence only
35116.00	2G5L.00	O/E - Left diabetic foot - ulcerated	√	PROCESS	Prevalence only
35316.00	2G5H.00	O/E - Right diabetic foot - ulcerated	√	PROCESS	Prevalence only
35321.00	8H3O.00	Non-urgent diabetic admission	√	PROCESS	Index
35785.00	F372100	Chronic painful diabetic neuropathy	√	Diagnostic	Index
38103.00	9N0m.00	Seen in diabetic nurse consultant clinic	√	PROCESS	Prevalence only
38129.00	9N0o.00	Seen in community diabetic specialist nurse clinic	√	PROCESS	Prevalence only
39420.00	F381300	Myasthenic syndrome due to diabetic amyotrophy	√	Diagnostic	Index
41686.00	Cyu2000	[X]Other specified diabetes mellitus	√	Diagnostic	Index
45250.00	ZL22500	Under care of diabetic liaison nurse	√	Diagnostic	Index
47011.00	8Hj0.00	Referral to diabetes structured education programme	√	PROCESS	Prevalence only
47058.00	8Hg4.00	Discharged from care of diabetes specialist nurse	√	PROCESS	Prevalence only
47328.00	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy	√	PROCESS	Prevalence only
47584.00	F420500	Advanced diabetic retinal disease	√	Diagnostic	Index
48078.00	F372000	Acute painful diabetic neuropathy	√	Diagnostic	Index
49640.00	2G5W.00	O/E - left chronic diabetic foot ulcer	√	PROCESS	Prevalence only
50609.00	L180600	Pre-existing diabetes mellitus, non-insulin-dependent	√	Diagnostic	Index
50937.00	8HTe.00	Referral to diabetes preconception counselling clinic	√	PROCESS	Prevalence only
50960.00	L180500	Pre-existing diabetes mellitus, insulin-dependent	√	Diagnostic	Index
52041.00	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy	√	PROCESS	Prevalence only
52212.00	Cyu2.00	[X]Diabetes mellitus	√	Diagnostic	Index
52237.00	9360.00	Patient held diabetic record issued	√	PROCESS	Prevalence only
52630.00	2BBo.00	O/E - sight threatening diabetic retinopathy	√	PROCESS	Prevalence only
53634.00	R054200	[D]Gangrene of toe in diabetic	√	Diagnostic	Index
55431.00	L180X00	Pre-existing diabetes mellitus, unspecified	√	Diagnostic	Index
57389.00	93C4.00	Patient consent given for addition to diabetic register	√	PROCESS	Prevalence only

57723.00	8HHy.00	Referral to diabetic register	√	PROCESS	Prevalence only
58639.00	8I57.00	Patient held diabetic record declined	√	PROCESS	Prevalence only
61210.00	TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS	√	Diagnostic	Index
61461.00	9M00.00	Informed consent for diabetes national audit	√	PROCESS	Prevalence only
62384.00	2G5V.00	O/E - right chronic diabetic foot ulcer	√	PROCESS	Prevalence only
65463.00	F420800	High risk non proliferative diabetic retinopathy	√	Diagnostic	Index
65684.00	U602311	[X] Adverse reaction to insulins and antidiabetic agents	√	Diagnostic	Index
67664.00	ZRBa.00	Education score - diabetes	√	Diagnostic	Prevalence only
68714.00	SL23.00	Insulins and antidiabetic poisoning	√	Diagnostic	Index
68818.00	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire	√	Diagnostic	Prevalence only
68928.00	TJ23.00	Adverse reaction to insulins and antidiabetic agents	√	Diagnostic	Index
69043.00	ZC2C900	Dietary advice for type I diabetes	√	Diagnostic	Prevalence only
69163.00	8HTi.00	Referral to multidisciplinary diabetic clinic	√	PROCESS	Prevalence only
72333.00	8HME.00	Listed for Diabetology admissn	√	PROCESS	Prevalence only
82474.00	8Hl4.00	Referral to community diabetes specialist nurse	√	PROCESS	Prevalence only
93390.00	9OLH.00	Attended DAFNE diabetes structured education programme	√	PROCESS	Prevalence only
93491.00	9OLJ.00	DAFNE diabetes structured education programme completed	√	PROCESS	Prevalence only
93529.00	9OLK.00	DESMOND diabetes structured education programme completed	√	PROCESS	Prevalence only
93631.00	9OLL.00	XPERT diabetes structured education programme completed	√	PROCESS	Prevalence only
93657.00	8Hj4.00	Referral to DESMOND diabetes structured education programme	√	PROCESS	Prevalence only
93704.00	8Hj3.00	Referral to DAFNE diabetes structured education programme	√	PROCESS	Prevalence only
93870.00	8Hj5.00	Referral to XPERT diabetes structured education programme	√	PROCESS	Prevalence only
94011.00	9OLG.00	Attended XPERT diabetes structured education programme	√	PROCESS	Prevalence only
94330.00	8H4e.00	Referral to diabetes special interest general practitioner	√	PROCESS	Prevalence only
94955.00	9NiE.00	Did not attend XPERT diabetes structured education programme	√	PROCESS	Prevalence only
94956.00	8I84.00	Did not complete XPERT diabetes structured education program	√	PROCESS	Prevalence only
95093.00	8I83.00	Did not complete DESMOND diabetes structured educat program	√	PROCESS	Prevalence only
95094.00	8I81.00	Did not complete diabetes structured education programme	√	PROCESS	Prevalence only
95159.00	9NiD.00	Did not attend DESMOND diabetes structured education program	√	PROCESS	Prevalence only

95553.00	9NiA.00	Did not attend diabetes structured education programme	√	PROCESS	Prevalence only
95813.00	9N1o.00	Seen in multidisciplinary diabetic clinic	√	PROCESS	Prevalence only
97281.00	9Nl4.00	Seen by general practitioner special interest in diabetes	√	PROCESS	Prevalence only
97809.00	8I82.00	Did not complete DAFNE diabetes structured education program	√	PROCESS	Prevalence only
97824.00	ZRB6.11	DWBQ - Diabetes wellbeing questionnaire	√	Diagnostic	Prevalence only
99277.00	9NiC.00	Did not attend DAFNE diabetes structured education programme	√	PROCESS	Prevalence only
99628.00	Kyu0300	[X]Glomerular disorders in diabetes mellitus	√	Diagnostic	Index
100033.00	U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS	√	Diagnostic	Index
100292.00	Cyu2300	[X]Unspecified diabetes mellitus with renal complications	√	Diagnostic	Index
100422.00	8HgC.00	Discharged from diabetes shared care programme	√	PROCESS	Prevalence only
100436.00	679L000	Education in self management of diabetes	√	PROCESS	Prevalence only
101190.00	66AQ100	Declined consent for diabetes year of care programme	√	PROCESS	Prevalence only
101801.00	66At100	Type II diabetic dietary review	√	PROCESS	Prevalence only
101881.00	2BBr.00	Impaired vision due to diabetic retinopathy	√	PROCESS	Prevalence only
102435.00	8CE0000	Gestational diabetes information leaflet given	√	PROCESS	Prevalence only
102611.00	66At111	Type 2 diabetic dietary review	√	PROCESS	Prevalence only
102704.00	66At000	Type I diabetic dietary review	√	PROCESS	Prevalence only
102767.00	67IJ100	Pre-conception advice for diabetes mellitus	√	PROCESS	Prevalence only
102768.00	9NiZ.00	Did not attend diabetes foot screening	√	PROCESS	Prevalence only
104287.00	8Hlc.00	Referral to community diabetes service	√	PROCESS	Prevalence only
104374.00	67D8.00	Provision of diabetes clinical summary	√	PROCESS	Prevalence only
104453.00	66At011	Type 1 diabetic dietary review	√	PROCESS	Prevalence only
104588.00	66Ay.00	Gestational diabetes mellitus annual review	√	PROCESS	Prevalence only
105207.00	8HTE100	Referral to community diabetes clinic	√	PROCESS	Prevalence only
105302.00	K08yA00	Proteinuric diabetic nephropathy	√	Diagnostic	Index
105740.00	2G5d.00	O/E - Left diabetic foot at increased risk	√	PROCESS	Prevalence only
105741.00	2G5e.00	O/E - Right diabetic foot at increased risk	√	PROCESS	Prevalence only
105937.00	8IEQ.00	Referral to community diabetes specialist nurse declined	√	PROCESS	Prevalence only
106218.00	9m0A.00	Declined diabetic retinopathy screening	√	PROCESS	Prevalence only

106328.00	9m07.00	Excluded diabetc retinop screen as under care ophthalmolgist	√	PROCESS	Prevalence only
106329.00	9m08.00	Excluded from diabetic retinopathy screening as blind	√	PROCESS	Prevalence only
106332.00	9m00.00	Eligible for diabetic retinopathy screening	√	PROCESS	Prevalence only
106350.00	9m05.00	Excluded from diabetic retinopathy screening as moved away	√	PROCESS	Prevalence only
106445.00	9m0E.00	Excluded from diabetic retinopathy screen physical disorder	√	PROCESS	Prevalence only
106778.00	9m0C.00	Excluded frm diabetic retinopathy screen as terminal illness	√	PROCESS	Prevalence only
107597.00	9m0D.00	Excluded from diabetic retinopthy screen as learn disability	√	PROCESS	Prevalence only

E12 Chronic Kidney Disease Code set

			Validation		Code type	
CPRD Medcode	**Read code**	**Read term**	**Previous studies**	**Qof listed**	**Read code type**	**Study code type**
49028	14S2.00	H/O: kidney recipient	√		Process	Prevalence
12720.00	1Z1..00	Chronic renal impairment	√		Process	Prevalence
29013.00	1Z10.00	Chronic kidney disease stage 1	√		Process	Prevalence
12586.00	1Z11.00	Chronic kidney disease stage 2	√		Process	Prevalence
12566.00	1Z12.00	Chronic kidney disease stage 3	√	√	Process	Prevalence
12479.00	1Z13.00	Chronic kidney disease stage 4	√	√	Process	Prevalence
12585.00	1Z14.00	Chronic kidney disease stage 5	√	√	Process	Prevalence
94965.00	1Z15.00	Chronic kidney disease stage 3A	√	√	Process	Prevalence
95179.00	1Z16.00	Chronic kidney disease stage 3B	√	√	Process	Prevalence
94789.00	1Z17.00	Chronic kidney disease stage 1 with proteinuria	√		Process	Prevalence
97980.00	1Z17.11	CKD stage 1 with proteinuria	√		Process	Prevalence
95572.00	1Z18.00	Chronic kidney disease stage 1 without proteinuria	√		Process	Prevalence
95146.00	1Z19.00	Chronic kidney disease stage 2 with proteinuria	√		Process	Prevalence
97979.00	1Z19.11	CKD stage 2 with proteinuria	√		Process	Prevalence
95121.00	1Z1A.00	Chronic kidney disease stage 2 without proteinuria	√		Process	Prevalence
97978.00	1Z1A.11	CKD stage 2 without proteinuria	√		Process	Prevalence
94793.00	1Z1B.00	Chronic kidney disease stage 3 with proteinuria	√	√	Process	Prevalence
95145.00	1Z1B.11	CKD stage 3 with proteinuria	√	√	Process	Prevalence
95123.00	1Z1C.00	Chronic kidney disease stage 3 without proteinuria	√	√	Process	Prevalence
95188.00	1Z1C.11	CKD stage 3 without proteinuria	√	√	Process	Prevalence
95408.00	1Z1D.00	Chronic kidney disease stage 3A with proteinuria	√	√	Process	Prevalence
95571.00	1Z1D.11	CKD stage 3A with proteinuria	√	√	Process	Prevalence
95175.00	1Z1E.00	Chronic kidney disease stage 3A without proteinuria	√	√	Process	Prevalence
95176.00	1Z1E.11	CKD stage 3A without proteinuria	√	√	Process	Prevalence
95178.00	1Z1F.00	Chronic kidney disease stage 3B with proteinuria	√	√	Process	Prevalence

95180.00	1Z1F.11	CKD stage 3B with proteinuria	√	√	Process	Prevalence
95177.00	1Z1G.00	Chronic kidney disease stage 3B without proteinuria	√	√	Process	Prevalence
100633.00	1Z1G.11	CKD stage 3B without proteinuria	√	√	Process	Prevalence
95122.00	1Z1H.00	Chronic kidney disease stage 4 with proteinuria	√	√	Process	Prevalence
99312.00	1Z1H.11	CKD stage 4 with proteinuria	√	√	Process	Prevalence
95406.00	1Z1J.00	Chronic kidney disease stage 4 without proteinuria	√	√	Process	Prevalence
97587.00	1Z1J.11	CKD stage 4 without proteinuria	√	√	Process	Prevalence
95508.00	1Z1K.00	Chronic kidney disease stage 5 with proteinuria	√	√	Process	Prevalence
99160.00	1Z1K.11	CKD stage 5 with proteinuria	√	√	Process	Prevalence
95405.00	1Z1L.00	Chronic kidney disease stage 5 without proteinuria	√	√	Process	Prevalence
97683.00	1Z1L.11	CKD stage 5 without proteinuria	√	√	Process	Prevalence
19473	66i..00	Chronic kidney disease monitoring	√		Process	Prevalence
30735	6AA..00	Chronic kidney disease annual review	√		Process	Prevalence
2997.00	7B00.00	Transplantation of kidney	√		Process	Prevalence
11745.00	7B00100	Transplantation of kidney from live donor	√		Process	Prevalence
24361.00	7B00200	Transplantation of kidney from cadaver	√		Process	Prevalence
105328.00	7B00212	Cadaveric renal transplant	√		Process	Prevalence
5504.00	7B00z00	Transplantation of kidney NOS	√		Process	Prevalence
68574.00	7B01011	Nephrectomy and excision of perirenal tissue	√		Process	Prevalence
1600.00	7B01100	Nephroureterectomy-unspecified	√		Process	Prevalence
34834.00	7B01300	Heminephrectomy for horseshoe kidney	√		Process	Prevalence
35225.00	7B01700	Nephroureterectomy with open lower ureterectomy	√		Process	Prevalence
49535.00	7B01800	Nephroureterectomy with pluck lower ureterectomy	√		Process	Prevalence
34999.00	7B02000	Heminephrectomy for duplex kidney	√		Process	Prevalence
31346.00	7B04200	Nephropexy	√		Process	Prevalence
71271	9Ot..00	Chronic kidney disease monitoring administration	√		Process	Prevalence
30739	9Ot0.00	Chronic kidney disease monitoring first letter	√		Process	Prevalence
72962	9Ot1.00	Chronic kidney disease monitoring second letter	√		Process	Prevalence
72964	9Ot2.00	Chronic kidney disease monitoring third letter	√		Process	Prevalence

88494	9Ot3.00	Chronic kidney disease monitoring verbal invite	√	Process	Prevalence
69679	9Ot4.00	Chronic kidney disease monitoring telephone invite	√	Process	Prevalence
2475.00	C104.11	Diabetic nephropathy	√	Diagnostic	Index
46963.00	C108000	Insulin-dependent diabetes mellitus with renal complications	√	Diagnostic	Index
47582.00	C10E000	Type 1 diabetes mellitus with renal complications	√	Diagnostic	Index
12640.00	C10FC00	Type 2 diabetes mellitus with nephropathy	√	Diagnostic	Index
11848.00	C314.11	Renal diabetes	√	Diagnostic	Index
52969.00	C341.00	Gouty nephropathy	√	Diagnostic	Index
25394.00	D215000	Anaemia secondary to chronic renal failure	√	Diagnostic	Index
4668.00	G22..00	Hypertensive renal disease	√	Diagnostic	Index
17434.00	G22..11	Nephrosclerosis	√	Diagnostic	Index
39649.00	G220.00	Malignant hypertensive renal disease	√	Diagnostic	Index
43935.00	G221.00	Benign hypertensive renal disease	√	Diagnostic	Index
32423.00	G222.00	Hypertensive renal disease with renal failure	√	Diagnostic	Index
15106.00	G22z.00	Hypertensive renal disease NOS	√	Diagnostic	Index
29310.00	G22z.11	Renal hypertension	√	Diagnostic	Index
63466.00	G23..00	Hypertensive heart and renal disease	√	Diagnostic	Index
21837.00	G232.00	Hypertensive heart&renal dis wth (congestive) heart failure	√	Diagnostic	Index
28684.00	G233.00	Hypertensive heart and renal disease with renal failure	√	Diagnostic	Index
16284.00	G701.00	Renal artery atherosclerosis	√	Diagnostic	Index
20074.00	K00..12	Bright's disease	√	Diagnostic	Index
7804.00	K02..00	Chronic glomerulonephritis	√	Diagnostic	Index
10647.00	K02..11	Nephritis - chronic	√	Diagnostic	Index
11875.00	K02..12	Nephropathy - chronic	√	Diagnostic	Index
34998.00	K020.00	Chronic proliferative glomerulonephritis	√	Diagnostic	Index
10809.00	K021.00	Chronic membranous glomerulonephritis	√	Diagnostic	Index
61494.00	K022.00	Chronic membranoproliferative glomerulonephritis	√	Diagnostic	Index
4669.00	K02y200	Chronic focal glomerulonephritis	√	Diagnostic	Index
15097.00	K02z.00	Chronic glomerulonephritis NOS	√	Diagnostic	Index

