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FASTTRACK – CLINICAL RESEARCH
Heart failure and cardiomyopathies

Benefit of early initiation of disease-modifying therapy in community-based patients with suspected heart failure

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Abstract

Background and Aims The initiation of heart failure (HF) therapies at the time of detection of an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in community-based patients with suspected HF may reduce the risk of early adverse outcomes. The aim of this analysis was to estimate the potential benefit of the early initiation of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and/or mineralocorticoid receptor antagonist (MRA) in patients with suspected HF and a pre-existing non-HF-related indication for treatment.

Methods A cohort study was performed from 1 January 2015 to 31 March 2023 using linked primary and secondary care data from the Clinical Practice Research Datalink (CPRD). Patients without a history of HF and who were not prescribed an SGLT2i or MRA were followed up for 12 months following a community-measured NT-proBNP ≥ 400 pg/mL. The primary outcome was a composite of a HF hospitalization as the first recorded HF diagnostic event or death from any cause in patients without a documented HF diagnosis during follow-up and who did not undergo echocardiography. The effect of the initiation of treatment with an SGLT2i, MRA, or both (effective treatments for HF regardless of ejection fraction) was modelled at the time of NT-proBNP measurement in patients with a pre-existing non-HF-related indication for these drugs (Type 2 diabetes, chronic kidney disease, or resistant hypertension) using treatment effect estimates from meta-analyses of randomized placebo-controlled trials in patients with established HF.

Results An NT-proBNP ≥ 400 pg/mL was recorded in 74 945, 24 082 (32%) of whom had a HF diagnosis recorded within 12 months, 15 398 (64%) as an outpatient and 8684 (36%) during a HF hospitalization. If both an SGLT2i and MRA were commenced at the measurement of an elevated NT-proBNP in those with a pre-existing non-HF-related indication, we estimated that for every 1000 patients treated, 84 would avoid either a HF hospitalization or death at 12 months, equating to a number needed to treat of 12 (95% confidence interval 11–14).

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Conclusions In community-based patients with suspected HF and elevated NT-proBNP, the early initiation of an SGLT2i and an MRA in patients with a pre-existing non-HF-related indication for treatment may reduce the risk of early adverse outcomes whilst awaiting diagnostic echocardiography. These findings suggest a simple clinical strategy with potentially large public health benefits.

Structured Graphical Abstract

Key Question