33580.00	K03..00	Nephritis and nephropathy unspecified	√		Diagnostic	Index
4850.00	K03..11	Nephritis and nephropathy unspecified	√		Diagnostic	Index
11873.00	K03..12	Nephropathy, unspecified	√		Diagnostic	Index
24384.00	K032400	Familial glomerulonephritis in Alport's syndrome	√		Diagnostic	Index
21423.00	K032600	Berger's IgA or IgG nephropathy	√		Diagnostic	Index
512.00	K05..00	Chronic renal failure	√		Diagnostic	Index
10081.00	K05..11	Chronic uraemia	√		Diagnostic	Index
53852.00	K05..12	End stage renal failure	√		Diagnostic	Index
104981.00	K05..13	Chronic kidney disease	√		Diagnostic	Index
6712.00	K050.00	End stage renal failure	√		Diagnostic	Index
105392.00	K051.00	Chronic kidney disease stage 1	√		Diagnostic	Index
105383.00	K052.00	Chronic kidney disease stage 2	√		Diagnostic	Index
104619.00	K053.00	Chronic kidney disease stage 3	√	√	Diagnostic	Index
104963.00	K054.00	Chronic kidney disease stage 4	√	√	Diagnostic	Index
105151.00	K055.00	Chronic kidney disease stage 5	√	√	Diagnostic	Index
26220.00	K07..00	Renal sclerosis unspecified	√		Diagnostic	Index
2304.00	K070.00	Atrophy of kidney	√		Diagnostic	Index
22876.00	K071.00	Renal fibrosis	√		Diagnostic	Index
7190.00	K072.00	Glomerulosclerosis	√		Diagnostic	Index
4480.00	K07z.00	Renal sclerosis NOS	√		Diagnostic	Index
29638.00	K080.00	Renal osteodystrophy	√		Diagnostic	Index
34637.00	K080z00	Renal osteodystrophy NOS	√		Diagnostic	Index
105302.00	K08yA00	Proteinuric diabetic nephropathy	√		Diagnostic	Index
7154.00	K09..00	Small kidney of unknown cause	√		Diagnostic	Index
43919.00	K090.00	Unilateral small kidney	√		Diagnostic	Index
38774.00	K091.00	Bilateral small kidneys	√		Diagnostic	Index
38768.00	K09z.00	Small kidneys unspecified	√		Diagnostic	Index
85659.00	K0A2800	IgA nephropathy	√		Diagnostic	Index
21297.00	K0A3.00	Chronic nephritic syndrome	√		Diagnostic	Index

36205.00	K0A5.00	Hereditary nephropathy not elsewhere classified	√	Diagnostic	Index
45523.00	K0B..00	Renal tubulo-interstitial disorders in diseases EC	√	Diagnostic	Index
48057.00	K0B5.00	Renal tubulo-interstitial disordrs in transplant rejectn	√	Diagnostic	Index
8607.00	K0C0.00	Analgesic nephropathy	√	Diagnostic	Index
41159.00	K0C1.00	Nephropathy induced by other drugs meds and biologl substncs	√	Diagnostic	Index
8330.00	K0D..00	End-stage renal disease	√	Diagnostic	Index
4654.00	K100.00	Chronic pyelonephritis	√	Diagnostic	Index
21158.00	K100200	Chronic pyelitis	√	Diagnostic	Index
35360.00	K100400	Nonobstructive reflux-associated chronic pyelonephritis	√	Diagnostic	Index
48111.00	K100z00	Chronic pyelonephritis NOS	√	Diagnostic	Index
27417.00	K130.00	Nephroptosis	√	Diagnostic	Index
5112.00	K130.11	Floating kidney	√	Diagnostic	Index
18329.00	K131.00	Hypertrophy of kidney	√	Diagnostic	Index
104079.00	K132.11	Acquired renal cystic disease	√	Diagnostic	Index
102947.00	K13yB00	Ischaemic nephropathy	√	Diagnostic	Index
11436.00	K13z000	Non-functioning kidney	√	Diagnostic	Index
30097.00	PD0..00	Renal agenesis and dysgenesis	√	Diagnostic	Index
27474.00	PD00.00	Renal agenesis, unspecified	√	Diagnostic	Index
31961.00	PD00100	Unilateral renal agenesis	√	Diagnostic	Index
27471.00	PD01.00	Congenital renal atrophy	√	Diagnostic	Index
3314.00	PD02.00	Congenital absence of kidney	√	Diagnostic	Index
23958.00	PD02100	Unilateral congenital absence of kidney	√	Diagnostic	Index
65407.00	PD02z00	Congenital absence of kidney NOS	√	Diagnostic	Index
4764.00	PD03.00	Hypoplasia of kidney	√	Diagnostic	Index
30650.00	PD03100	Unilateral renal hypoplasia	√	Diagnostic	Index
10063.00	PD04.00	Dysplasia of kidney	√	Diagnostic	Index
9500.00	PD04000	Bilateral renal dysplasia	√	Diagnostic	Index
24120.00	PD04100	Unilateral renal dysplasia	√	Diagnostic	Index
29659.00	PD0z.00	Renal agenesis or dysgenesis NOS	√	Diagnostic	Index
15917.00	PD1..00	Congenital cystic kidney disease	√	Diagnostic	Index

20629.00	PD1..11	Congenital cystic renal disease	√	Diagnostic	Index
4504.00	PD1..13	Polycystic kidney	√	Diagnostic	Index
27436.00	PD1..14	Sponge kidney	√	Diagnostic	Index
4503.00	PD11.00	Polycystic kidney disease	√	Diagnostic	Index
21381.00	PD11000	Polycystic kidneys, infantile type	√	Diagnostic	Index
4505.00	PD11100	Polycystic kidneys, adult type	√	Diagnostic	Index
56852.00	PD11z00	Polycystic kidney disease NOS	√	Diagnostic	Index
9240.00	PD11z11	Cystic kidney disease NEC	√	Diagnostic	Index
42632.00	PD12.00	Medullary cystic disease	√	Diagnostic	Index
47135.00	PD12100	Medullary cystic disease, adult type	√	Diagnostic	Index
7718.00	PD12111	Medullary sponge kidney	√	Diagnostic	Index
11946.00	PD13.11	Multicystic kidney	√	Diagnostic	Index
50331.00	PD1z.00	Congenital cystic kidney disease NOS	√	Diagnostic	Index
5379.00	PD23.00	Congenital hydronephrosis	√	Diagnostic	Index
22571.00	PD23.11	Congenital dilated renal pelvis	√	Diagnostic	Index
4430.00	PD3..00	Other specified renal anomaly	√	Diagnostic	Index
52700.00	PD30.00	Accessory kidney	√	Diagnostic	Index
28362.00	PD34.00	Double kidney with double pelvis	√	Diagnostic	Index
4431.00	PD34.11	Duplex kidneys	√	Diagnostic	Index
15142.00	PD35.00	Ectopic kidney	√	Diagnostic	Index
2810.00	PD38.00	Horseshoe kidney	√	Diagnostic	Index
16523.00	PD39.00	Hyperplasia of kidney	√	Diagnostic	Index
53965.00	PD3B.00	Malrotation of kidney	√	Diagnostic	Index
29780.00	PD3D.00	Enlarged kidney	√	Diagnostic	Index
15420.00	PD3z.00	Other specified renal anomaly NOS	√	Diagnostic	Index
17356.00	PDz0.00	Unspecified anomaly of kidney	√	Diagnostic	Index
47342.00	Q48y000	Congenital renal failure	√	Diagnostic	Index
34320.00	R135300	[D]Renal scarring	√	Diagnostic	Index
11553.00	SP08300	Kidney transplant failure and rejection	√	Diagnostic	Index

54990.00	TB00100	Kidney transplant with complication, without blame	√	Diagnostic	Index
18774.00	TB00111	Renal transplant with complication, without blame	√	Diagnostic	Index
5911.00	ZV42000	[V]Kidney transplanted	√	Diagnostic	Index
26880.00	ZV59400	[V]Kidney donor	√	Diagnostic	Index
36356.00	ZV6G500	[V]Acquired absence of kidney	√	Diagnostic	Index

E13 Comorbidity and covariate CPRD physiological data conversion and cleaning

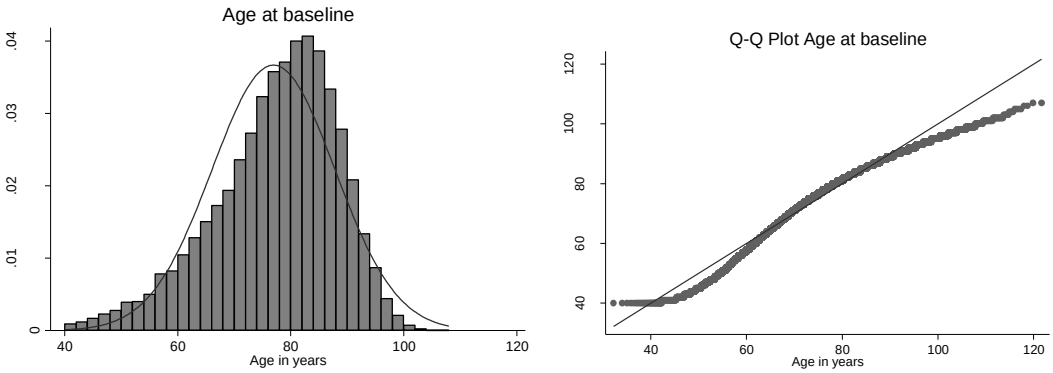
Physiological measure	Units reported	Standard unit	Formula	Biological plausible range
HbA1c	mmol/mol	%	New number/10.929)+2.15	2.6 to 20%
FEV_1	L	% predicted (pp)	Predicted L (PL) **Men :** FEV1{litres} = 4.30*height{metres} – 0.029*age{years} – 2.49 **Women :** FEV1{litres} = 3.95*height{metres} – 0.025*age{years} -2.60 % predicted 100*(L/PL)	10-130%
eGFR	Creatinine umol/L OR mg/dl	eGFR ml/min/m^2	32788 x serum creatinine(umol/L)$^{-1.154}$ x age$^{-0.203}$ x [0.742 if Female] OR 186 x serum creatinine(mg/dl)$^{-1.154}$ x age$^{-0.203}$ x [0.742 if Female]	Creatinine 41-2226 eGFR upto 130
BMI	kg/m2	kg/m2		10-80
Cholesterol	mmol/L	mmol/L		2-20
Haemoglobin	g/dL	g/dL		3-23
Systolic blood pressure	mm/Hg	mm/Hg		40-300
Diastolic blood pressure	mm/Hg	mm/Hg		≥20

HbA1c; Glycated haemoglobin, mmol/mol; millimoles per mole, FEV_1; forced expiration volume in 1 second, pp; percent predicted, L; litres, PL; predicted litres, eGFR; estimated glomerular filtration rate, umol/L; micromole per liter, mg/dl; milligram per decilitre,

E14 Exploration of continuous variables in the CPRD mortality sample

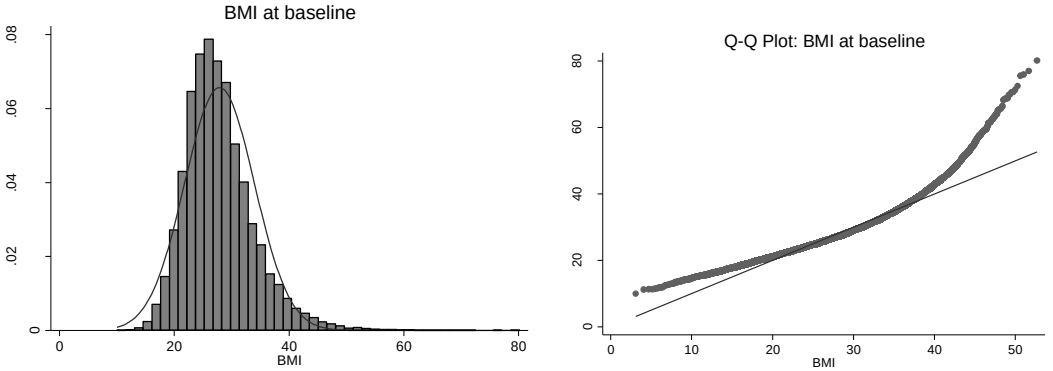
Baseline sample

Age at baseline



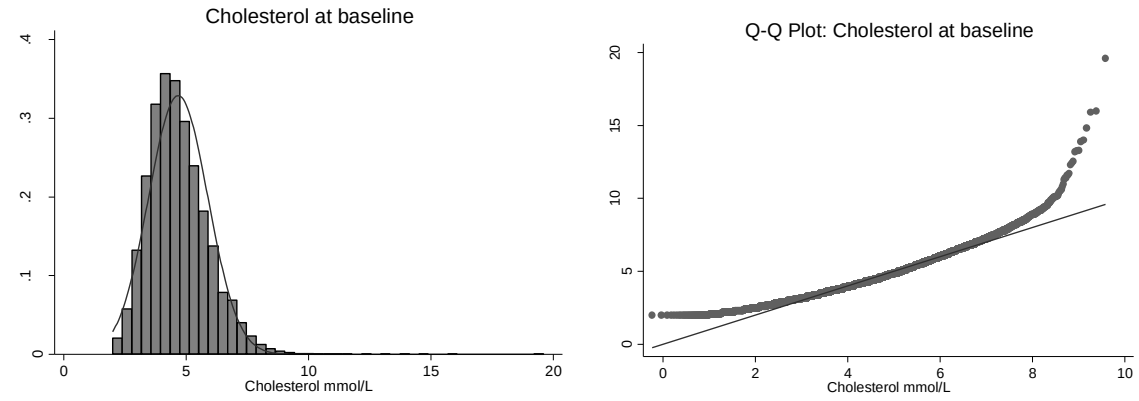
Mean 76.9±10.9 Median 78 (IQR 71-85)

Body mass index at baseline



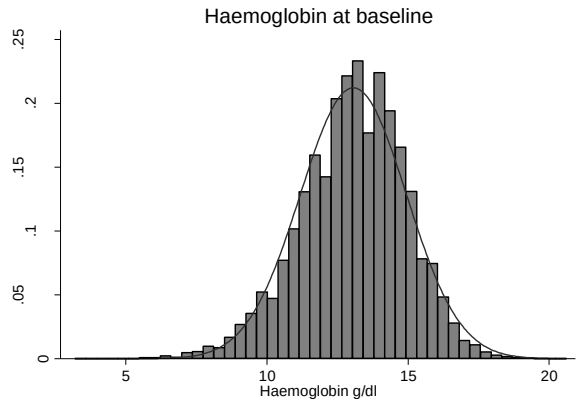
Mean 27.9±6.1 Median 27(IQR 23.8-31)

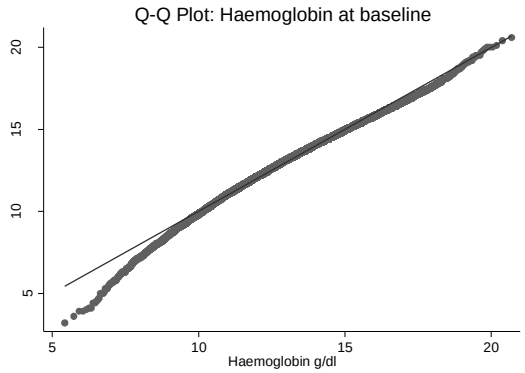
Cholesterol at baseline



Mean 4.7±1.2, Median 4.5(IQR 3.8-5.4)

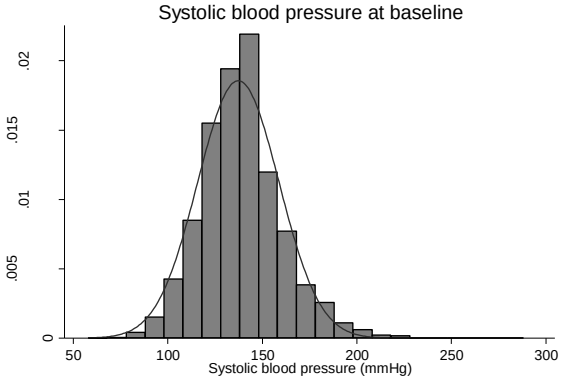
Haemoglobin at baseline

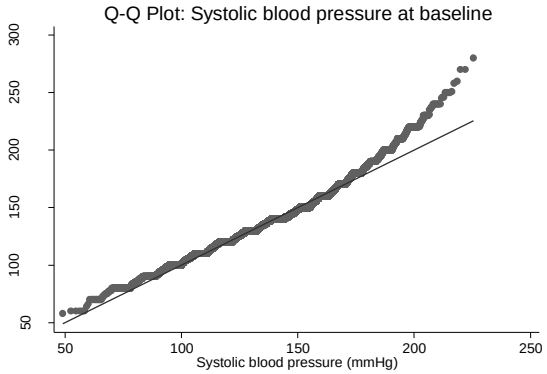




Mean 13.1±1.9, Median 13.2(IQR 11.9-14.3)

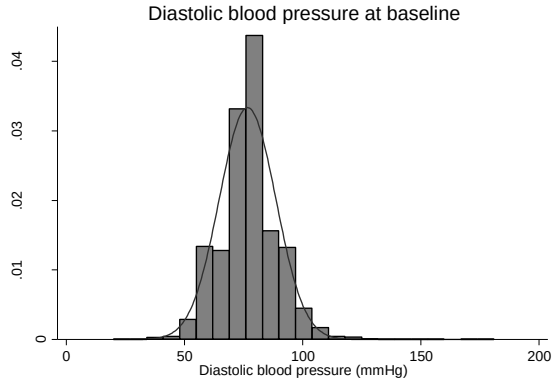
Systolic blood pressure at baseline

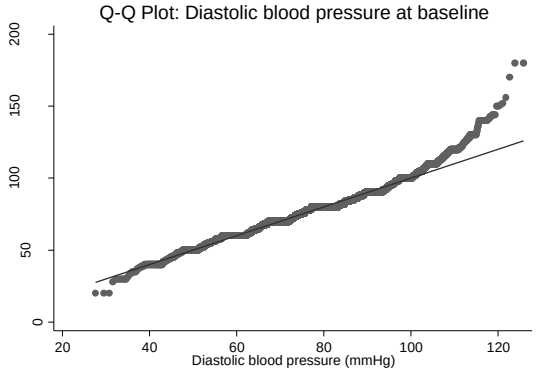




Mean 137.3±21.5 Median 138(IQR 122-150)

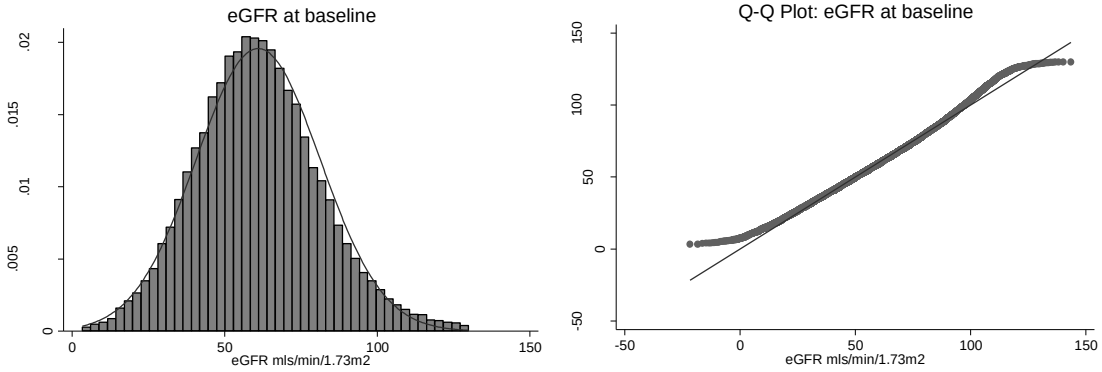
Diastolic blood pressure at baseline





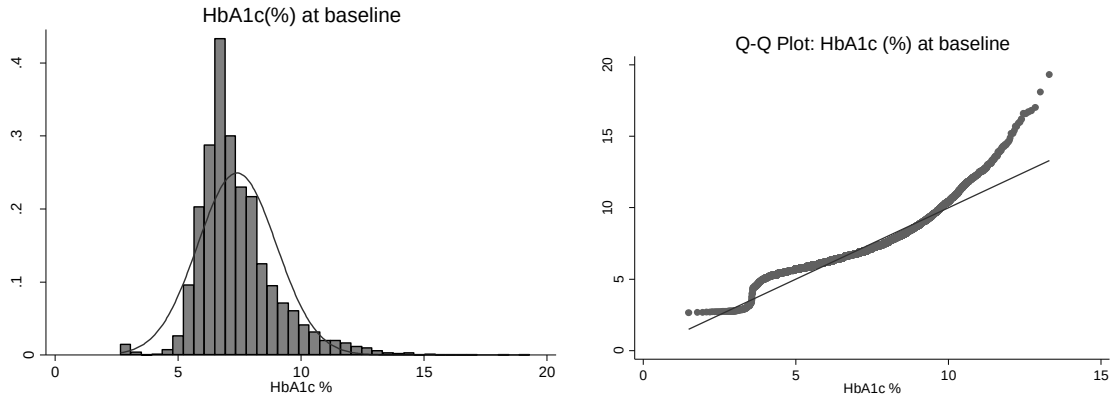
Mean 76.7±12.0, Median 78 (IQR 70-83)

eGFR at baseline



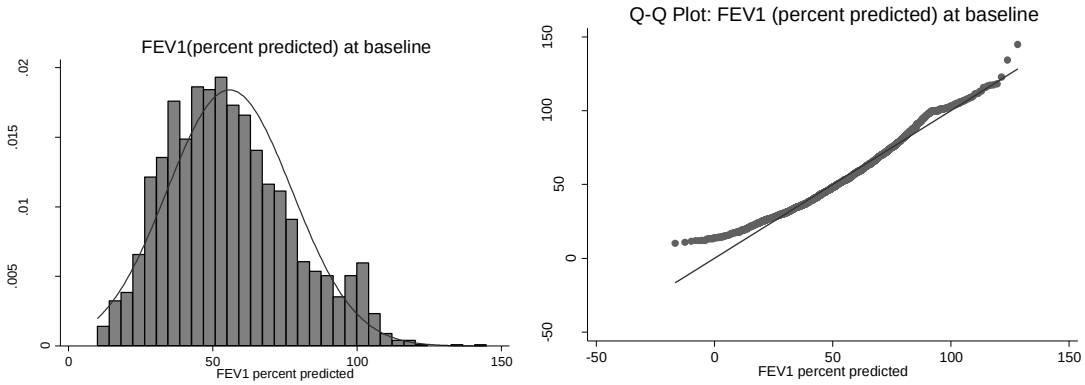
Mean 61±20.4 Median 60.1(IQR 47.1-73.7)

HbA1c (%) at baseline



Mean 7.4±1.6, Median 7.1(IQR 6.4-8.1)

FEV1 percent predicted at baseline

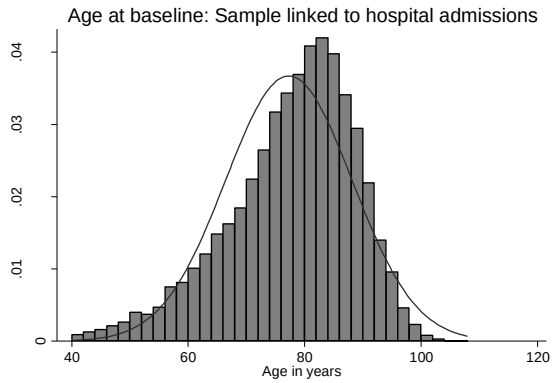


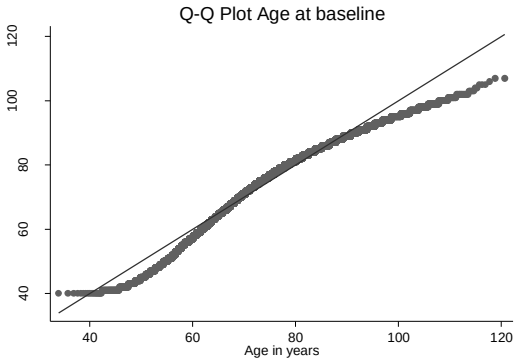
Mean 55.8 21.7 Median 53.3(IQR 39-69.6)

E15 Exploration of continuous variables in the CPRD hospital admission sample

Pre match sample

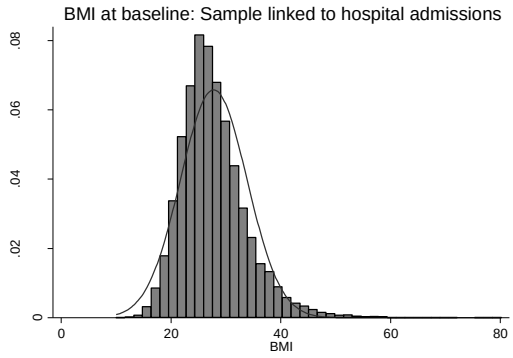
Age at baseline

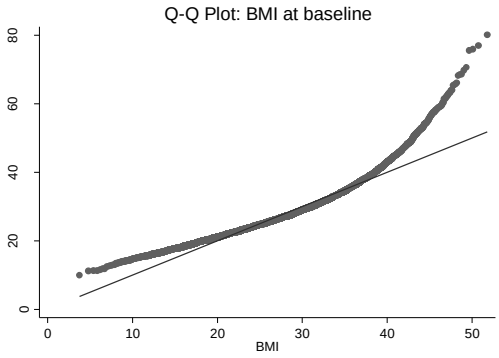




Mean 77.3±10.9 Median 79 (IQR 71-85)

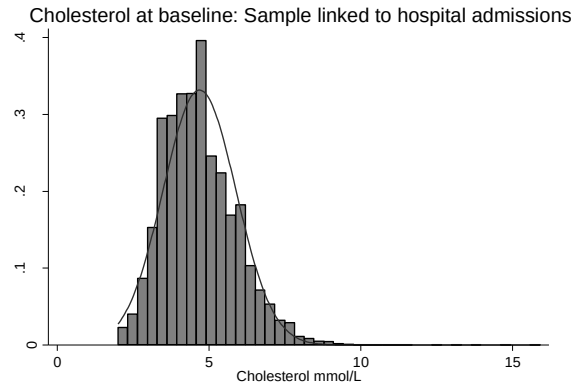
Body mass index at baseline

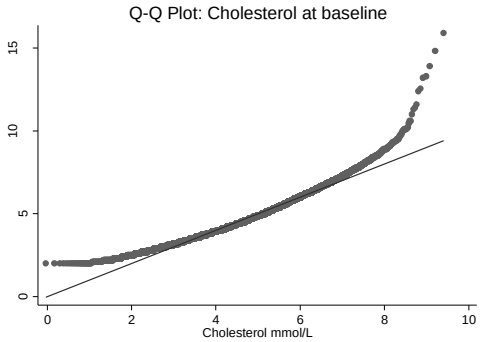




Mean 27.8±6.1 Median 26.9(IQR 23.7-31)

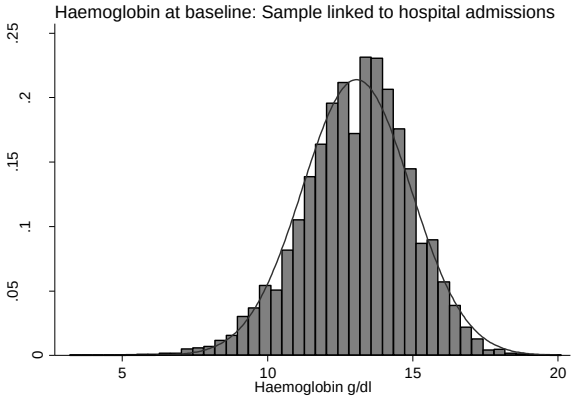
Cholesterol at baseline

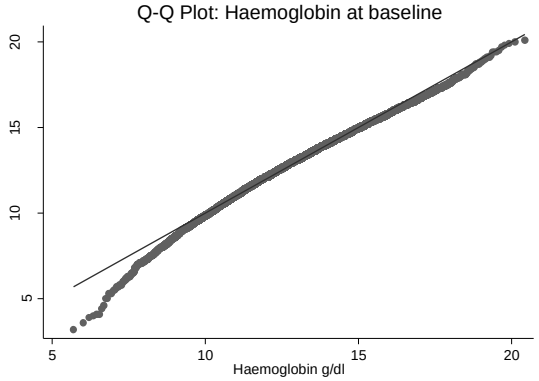




Mean 4.7±1.2, Median 4.6(IQR 3.8-5.4)

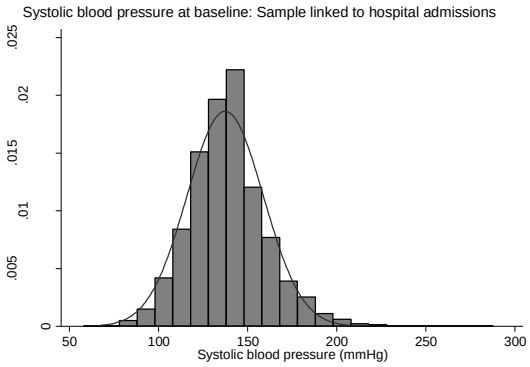
Haemoglobin at baseline

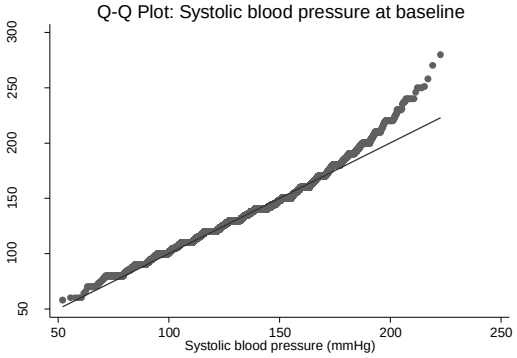




Mean 13.1±1.9, Median 13.2(IQR 11.9-14.3)

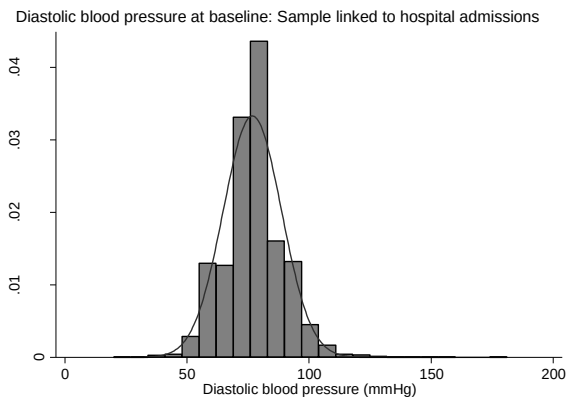
Systolic blood pressure at baseline

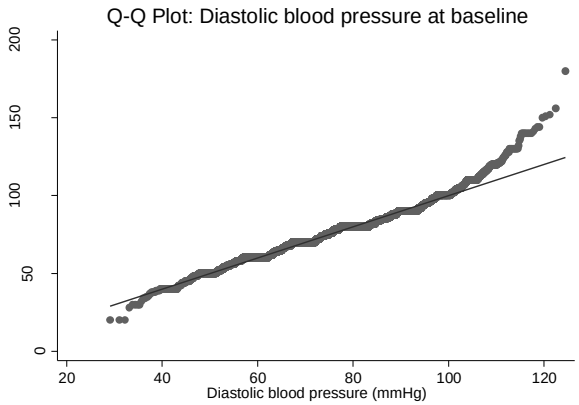




Mean 137.4±21.4 Median 138(IQR 123-150)

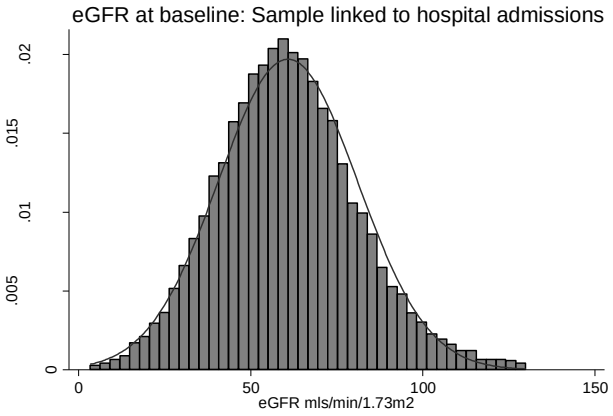
Diastolic blood pressure at baseline

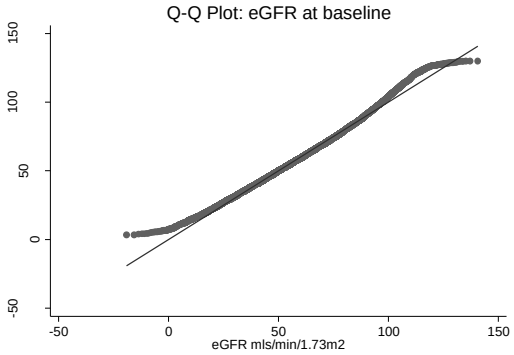




Mean 76.8±12.0, Median 78 (IQR 70-83)

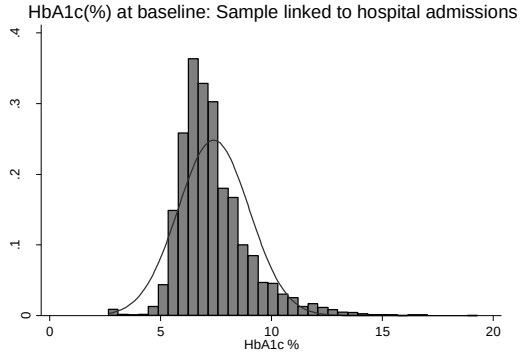
eGFR at baseline

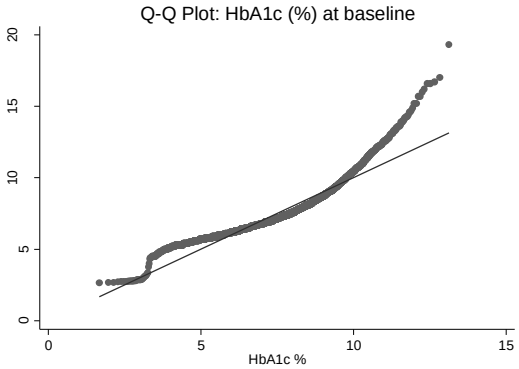




Mean 60.8±20.3 Median 60.0(IQR 47.0-73.4)

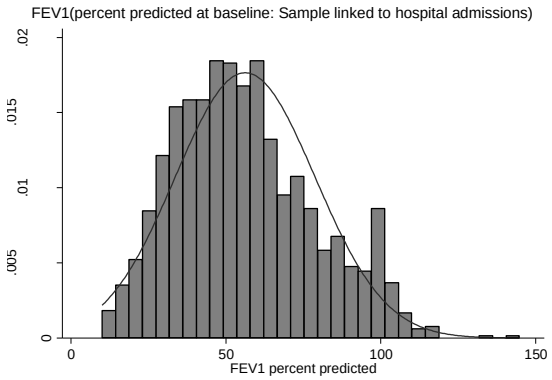
HbA1c (%) at baseline

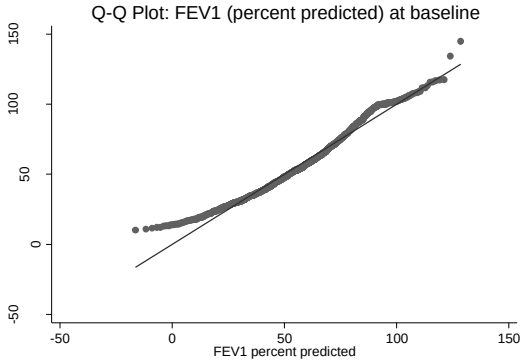




Mean 7.4±1.6, Median 7.1(IQR 6.4-8.1)

FEV1 percent predicted at baseline





Mean 56.2±22.6 Median 53.5(IQR 38.8-70.7)

E16 Testing the linearity assumption; continuous variable and all-cause mortality

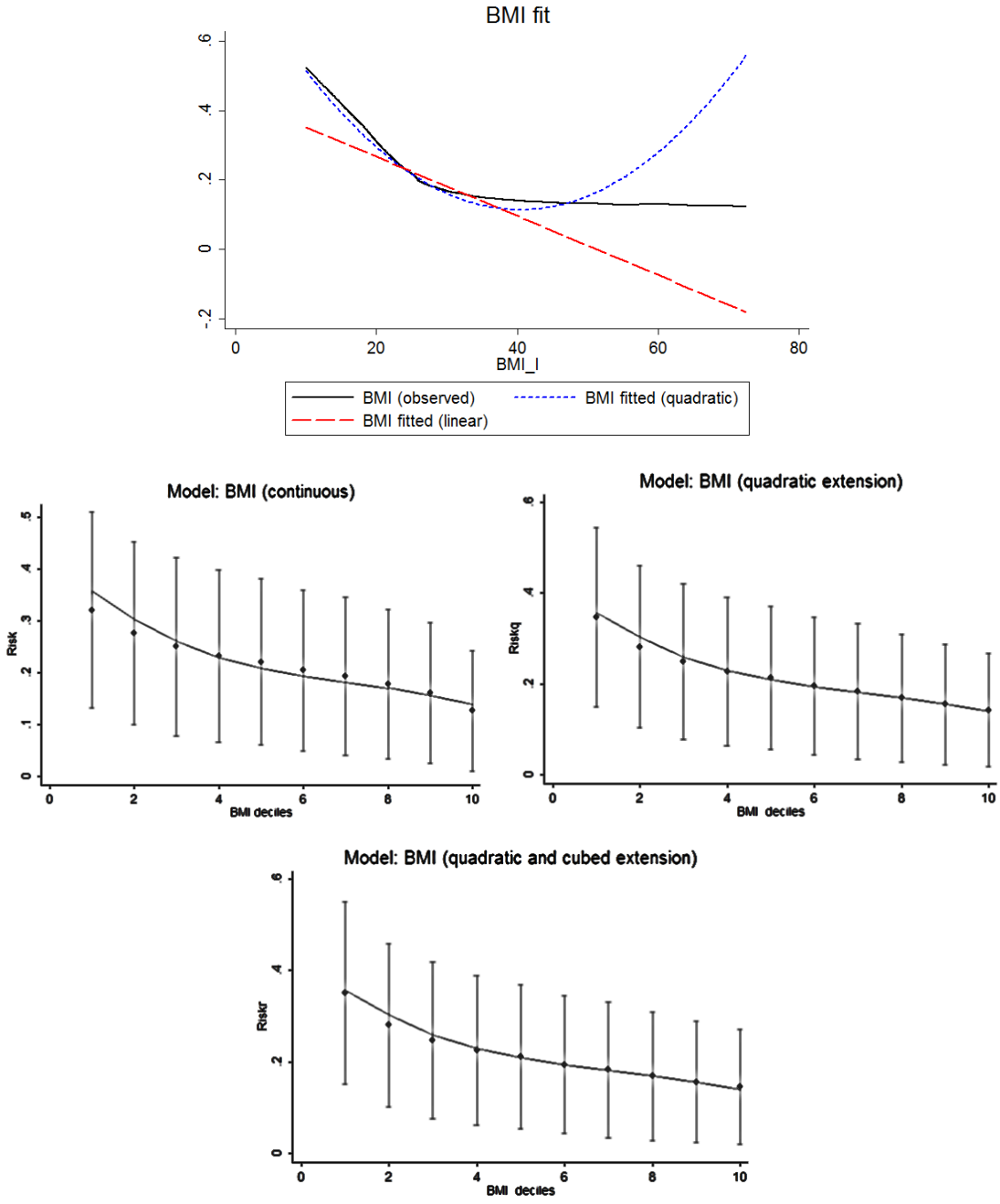
BMI

Unadjusted	Log likelihood	LR test
BMI	- 41897.411	
BMI+BMI^2	- 41694.718	<0.001
BMI+BMI^2+BMI^3	- 41686.874	<0.001

Multivariable	Log likelihood	LR test
BMI	- 30016.982	
ŧBMI+BMI^2	-29895.289	<0.001
*BMI+BMI^2+BMI^3	-29890.704	0.003

*Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom

Calibration plots of observed versus predicted (fitted) effect



Cholesterol

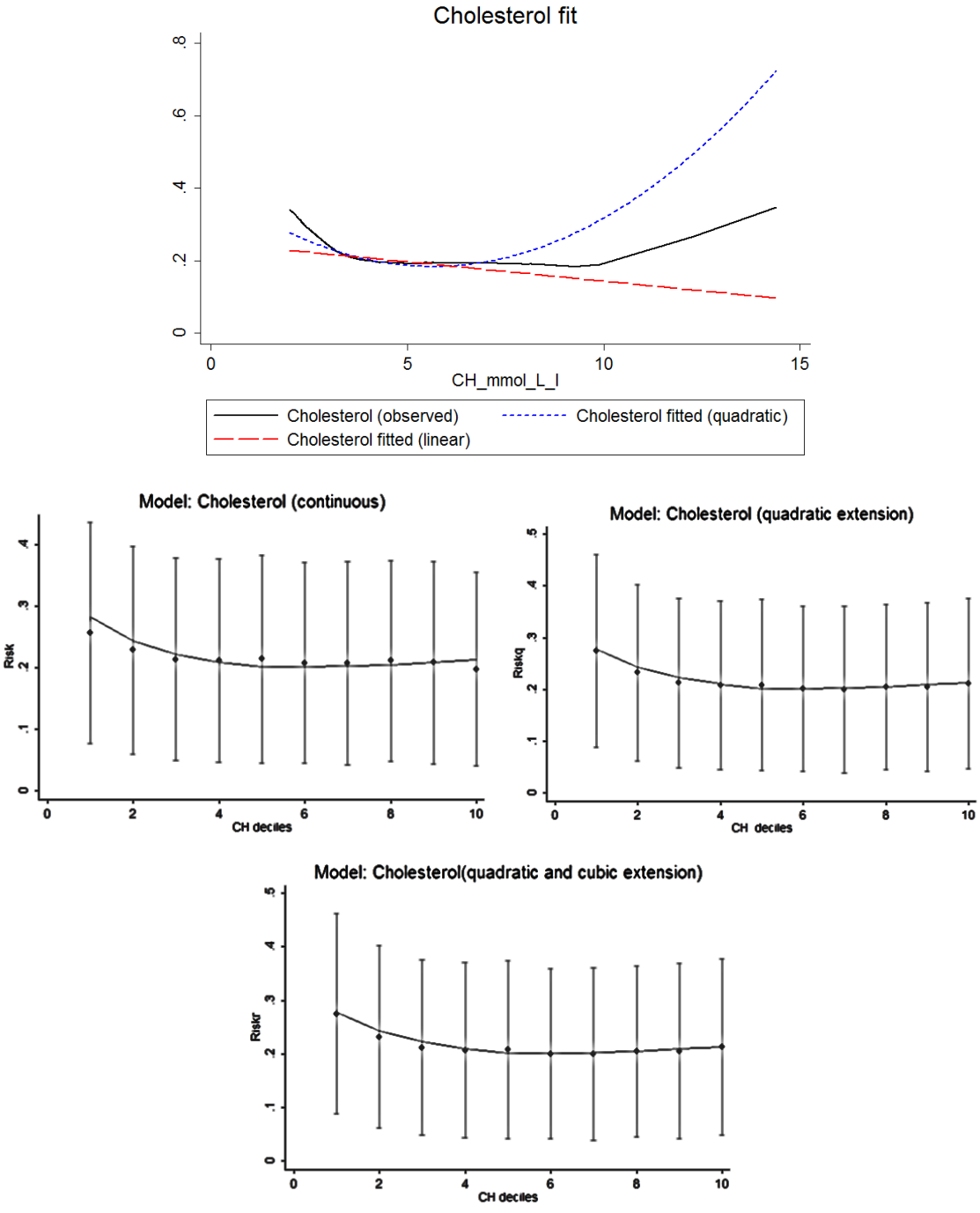
Plots of predicted cholesterol effect where other effects are fixed at zero

Unadjusted	Log likelihood	LR test
CH	-42952.338	
CH + CH^2	-42845.726	<0.001
CH + CH^2 + CH^3	-42818.515	<0.001

Multivariable	Log likelihood	LR test
ŧCH	-30016.982	
CH + CH^2	-29966.281	<0.001
*CH + CH^2 + CH^3	-29965.575	0.2347

*Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom

Calibration plots of observed versus predicted (fitted effects)



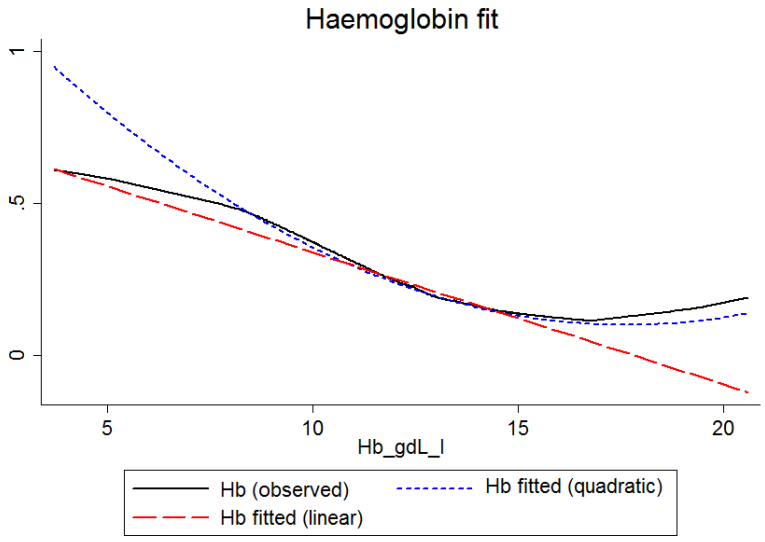
Haemoglobin

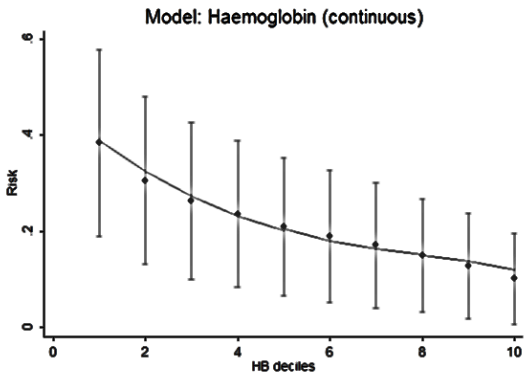
Unadjusted	Log likelihood	LR test
HB	-40745.527	
HB+HB^2	-40668.677	<0.001
HB+HB^2+HB^3	-40532.707	<0.001

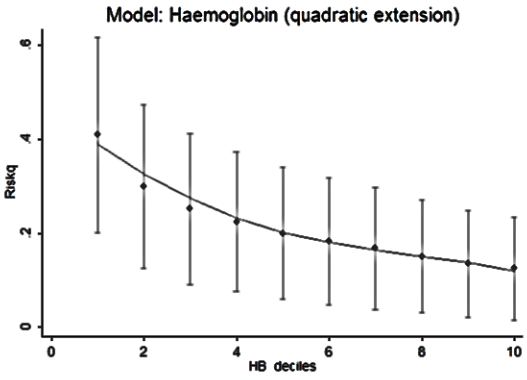
Multivariable	Log likelihood	LR test
HB	-30016.982	
ŧHB+HB^2	-29902.455	<0.001
***HB+HB^2+HB^3**	-29831.089	<0.001

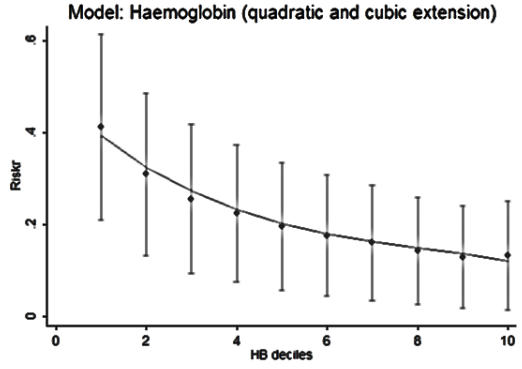
***Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom**

Calibration plots of observed versus predicted (fitted) effects









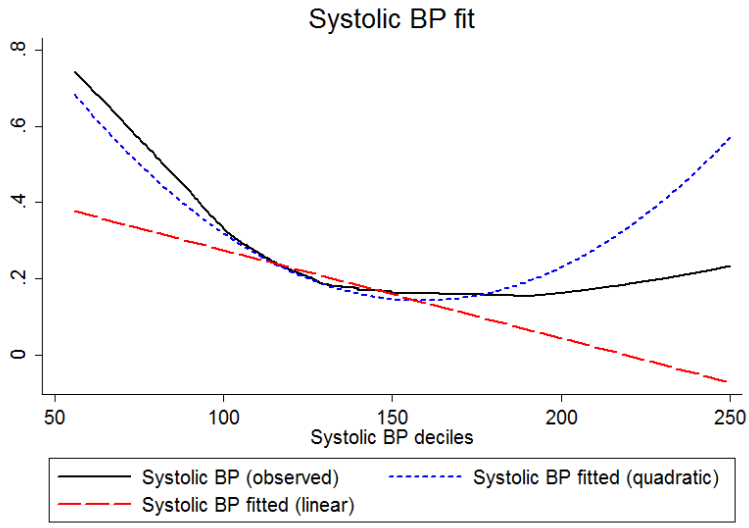
Systolic blood pressure

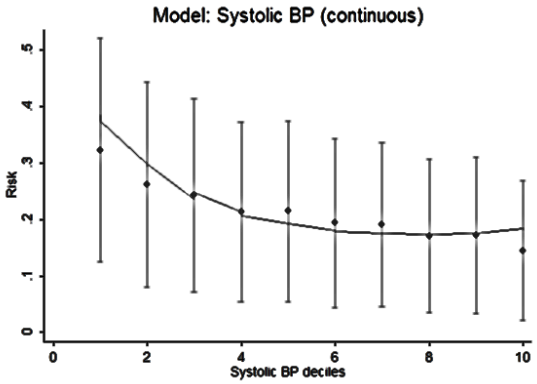
Unadjusted	Log likelihood	LR test
SBP	-42172.59	
SBP+SBP^2	-41736.52	<0.0001
SBP+SBP^2+SBP^3	-41685.97	<0.0001

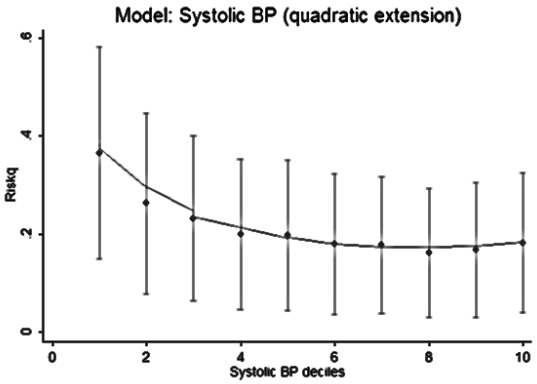
Multivariable	Log likelihood	LR test
SBP	-30016.982	
ŧSBP+SBP^2	-29719.731	<0.0001
***SBP+SBP^2+SBP^3**	-29692.432	<0.0001

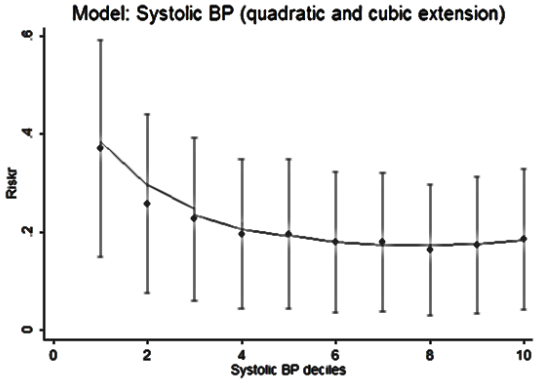
***Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom**

Calibration plots of observed versus predicted (fitted) effects









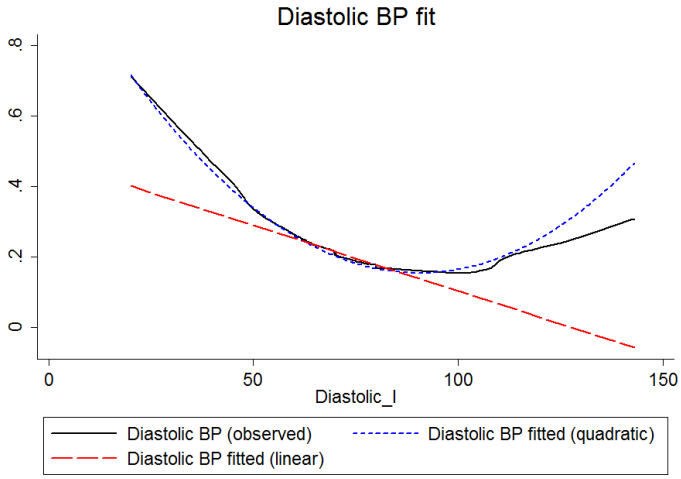
Diastolic blood pressure

Unadjusted	Log likelihood	LR test
DBP	-42373.877	
DBP+DBP^2	-42244.937	<0.001
DBP+DBP^2+DBP^3	-42237.05	<0.001

Multivariable	Log likelihood	LR test
DBP	-30016.982	
ŧDBP+DBP^2	-29919.327	<0.001
***DBP+DBP^2+DBP^3**	-29913.395	<0.001

***Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom**

Calibration plots of observed versus predicted (fitted) effects



E17 Testing the linearity assumption; continuous variable and first hospital admission

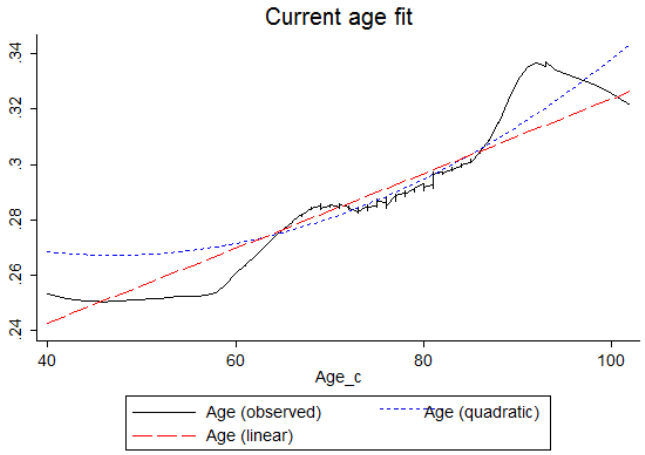
Age

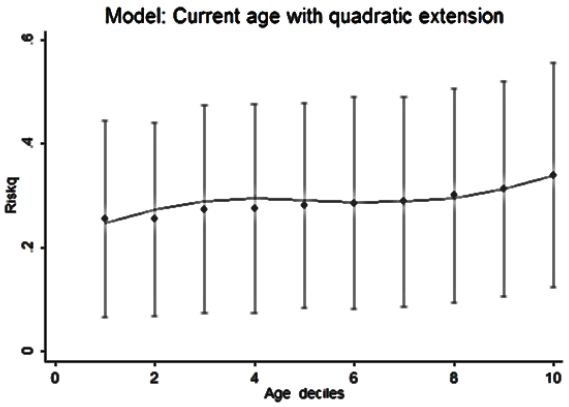
Unadjusted	Log likelihood	LR test
Age	-36228.07	
Age+Age^2	-36198.66	<0.001
Age+Age^2+Age^3	-36196.52	0.039

Multivariable	Log likelihood	LR test
ŧAge	-17245.36	
*Age+Age^2	-17233.58	<0.001
Age+Age^2+Age^3	-17233.39	0.55

*Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom

Calibration plots of observed versus predicted (fitted) effects





Cholesterol

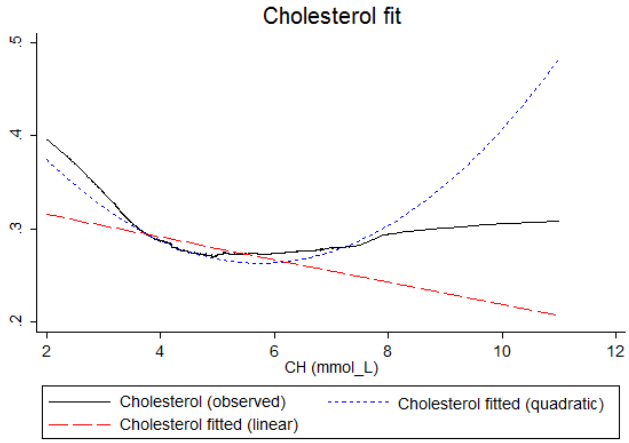
Plots of predicted cholesterol effect where other effects are fixed at zero

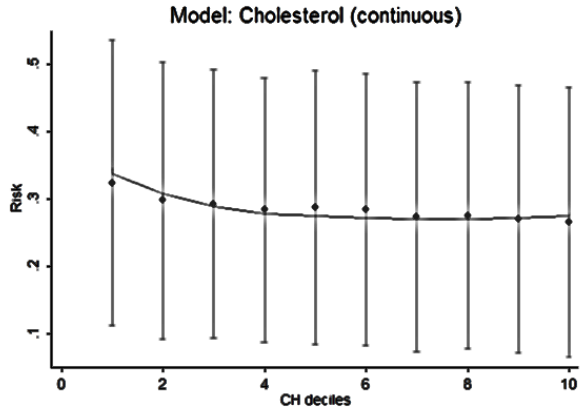
Unadjusted	Log likelihood	LR test
CH	-36310.41	
CH + CH^2	-36276.84	<0.001
CH + CH^2 + CH^3	-36271.24	<0.001

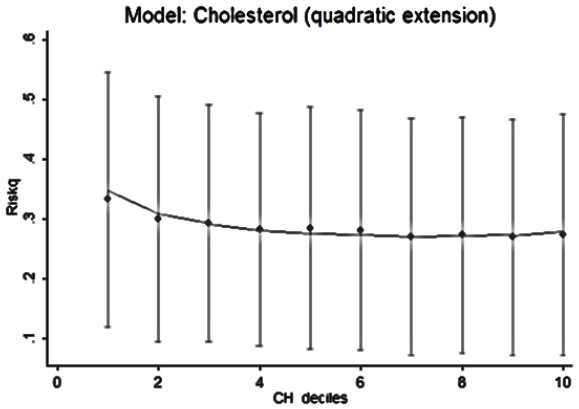
Multivariable	Log likelihood	LR test
ŧCH	-17245.36	
*CH + CH^2	-17236.45	<0.001
CH + CH^2 + CH^3	-17235.66	0.21

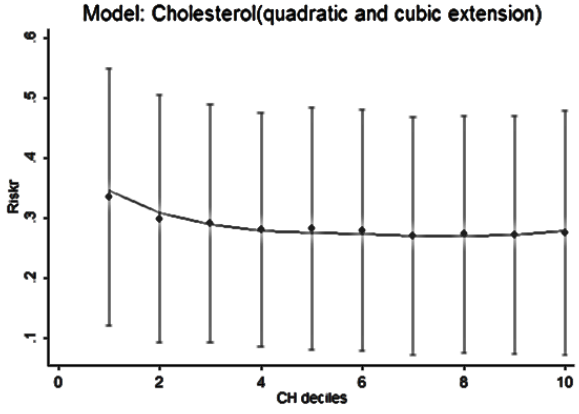
***Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom**

Calibration plots of observed versus predicted (fitted) effects









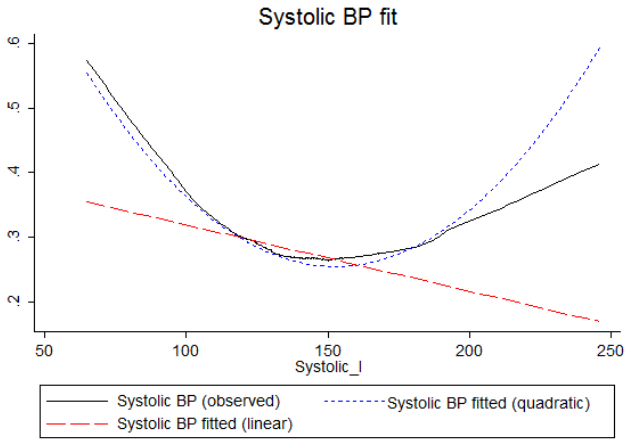
Systolic blood pressure

Plots of predicted systolic BP effect where other effects are fixed at zero

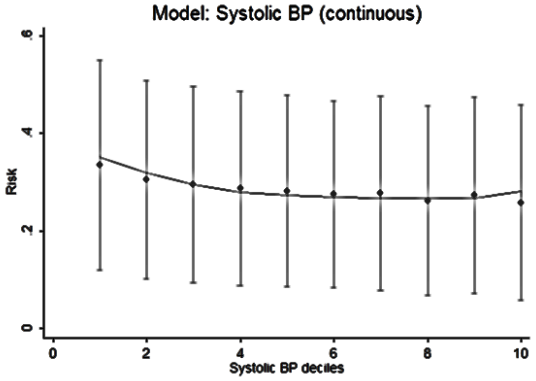
Unadjusted	Log likelihood	LR test
SBP	-36246.67	
SBP+SBP^2	-36104.33	<0.001
SBP+SBP^2+SBP^3	-36075.66	<0.001

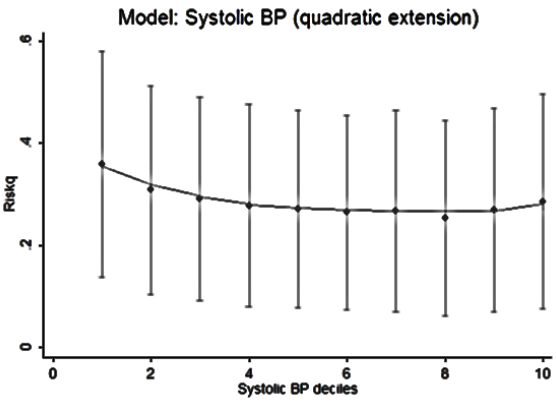
Multivariable	Log likelihood	LR test
SBP	-17246.30	
ŧSBP+SBP^2	-17169.25	<0.001
***SBP+SBP^2+SBP^3**	-17163.80	<0.01

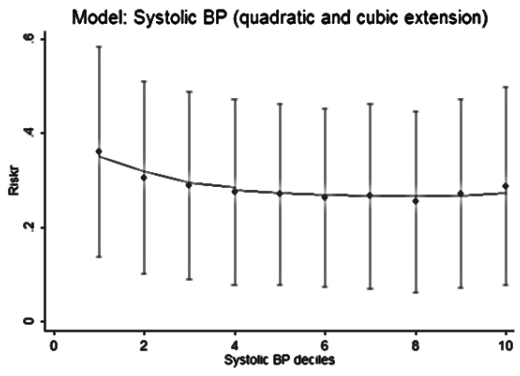
***Best statistical fit; ŧChoice of fit taking account of difference in Log likelihood and degrees of freedom**



Calibration plots of observed versus predicted (fitted) effects







eGFR

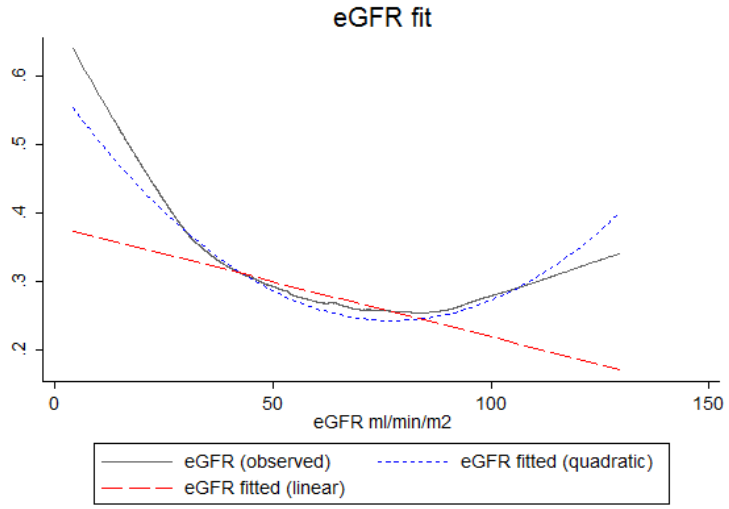
Plots of predicted eGFR effect where other effects are fixed at zero

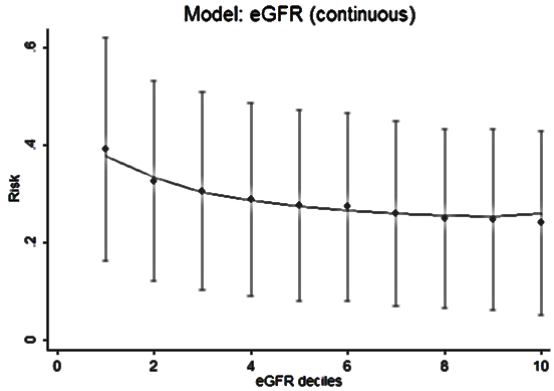
Unadjusted	Log likelihood	LR test
eGFR	-18197.63	
eGFR+eGFR^2	-18014.42	<0.001
eGFR+eGFR^2+eGFR^3	- 17983.58	<0.001

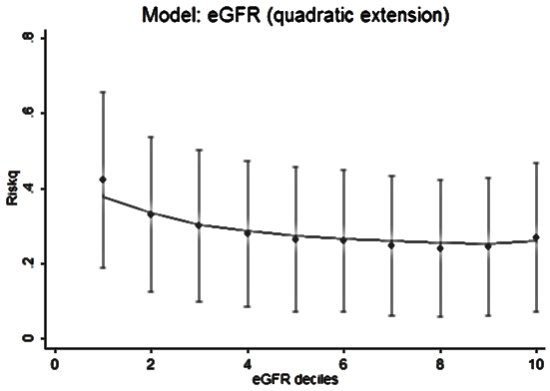
Multivariable	Log likelihood	LR test
eGFR	-17213.34	
łeGFR+eGFR^2	-17128.67	<0.001
***eGFR+eGFR^2+eGFR^3**	-17109.42	<0.001

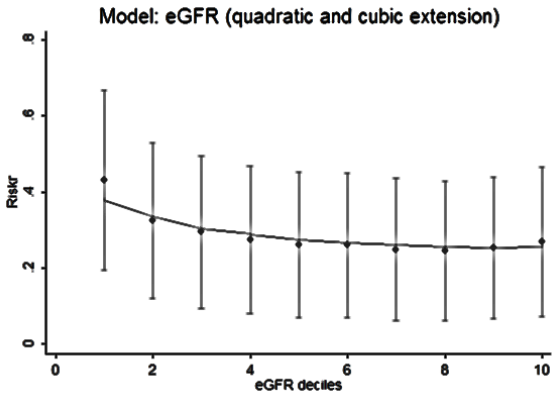
***Best statistical fit; łChoice of fit taking account of difference in Log likelihood and degrees of freedom**

Calibration plots of observed versus predicted (fitted) effects









E18 Quality of life outcome study 1: HF and OA publication on QoL

Rushton_IJC.pdf

E19 Quality of life outcome study 2: 2C_HF prospective hospital investigation

Protocol

Title: Comorbidity and changing prognosis in heart failure patients: Comorbidity Cohort in Heart Failure (2C-HF) study

Investigators: Rushton CA (PI), Satchithananda D, Jones P, Kadam UT

Wider Study Team: Simon Davies (Professor of Nephrology), Anthony Fryer (Professor of Clinical Biochemistry), Pauline Walsh (Head of School of Nursing), George Hughes (patient representative).

Abstract

The overall plan is to investigate the short and longer-term impact of chronic disease comorbidity on developing health status of heart failure patients. The specific objectives are to:

(i) investigate the influence of comorbid chronic diseases on general physical and heart failure specific health status in adults with heart failure, aged 40 years and over, using self-completed questionnaires at baseline, 1 and 3 months follow-up

(ii) examine the contribution of comorbidity prognostic factors to an overall prognostic model for health status change over 2 months in heart failure patients.

The outcomes of the study will result in the determination of the effect of chronic disease comorbidity on the change and progression of health status in individuals with heart failure and on the contribution of such factors to heart failure prognostic models. This will provide clinicians with important information to enable them to target interventions aimed at improving health outcomes and provide patients with improved understanding of their heart failure trajectory so that they can participate in shared decision making.

Background

Heart failure is a serious, life limiting cardiovascular disease which is an increasing burden in older populations affecting up to 15% of people aged over 85 years(12), a figure set to rise over the next 25 years as the population ages(13). Among older people, HF is one of the most common causes of consultation in general practice(14) and accounts for 2% of all hospital inpatient bed days, with over 61,000 hospital admissions between 2011-2012 in the UK(15).

Heart failure carries a high mortality risk with 14-30% of patients dying in the first six months of diagnosis and 38% within a year(16,17). About half of all patients experience daily symptoms including breathlessness and fatigue(18) and up to half of patients remain symptomatic despite optimisation of treatments during hospital admission(19). Patients suffer problems with walking, activities of daily living, self-care, pain and depression and these symptoms are exacerbated with increasing age(20). Consequently the quality of life of patients with heart failure is poor(21), worsens over time as the disease progresses(21) and is associated with hospital admission(22) and mortality(23).

HF patients commonly experience other chronic diseases at the same time, partly due to age-association and partly due to cardiovascular complications. A range of comorbidities have been found in HF patients including chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), dementia, diabetes, hypertension, osteoarthritis and osteoporosis(24,25) and some older heart failure patients have been found to have in excess of five comorbidities(26,27). Psychological co-morbidity such as depression is also becoming recognized as important in heart failure outcomes(28,29). Comorbidity has been shown to influence the clinical course of HF and associated outcomes to vary. In general population studies the existence of comorbidities inherent in the average elderly heart failure patient has been associated with increased risk of hospitalization (COPD, CKD, diabetes and depression)(30), higher mortality risk (COPD, CKD, diabetes, depression and cancer)(31-35) increased symptom burden (the number of co-morbidities)(36) and reduced physical function and quality of life (depression, diabetes and respiratory disease)(37). In hospital settings comorbidity has been found to predict increased mortality (cerebrovascular accident (CVA), COPD, hepatic cirrhosis, cancer, dementia)(38) and readmissions (ischemic heart disease (IHD), diabetes, CKD, COPD)(39).

Prognosis is the prediction of the probable course and outcomes of disease and has the potential to provide clinicians with necessary information to enable them to tailor care and communication of risk to individual patients and to guide shared decision-making (40). 'Prognostication' is challenging in heart failure which has an uncertain disease trajectory and this is

further complicated by comorbidity. Heart failure patients can have a period of relative functional stability, before a gradual and chronic decline in health status, interrupted by acute episodic exacerbation of symptoms and frequent hospital admissions. Sudden death at any point is common(41). In heart failure prognostic information that identifies patients whose health is changing as their disease progresses, would enable clinicians to reassess and optimise patient interventions that could prevent hospitalisation and health deterioration as well as prolong life.

However current prognostic approaches in HF commonly rely on complex and invasive clinical data and biometrics and focus mainly on the imminent risk of mortality at a fixed point in time (usually during hospital admission)(42-44). This means that available prognostic tools have limited use in identifying how heart failure patients' health changes over their disease course from stability to instability from diagnosis until death. This has led to the reluctance of some health professionals to discuss prognosis with patients and patients' preferences in clinical care have been poorly represented in healthcare outcomes(45-47). Despite the recognition that comorbidity in heart failure is significant in determining outcomes for patients, some of the more widely used prognostic tools do not include comorbidity(48,49). Whilst current prognosis research has focused on outcomes such as hospital admissions and death, few studies have investigated patient-centred outcomes such as health related quality of life and there is recognition that good clinical assessments will address patient-centred outcomes in addition to disease risk(41,50)

There is growing evidence that the severity of comorbid chronic disease such as COPD and diabetes is important in determining outcomes in HF(51-53) and that change in the severity of chronic disease may pre-empt subsequent change in HF. The risk of mortality and readmission in HF for instance has been demonstrated to increase in patients recently discharged for another condition, including stroke, diabetes, AF or renal dysfunction[13]. This temporal relationship between comorbid chronic disease and HF has mainly focused on cardio-renal syndrome and the outcome of mortality(54-59). How comorbid chronic disease and its progression influences the health and subsequent change in health for heart failure patients has not yet been investigated. This is important as evidence demonstrates that health related quality of life (HRQoL) measures in heart failure are associated with the severity of the disease(60) and so change in these measures over time provides the potential to identify change in heart failure severity at different stages of heart failure disease from new onset to end stage disease. Each comorbid chronic disease will carry its own prognostic 'value' and one crucial question from patients' point of view is how these combine together to influence either their overall health or, separately, the course of their heart failure over time. Incorporating more sensitive comorbidity factors within prognostic approaches provides the

potential to observe changes in health status and transitions across the primary care and specialist care interfaces and for identifying more specific and useful patient outcomes.

This phase 3 study builds on two initial phases. Phase 1 was a systematic review with the objective to identify and synthesise the current evidence on comorbidity and heart failure prognosis. Phase 2 was to develop comorbidity prognosis factors in non-selected heart failure populations for hospital admissions and mortality using the Clinical Practice Research Datalink (CPRD). The primary objective of this phase is (i) to test the comorbidity prognostic factors in a new cohort of HF patients using changing self-reported health status over a 3-month follow-up period. Evidence has shown that severity of HF disease, usually demonstrated via an increased mortality risk, is associated with patients who have had a hospital admission. This risk further increases in those with repeat admissions and before death. Given the association of these outcomes with poor quality of life, a hypothesis is generated that the factors that predict hospital admissions and death will also predict change in quality of life measures. The primary hypothesis tested (objective 1) will be:

H_1 Chronic disease comorbidity is associated with change in self-reported heart failure specific and general health status

H_0 Chronic disease comorbidity is not associated with change in self-reported heart failure specific and general health status.

The secondary objectives are (ii) to refine comorbidity prognostic factors developed from the first two phases within a specialist-based setting and (iii) to investigate the contribution of comorbidity prognostic factors to heart failure prognostic models for health status change (objective 2) with the hypothesis:

H_1 Chronic disease comorbidity factors will improve the fit of a pre-specified HF prognostic model for self-reported health status.

H_0 Chronic disease comorbidity factors will not improve the fit of a pre-specified HF prognostic model for self-reported health status.

Methods

Setting: This cohort study will be based in a local specialist HF clinic in the University Hospital North Staffordshire (UHNS) and will recruit patients from both the hospital setting (heart failure specialist clinic and non-surgical wards) and from heart failure specialist clinics in the community. The hospital

specialist clinic acts as a diagnostic and treatment hub for patients referred from within the hospital or externally from general practice. The heart failure service based at the University Hospital of North Staffordshire sits within a large catchment area that covers North Staffordshire, South Staffordshire, Shropshire, South Cheshire and other areas of England. The clinic routinely collects and records clinical data using hospital based electronic systems and works closely with heart failure community services.

Study Population: The 2C-HF cohort study will be based on the recruitment of adults aged 40 years and over with heart failure diagnosed using a combination of signs, symptoms and objective evidence of cardiac abnormality(13,61). Both incident and prevalent HF patients will be recruited over an 8month period and there will be no selection on the basis of ejection fraction. Patients at end stage of disease will be included in order to understand the health progression of patients from across the spectrum of disease although special consent procedures will be developed for this group. A recent Health Foundation funded 'Acute Ambulatory Heart Failure Clinic' project that has recruited Heart Failure patients (including end-stage patients) will form the basis for the development of consent procedures along with patient involvement as part of a steering group. Recruited patients will be categorised by New York Heart Association (NYHA) classification stages 1-1V[(50)] (see Appendix 1).

Identifying the cohort sample:
HF cohort patients will be identified through regular checks with the heart failure specialist teams (hospital and community) and their diagnostic status verified. The project principal investigator (CR) as a heart failure nurse specialist and an honorary member of the hospital clinical team and working with Duwarakan Satchithananda, the heart failure consultant lead, will develop standard systems for identification and data collection.

Cohort follow-up and measures of health status:
The baseline and follow-up questionnaire includes validated measures of health status as well as socio-demographic data, which have been successfully collected in previous local studies.

Overall participants will be invited to complete 3 questionnaires – one at baseline and one at 1 and 3 months follow-up (see flow-chart Appendix 2). The 1-month questionnaire will allow us to measure the immediate change in patients' health following specialist care. 1-month following heart failure

decompensation or hospital admission has been found to carry an increased risk of death or readmission for heart failure patients(62). The 1-month period following specialist input will also give patients a period of stabilisation(63) before measurement of health status change over the next 2 months.

To reduce the burden of completing questionnaires the short form of tools where available and previously tested will be used. Patients will be offered assistance with the baseline questionnaire if required. All questionnaires have been designed using large font and require tick box answers for ease of completion and the introductory section of each questionnaire informs patients that their answers will be treated in the strictest confidence. The questionnaires will be coded to allow the research team to make relevant linkages with anonymised data that they have collected about the demographic and clinical characteristics of the patients.

Baseline survey

The identified sampled cohorts will be given a baseline questionnaire (Q1), which will include specific and generic health measures. Heart failure specific and generic measures have been identified that have been previously tested in heart failure populations and that have been found to be responsive and sensitive to clinical change.

For the *primary outcome* of interest, we will use the overall score from The Kansas City Cardiomyopathy Questionnaire (KCCQ)(64-66) which is sensitive to clinical change over 6 weeks(67).

Other CVD-specific measure: The European Heart Failure Self-care Behaviour Scale (EHFScB) is an additional measure that includes different concepts to the measures of health(68) and will be important in understanding the impact of changing comorbidity burden on the patient .

Generic Health Measure: We will use the Physical Component Summary (PCS) of the Short-Form-12 questionnaire as a generic measure of physical health, which has been found to differentiate between stages of HF(69) and be superior to HF specific measures at detecting physical health change(70,71).

Generic Patient Measure: The Brief Illness Perception Questionnaire (IPQ) which has been

used successfully in HF studies(57,58) will provide insight into how patients with HF comorbidity make sense of their overall health burden and symptom experience.

In addition to the health measures the following data will be extracted from patient case notes at baseline (see appendix 3):

- Cardiovascular risk factors (e.g. family history)
- Comorbidity factors
- Heart failure aetiological factors (e.g. valve disease, ischemic heart disease)
- Indicators of HF status (e.g. blood tests, ECG and ECHO)
- Drug therapies in the previous 12 months and at discharge from the current episode of care

The collection of the data items listed above will not place any additional burden on patients as they are routinely collected as part of the normal delivery of clinical care.

Follow-up questionnaires

These will include the same brief health scales as in the baseline questionnaire but will be shorter as they will not include the socio-demographic information.

The baseline and follow-up health questionnaire will have the same format with the proviso that the baseline questionnaire will be administered in clinic and the one month follow-up will be given to the patient with a stamped addressed envelope for self-completion. At baseline consent will also be requested from survey participants to the 3 month follow-up questionnaire to be sent by post and to give permission for the subsequent review of their electronic clinical records.

To maximise response rates, a reminder follow up telephone call will be made to patients who have not returned the follow-up questionnaires. The call will be made by a research nurse and only to patients who had stated at baseline that they were willing to be contacted in this way. Prior to the research nurse making reminder calls, they will access electronic clinical records which are linked to the register of deaths to check that patients are not deceased. This system has been used successfully in other studies.

Anonymised database of survey sample

For the survey sample, with consent, linked general practice and hospital records will be requested for the two years prior to baseline survey and until the end of the cohort follow-up. This will allow for the identification of chronic disease comorbidity indicators that change before or at the same time as general and heart failure specific health status. The linked database of cohort participants will be anonymised and kept securely through governance procedures and using an authorised data custodian.

Analytic plan and numbers

Sampling

The sample size calculation is based on the primary objective to investigate the influence of comorbid chronic diseases on heart failure specific health status in adults with heart failure, using self-completed questionnaires at baseline, 1 and 3 months follow-up. There is limited evidence available that has investigated the association between prognostic factors and change in health measures. A change of 5 points in KCCQ (dependant variable) has been found to be a clinically significant change(66). Prior evidence has demonstrated that 14% of patients measured between 1 and 3 months post hospital admission experienced a reduction in KCCQ of >10 points(63). For common chronic diseases (independent variables) the ratio of exposed to unexposed heart failure patients is commonly 1:2(32). This means that if 5% of unexposed heart failure patients and 21% of exposed heart failure patients were to experience a 5 point reduction in KCCQ (13% of total patients) then a sample size of 173 would give us 90% power with a two sided significance level of 5% to detect this change.

Targeting a population of around 600 HF patients with the recruitment of 220 at baseline (37% response), and allowing for a dropout of 20% at follow-up means that it is estimated that 175 patients would be recruited to completion within the planned timescale.

Analysis

(i) Descriptive analyses - First, data on the HF cohort will be presented by socio-demographic factors (age, gender and deprivation as measured by Index of Multiple Deprivation), comorbidity status and HF measures. Second, cohort data will be presented by the SF-12, KCCQ, IPQR and EHFScB outcomes.

(ii)(a) Comorbidity prognosis factor testing - Multiple logistic regression methods will be used to compare comorbid groups within the HF population in relation to a five point reduction or more in the KCCQ (overall summary score) between baseline and 1 month and between 1 and 3 months. Unadjusted associations will be presented first followed by associations adjusted for known confounders. These will include age, gender, deprivation, BMI, smoking, alcohol, NYHA class, left ventricular ejection fraction, prior hospital admission, atherosclerotic aetiology and drug prescriptions (beta blocker, angiotensin converting enzyme inhibitor and multi-drug count).
(ii)(b) Multiple linear regression methods will be used to compare comorbid groups (independent variables) within the HF population in relation to KCCQ (physical and overall summary score), Brief IPQ and EHFScB summary scores and the physical component summary of SF-12 (dependant variables) and to investigate change from baseline to 1 month and from 1 to 3 months.

(iii) Modelling change – Multiple logistic regression models will be used to test a pre-specified model (using prior systematic review and general database studies to identify covariates) for a five point reduction in 1-3 months KCCQ (overall summary score). The model will be first fitted with known covariates including comorbidity type indicators. Then the new comorbidity measures that include severity and severity change will be fitted. Measures of Goodness of fit will be used to investigate the contribution of the new comorbidity indicators to an overall prognostic model to predict health status change.

Ethical considerations

New cohort recruitment: The initial study design and recruitment has been based on previously completed studies with patient and public involvement. The cohort study will potentially include patients with end-stage heart failure. Participants will be fully informed of the study's objectives and follow up. Specific consent procedures will be developed through links with Patient and Public Involvement Groups (PPI) including the local British Cardiac Patients' Association group. Participants will be offered assistance in completion of questionnaires at their convenience and informed of the right to withdraw from the study at any time.

Cohort consent and medical record review: The selected HF cohort sample will be cross checked with the healthcare professionals to exclude patients that they consider inappropriate for the study.

When a patient attends the hospital-based clinic in the recruitment period (estimated 8 month time-window), they will be provided with a fully detailed study information sheet explaining the study and asked if they would like to take part. If the patient agrees, then by completing the health survey questionnaire they will be consenting for researchers to use that data and specific consent will be sought to access the patients' medical records. This will enable the collected survey data to be linked with their clinical data, either from hospital or their general practice. This approach will be fully explained to the patient, both verbally and in the study information sheet. The linkage of clinical data to health status information is key to this study and will allow us to examine how health status and health care change over time, and as we have completed in previous studies. These data will be anonymised and stored on secure networks with a data custodian and with access under governance procedures. In terms of cohort follow-up, we will request permission from the patient to send the postal questionnaire in 3-months' time and inform them, that they or their carer can contact us at any time to withdraw from the follow-up study. Permission will also be requested for a telephone reminder conversation from the research nurse if the follow-up questionnaire is not returned within two weeks of the follow-up time points.

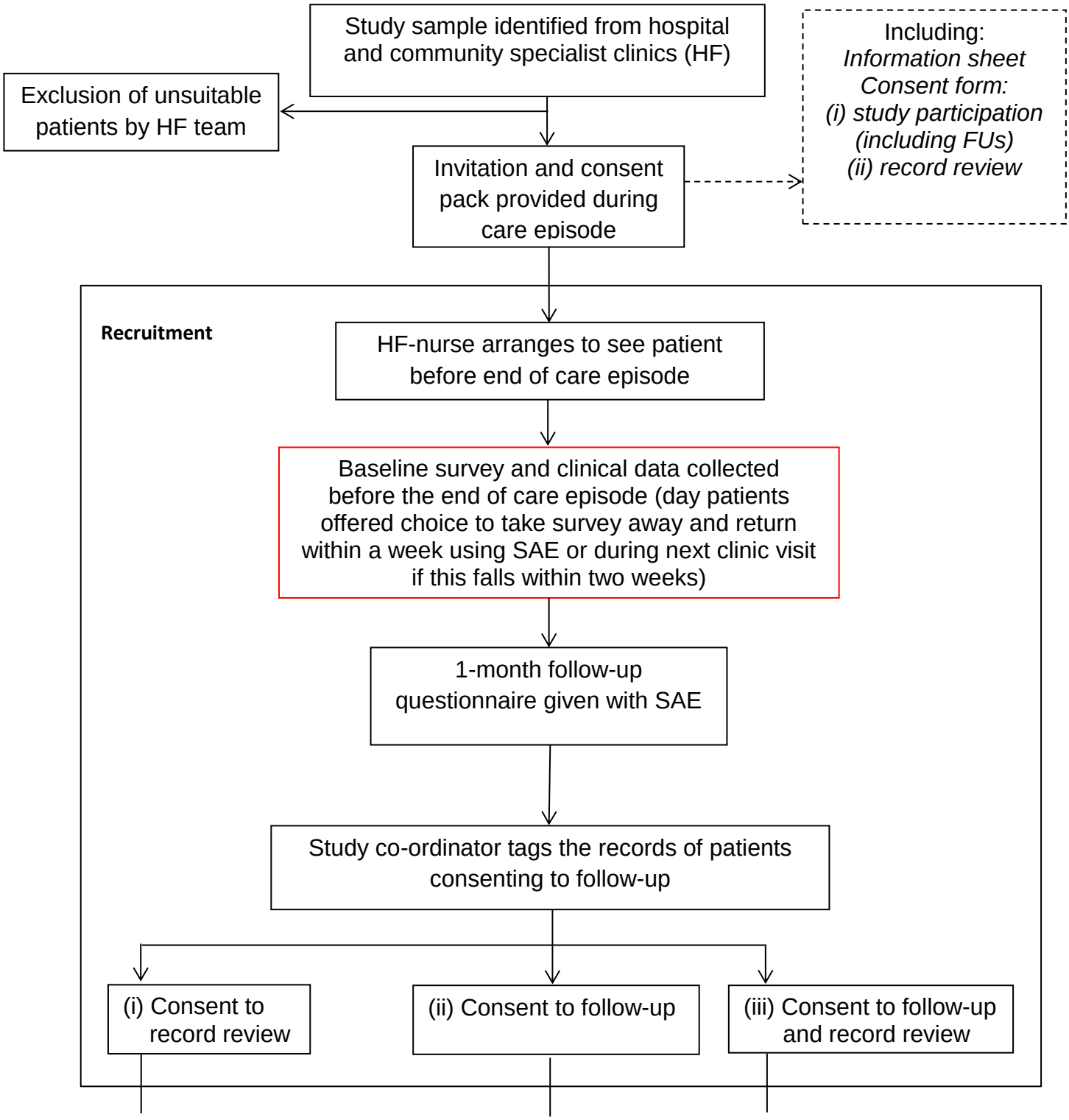
Cohort Steering group: A steering group consisting of health care professionals from the community and hospital teams and patients representatives will be formed for oversight of the study. This steering group will continue to advise on the cohort approach and progression of study recruitment and follow-up.

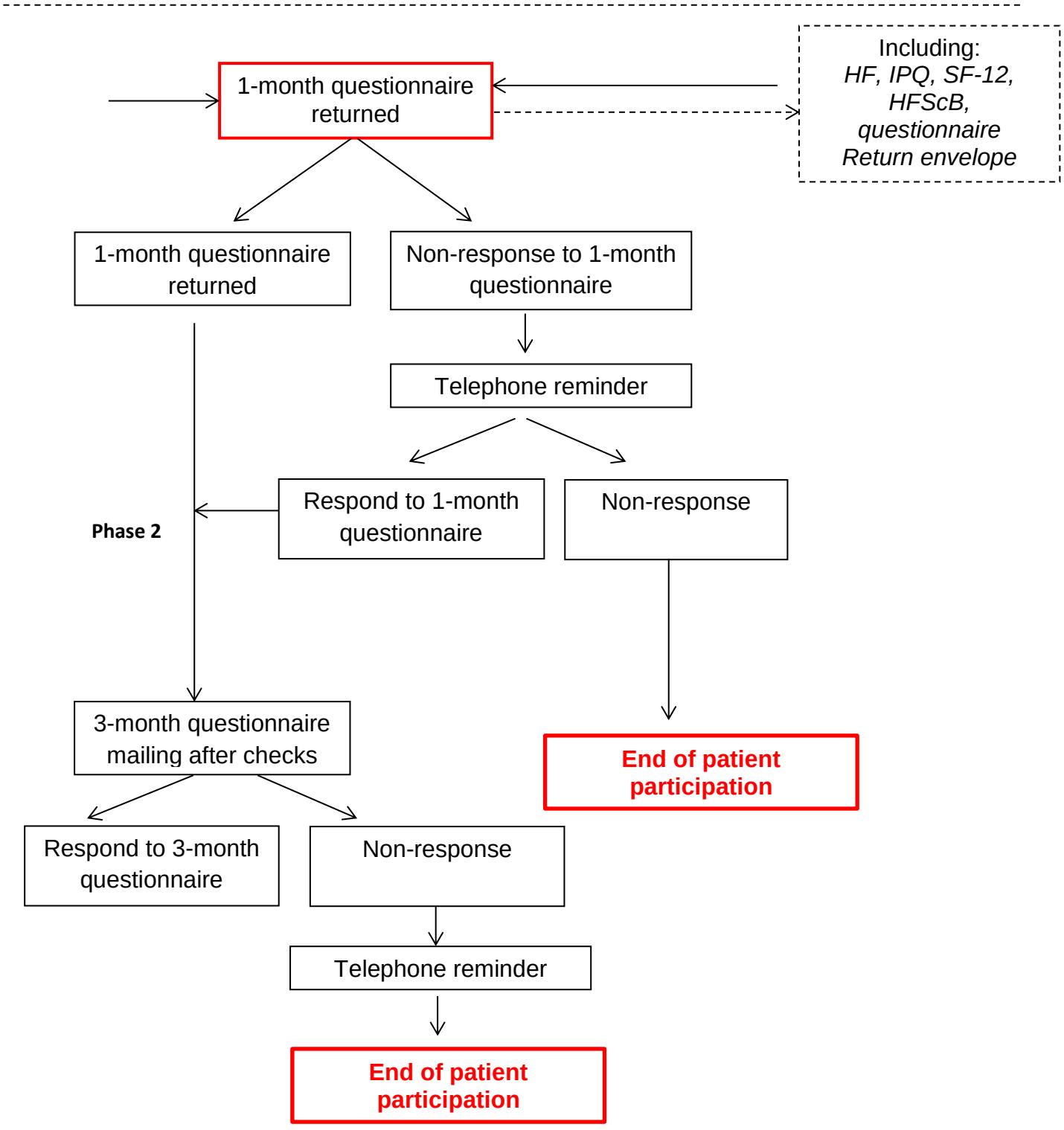
Appendix 1: New York Heart Association functional classification based on severity of symptoms and physical activity[50]

Class 1	**No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.**
Class 2	**Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.**
Class 3	**Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.**
Class 4	**Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.**

Appendix 2: 2C_HF Study - Study Flowchart

Phase 1




1-month questionnaire returned
Including:
HF, IPQ, SF-12, HFScB, questionnaire Return envelope
1-month questionnaire returned
Non-response to 1-month questionnaire
Telephone reminder
Respond to 1-month questionnaire
Non-response
Phase 2
3-month questionnaire mailing after checks
End of patient participation
Respond to 3-month questionnaire
Non-response
Telephone reminder
End of patient participation

Appendix 3: Data collection	**Survey**		**Linked medical records**
Health measures	**Baseline**	**Follow-up**	
KCCQ	**x**	**x**	
SF-12	**x**	**x**	
Brief IPQ	**x**	**x**	
EHFScB	**x**	**x**	
Socio-demographic			
Age	**x**		
Gender	**x**		
Index of Multiple Deprivation	**x**		
Cardiovascular risk factors: smoking, BMI, family history	**x**		**x**
Comorbidity status:			
• Type			**x**
• severity measure if available e.g. eGFR (renal), FEV1 (COPD), HBA1C (diabetes) and drug prescriptions and dose for previous year			**x**
• Previous comorbidity admissions			**x**
• Previous comorbidity general practice consultations			**x**
• Multi-drug count			**x**
Heart failure status:			
• Aetiological factors			**x**
• Indicators of HF status (blood tests, ECG and ECHO)			**x**
• NYHA class	**x**	**x**	
• Drug therapies in the previous 12 months.			**x**
• Previous HF admissions			**x**
• Previous HF general practice consultations			**x**

E20 Quality of Life Outcome study 3: Swedish HF registry study

Title: Heart failure comorbidity and self-reported symptoms and quality of life: the Swedish Heart Failure study.

Abstract:

Background: Comorbidity is common in HF and is associated with much worse outcomes. How comorbidity influences patient-centred symptoms and Quality-of-Life (QoL) is unknown.

Research Question: What is the effect of comorbidity on symptoms, functional capacity and QoL in the general population of HF?

Method: Observational cohort design using the Swedish Heart Failure Registry (S-HFR).

Database and Analysis: The S-HFR database contains information on 50,000 patients with data on HF, comorbidity and patient-reported outcome measures (PROMs). Patient factors will be investigated for their mediator and moderator effects on the association between the comorbidities and PROMs using linear and logistic regression methods.

Dissemination Plan: International workshop of nurse specialists to integrate findings into guidelines and practical tools for patient care. Dissemination through Heart Failure Nurse Curriculum, publication and conference presentations

Expected Value to Patients: Better trained HF nurses and patient-centred interventions aimed at improving the QoL of HF patients with comorbidity.

Introduction:

Context: Heart failure (HF) carries a high mortality risk with 38% of patients dying within a year of diagnosis[1]. Despite advances in medical treatments, quality of life in heart failure remains poor with half of all patients experiencing daily symptoms including breathlessness and fatigue[2] and up to half of patients remaining symptomatic despite optimisation of treatments[3]. Patients suffer problems with walking, activities of daily living, self-care, pain and depression and these symptoms are exacerbated with increasing age[4]. This poor quality of life worsens over time as the disease progresses[5] and is itself associated with hospital admission[6] and death. Comorbidity is a major contributor to these poor outcomes in HF with 68% of patients having at least 2 additional chronic conditions[7] and most more than five[8-12]. These comorbidities have been associated with increased hospital admissions, mortality[8,13-15], symptom burden[16-17] and reduced physical function and quality of life[18]. Most of the current evidence has focused on the risk of hospital admission and death, but much less is known about which and how comorbidities influence HF patient-reported outcome measures.

Heart failure nursing: Heart failure specialist nurses (HFSN) have advanced knowledge and nursing skills to prevent and manage HF patients' symptoms and to provide interventions to prevent deterioration. The efficacy of this service in now well documented[19] with HFSN services leading to fewer hospital admissions and deaths and improved QoL[20-22]. However nurses are now seeing increasing numbers of HF patients with comorbidity. This poses new and important challenges for HF nursing and clinical care. Comorbidity in HF can cause conflicts in treatments and drug interactions. For HF patients with comorbidity, self-care is managed through multiple different disease-specific self-management plans which leads to confusion, poor knowledge, conflicting or duplicated information and poor sense of control and adherence[23-35] ultimately leading to worse outcomes[26].

The management of co-morbidities is a key component of the holistic nursing care of HF patients. Whilst guidelines should help nurses to make decisions in their daily practice, much of the guidance that nurses' provide patients on the key components of self-care behaviour such as lifestyle advice and symptom monitoring and management, are not adequately included in guidelines. Comorbidity, which is an important consideration, has only brief inclusion in this guidance and focuses on medical management[27]. In the same way that clinical care is organised around specialism, the review of individual conditions is most often the focus of nurse education and particularly specialist nurse curricula. These combined factors mean that specialist HF nurses lack knowledge about comorbidity, shared disease mechanisms or how to provide optimal management for the HF and the comorbidities for a high percentage of HF patients. Whilst SHFN has demonstrated excellent advantages for HF patients through focused nursing care approaches on the management of aetiology, pathophysiology and symptoms, there now needs to be a broader specialist approach which takes account of the growing number of patients with comorbidity.

HF nursing care gap: Comorbidity care needs to be better incorporated into the overall management of HF patients so that they receive integrated information and nursing care for the main comorbidities that burden them. This needs to be facilitated by more comprehensive inclusion of comorbidities in HFSN education programmes. In order to achieve this we need to know which comorbidities are the most burdensome to HF patients by investigating patient reported outcome measures. In understanding the relationship between comorbidity in HF and outcomes, two questions raised are:

- which other factors in comorbid groups *influence* HF outcomes, (factors that also require addressing to improve outcomes – i.e. mediators)?

- which other factors in comorbid groups *determine* HF outcomes, (factors which interact with the comorbidity to make it worse – i.e. *moderators*)?

There are a range of potential factors that might mediate or moderate the association between comorbidity and poor outcomes in HF which include *patient factors and healthcare interventions*.

Patient factors that complicate HF outcomes have been identified but their interrelationships have not been clearly disentangled. Gender is one factor indicated as important in HF comorbidity. Comorbidity profiles and prevalence differs by gender and whilst women with HF have lower overall risk of mortality, this differs in the context of comorbidity. Diabetes has been found in a number of studies to have a stronger association with mortality in women than men[28-30]. In addition women often have a higher symptom burden and poorer functional capacity[31-32]. Other patient factors that have been found to influence the effect of comorbidity have included aetiology[33] and age[34-35]. Less investigated factors are the burden and challenges of self-care. Whilst better self-care behaviour reduces hospital admissions in HF[36], its relationship with comorbidity and QoL is not clear [37-38]. Prior patient factor studies have focused on specific diseases or used composite scores such as the Charlson Comorbidity Index but information on the range of individual comorbidities that are most influential on quality of life or their mediating patient factors has not been investigated.

Healthcare factors include the differential application of evidence based interventions across comorbid HF groups. The majority of evidence for the benefits of pharmacological treatments in HF is derived from large clinical trials that have excluded patients with complex comorbidities[39]. The application of these guidelines can be challenging as there is little evidence of potential risks and benefits in patients with comorbidities or on how to reconcile optimal treatment in the presence of co-existing chronic disease, the management of which may conflict with that of HF. We do not know how differential treatment might influence the relationship between comorbidity and quality of life in HF.

Key questions this project will address are:

- Which HF comorbidity groups are important determinants of poor patient-reported outcomes and how can such high-risk groups be identified using routinely collected clinical data by HF nurses?
- Which factors in comorbidity and HF are important in influencing poor patient-reported outcomes and how might these factors be targeted in the nursing care of the patients?
- How will identifying important comorbidity and patient factors in poor HF outcomes be incorporated in nurse education and guidelines and practical tools for patients?

We have completed a systematic review[40] of comorbidity and prognosis in the general population of HF and found no comorbidity prognosis studies that focused on quality of life. Therefore, this proposal has been developed in collaboration with Professors Strömberg, Jaarsma, Dahlström and Kadam to answer the questions on the relationship between HF, comorbidity and patient-reported outcomes using the largest available database, the Swedish Heart Failure registry, which has collected prospective data on HF patients since 2001.

Aim & Objectives:

The overall aim is to investigate the influence of comorbidities on symptoms, functional capacity and quality of life outcomes in HF. The objectives using the Swedish HF registry data will be to investigate:

i) the association between cardiovascular disease (CVD) and non-CVD comorbidities and patient-reported symptoms, physical function and quality of life at one year follow-up

ii) whether the association between cardiovascular disease and non-CVD comorbidities and patient reported outcomes at one year are mediated or moderated by patient or healthcare factors.

Design: An observational cohort study.

Methods

Data: The Swedish Heart Failure Registry (S-HFR) is a National Quality Register, created in 2001 at Linköping University, which provides an enriched source of prospective clinical and patient data from the general population of HF patients in Sweden. The S-HFR consists of about 70 variables including demography, concomitant diseases, diagnostic procedures, haemodynamics, laboratory data, symptoms, functional capacity, medication and quality of life. After 1 year of follow-up, data on mortality and morbidity are collected from National official databases. Information on medications, quality of life, and functional capacity are also collected from a questionnaire sent out to all patients after 1 year of follow-up with >80% response rate. Patients diagnosed with HF are registered either at discharge from hospital (within 1 month) or following an out-patient visit and so the registry captures patients from both primary and secondary care settings which makes it an important resource for epidemiological research

Sample: A cohort of HF patients from the S-HFR will be used to investigate the effect on cardiac and non-cardiac comorbidities on symptoms, physical function and quality of life. Clinical data will be extracted at baseline and one year follow-up from the S-HFR of all acceptable patients who were registered in a ten year time window from January 2005 until January 2015 and aged ≥40 years and over.

Exposures: Cardiovascular (Myocardial Infarction, hypertension, Atrial Fibrillation/flutter, Heart valve disease, Dilated cardiomyopathy) and non-cardiovascular comorbidities (depression, diabetes (including Hba1c), Chronic Obstructive Pulmonary Disease, chronic kidney disease (based on eGFR), cancer, dementia.

Mediators and Moderators:

Patient factors: Demographic (Age, gender), lifestyle (alcohol, smoking), clinical and risk factors (aetiology, BMI, number of non-CV drugs), heart failure severity (LVEF%, BNP, NYHA), self-care ability, activities of living and physical activity.

Healthcare factors: Procedures (revascularisation, devices, heart valve replacement), drugs (ACEi/ARB, beta blocker).

Outcomes: The EQ5D will be used as the primary 'outcome' measure in this analysis, with a high score indicating better perceived health status. Secondary outcomes will include symptoms (Shortness of Breath (SOB), fatigue, pain/discomfort, anxiety/depression), physical function (mobility, self-care, usual activities) and mortality.

Analysis

Analysis will be performed in four steps; descriptive analyses, crude associations, test of indirect effects (mediators), test of interactions (moderators).

(i) Comorbidities will be described by the patient and healthcare factors and by the physical function, symptoms and quality of life outcomes. Data will be presented as means and standard deviations (SD) for normally distributed continuous data, whilst skewed continuous data will be presented as medians with interquartile ranges [IQR]. Dichotomous data will be presented as counts and percent prevalence. Significant difference between groups will be determined by parametric tests using independent samples t-test, non-parametric tests using the Wilcoxon rank-sum test and categorical variables between groups using the Chi-square test. A p-value will be considered significant if ≤0.05.

(ii) The associations between the comorbid exposure groups and EQ-5D score compared to the reference groups will be estimated using linear regression methods, and expressed as the difference in EQ-5D score. These analyses are presented as unadjusted values with 95% CI, adjusted first for all remaining factors. Ordinal logistic regression will be used to measure the strength of association between the comorbidities and other symptom and physical function outcomes.

(iii) Investigation of mediators: The patient and healthcare factors that differed significantly between comorbid and non-comorbid groups in step (i) will be investigated for their strength of association with the comorbidity exposures and separately with the outcomes. Where both are significant and the association between the comorbidity and outcome is significant in step (ii) further investigation will be as follows a) The comorbidity association with the outcome will be adjusted by the factor. Other potential confounding variables between the potential mediator and the outcome will then also be entered into the model to prevent collider bias[41]. Indirect effects will then be calculated using the Kenny and Judd difference of coefficients approach[42] where:

$$B_{\text{indirect}} = B - B_1$$

Where B is the coefficient of the exposure in the unadjusted association between the comorbidity and the outcome and B_1 is the coefficient of the comorbidity exposure which is adjusted by the mediator.

Statistical test of the indirect effect will use bootstrapping for standard errors and to calculate 95% confidence intervals for the indirect effect, an approach that increases power in smaller samples[43].

(iv) Investigation of moderators:

Comorbid effects on one year patient-reported outcomes will first be stratified by patient and healthcare factors. Where there is separation of the confidence intervals across strata we will estimate how the observed associations between a combined group (comorbid exposure with a specific patient or healthcare factor) and EQ-5D score differed from the expected estimates compared to the reference group. The observed estimates will be calculated for the comorbid exposure group, the factor group and the combined group in linear regression, and then the expected figures will be calculated by adding the estimates for the comorbid exposure to the estimate for the factor of interest. The difference between the observed and expected estimates for the combined groups in this additive approach would allow the assessment of the potential casual interaction between the comorbid exposure and the factor of interest. Product terms will be tested in the model using log-likelihood ratio tests to investigate the statistical significance of the interaction. Finally, we will compare each combined group directly with the respective comorbid exposure group, to assess the magnitude of the factor impact on EQ-5D score. Each comparison will be adjusted for the remaining factors.

Steering group

1. A steering group of HF patients and clinical nurse experts in heart failure, renal disease, respiratory disease and diabetes has informed the development of the questions in this proposal (UK).

2. The study project steering group will be Professor Strömberg and Professor Jaarsma (HF nurse research expertise), Professor Dahlström (S-HFR expertise), Professor Kadam (comorbidity and epidemiology expertise) and a S-HFR Statistician (methodological expertise - TBA).
3. As part of the workshop and dissemination activity a steering group will be set up. The purpose of the steering group will be to develop research, training and guidelines activity as result of the study findings. The steering group will draw on international network of nursing academics and work with appropriate PPI members.

Time-lines with achievable milestones

HFA Project	March 16-May 16	June 16 – Aug 16	Sept 16-Nov 16	Dec 16 – Feb 17	March-May 17 (post fellowship)
Academic skills development					
ANOVA/GLMs with SPSS Short course (UCL)	April 2016				
Linear and Logistic Regression Models using STATA (Bristol University)	May 2016				
Writing for publication					
Project					
Ethics and Governance					
Expert guidance in the S-HFR and statistical analysis (Sweden)					
Collaborative working (UK & Sweden)					
Data analysis					
Retrieval of data and cleaning					
Analysis					
Writing up					
Outputs					
Nurse Workshop					
Update of heart failure matters website					
Report for ESC					
EuroHeartCare					April 2017
Heart Failure conference					May 2017
Publication submission					

Dissemination plan:

International Nurse Workshop: As part of the dissemination an international workshop of nurse specialists will be held including nurses from specialists groups guided by the findings of the study. These are likely to include nurses from the HFA heart failure curriculum development task force group, the National kidney Foundation, International Diabetes Federation, European respiratory society and the European depression association. The remit of the group will be to perform an analysis of current specialist guidelines to identify specific, common and potentially conflicting guidance across guidelines. The intention will be to develop combination nurse guidelines targeting the most prevalent and important HF comorbidities that influence poor quality of life and underpinned by the research findings. The combining of guidelines is likely to include (i) HF specific components (ii) add on advice (comorbidity specific) (iii) shared advice tailored to the comorbidity and (iv) potential conflicts to be resolved (see attached table for a diabetes mellitus and COPD example). These will additionally be incorporated into a combined patient self-care check list.

Nurse curriculum: The research findings together with the information from the workshop will be used to inform the HFA nurse curriculum.

Wider dissemination: The findings of the study will be presented at ESC congresses including EuroHeartCare and Heart Failure 2017. Abstracts will be submitted for publication with the aim to publish at least one article by the end of the fellowship (aimed at the European journal Heart Failure).

Expected value of results to patient care

Comorbidity has become a key challenge for healthcare services globally[44]. With up to 50 million Europeans with comorbidity, a figure set to rapidly increase[45], better integration of healthcare policies to improve outcomes for patients has become a European health policy priority[46]. HF patients with comorbidity currently receive fragmented care by different specialists which leads to poor integration of information and self-care deficits for patients. These patients are admitted into hospital more frequently, experience poor quality of life and earlier death. Better scientific knowledge about which comorbidities influence patient reported outcomes will provide the necessary information to develop integrated nurse guidelines (International Nurse Workshop), practical patient tools (comorbidity self-care checklists that are tailored to patients' needs) and improve HF nurse education (HFA nurse curriculum group). This will provide patients with holistic, patient-centred care with the most potential benefits for improving quality and quantity of life.

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Examples: integrated guideline

	Diabetes	COPD
HF specific care		
Patient self-care	Daily weights, HF medication and diuretic self-titration, symptom assessment (breathlessness, swelling, fatigue), cardiac rehabilitation.	
Clinical care	Diagnostic tests (echoe, ECG, BNP), HF drug up titration and monitoring, assessment for devices, heart rate control	
Add on comorbidity care		
Patient self-care	Medicines management including for example oral hypoglycaemic drugs and insulin. Monitoring (blood glucose). Dietary advice (high fibre, low –glycaemic-index carbohyrates, low-fat dairy products and avoidance of hypoglycaemia with regular meals). Personal care (e.g. skin and foot care)	Medications management and use and assessment of inhaler effectiveness. Monitoring (peak flow), dietary advice (good healthy diet but avoid low BMI <21 kg/m^2). Personal care (e.g. oral care with inhaler use).
Clinical care	Extra renal monitoring in diabetes, eye surveillance. Optimising glucose management and monitoring (HbA1c, serum glucose).	Severity assessment using symptoms, exacerbation history and spirometry. Optimising COPD medication and monitoring effectiveness.
Tailored shared care		
Patient self-care	Smoking cessation, exercise training, symptom recognition for example depression and erectile dysfunction, understanding prognosis in context of comorbidity.	Smoking cessation, pulmonary and cardiac rehabilitation, exercise training, symptom recognition for depression, muscle weakness and fatigue, understanding prognosis in context of comorbidity. Influenza vaccine.
Clinical care	Management of common shared comorbidities such as depression, erectile dysfunction and hypertension, blood monitoring and interpretation in context of comorbidity, prognosis in context of comorbidity, palliative end of life care.	Management of common shared comorbidities such as depression, metabolic syndrome, skeletal muscle dysfunction, hypertension. Tailored exercise training (attention to both diseases causing weight loss, nutritional abnormalities and skeletal muscle dysfunction), blood monitoring and interpretation in the context of comorbidity, prognosis in context of comorbidity, palliative end of life care.
Potential conflicts		
Patient self-care	Symptom recognition (diabetic neuropathic pain may confuse cardiac pain or diabetic neuropathy may mask pain and require closer recognition of other symptoms indicative of cardiac events). Burden of self-maintenance/management and polypharmacy with both diseases.	Symptom recognition (breathlessness – how to attribute to which disease for guiding self-management – inhalers or diuretic?). Burden of self-maintenance/management and polypharmacy with both diseases.
Clinical care	Avoid thiazolidinediones (glitazones) due to their effects on sodium and water retention and increased risk of worsening HF. Avoid metformin in patients with severe renal or hepatic impairment	Interpretation of spirometry in hypervolemic states. Use of selective beta-1 adrenoceptor antagonist. Caution with oral corticosteroids (cause sodium and water retention and worse HF)

E20 Trials acronyms

CHARM: The Candestartan in Heart Failure: Assessment of reduction in mortality and morbidity

CHART: Chronic heart failure analysis and registry in Tohoku district

COACH: Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure

DIAMOND: Danish Investigations of Arrhythmia and Mortality on Dofetilide

DIG: Digitalis Investigation group

ECHOS: EchoCardiography and Heart Outcome Study

EFFECT: Enhanced feedback for effective cardiac treatment

EHFS: EuroHeart Failure Survey 11

GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure

HOLA: HF: Observation of local admissions

HSIS: HF survey in Israel

VMAC: Vasodilation in the management of acute decompensated heart failure

SENIORS: The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with HF

OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure

REMADHE: Long-term Prospective Randomized Controlled Study Using Repetitive Education at Six-Month Intervals and Monitoring for Adherence in Heart Failure Outpatients

VMAC: Vasodilation in the management of acute decompensated heart failure

JCARE-CARD: The Japanese Cardiac Registry of Heart Failure in Cardiology

TIME-CHF: Trial of intensified medical therapy in Elderly patients with Congestive Heart failure Norwegian HF register

JCARE-CARD: The Japanese Cardiac Registry of Heart Failure in Cardiology

MAGIC database: Meta-Analysis Global Group in Chronic Heart Failure

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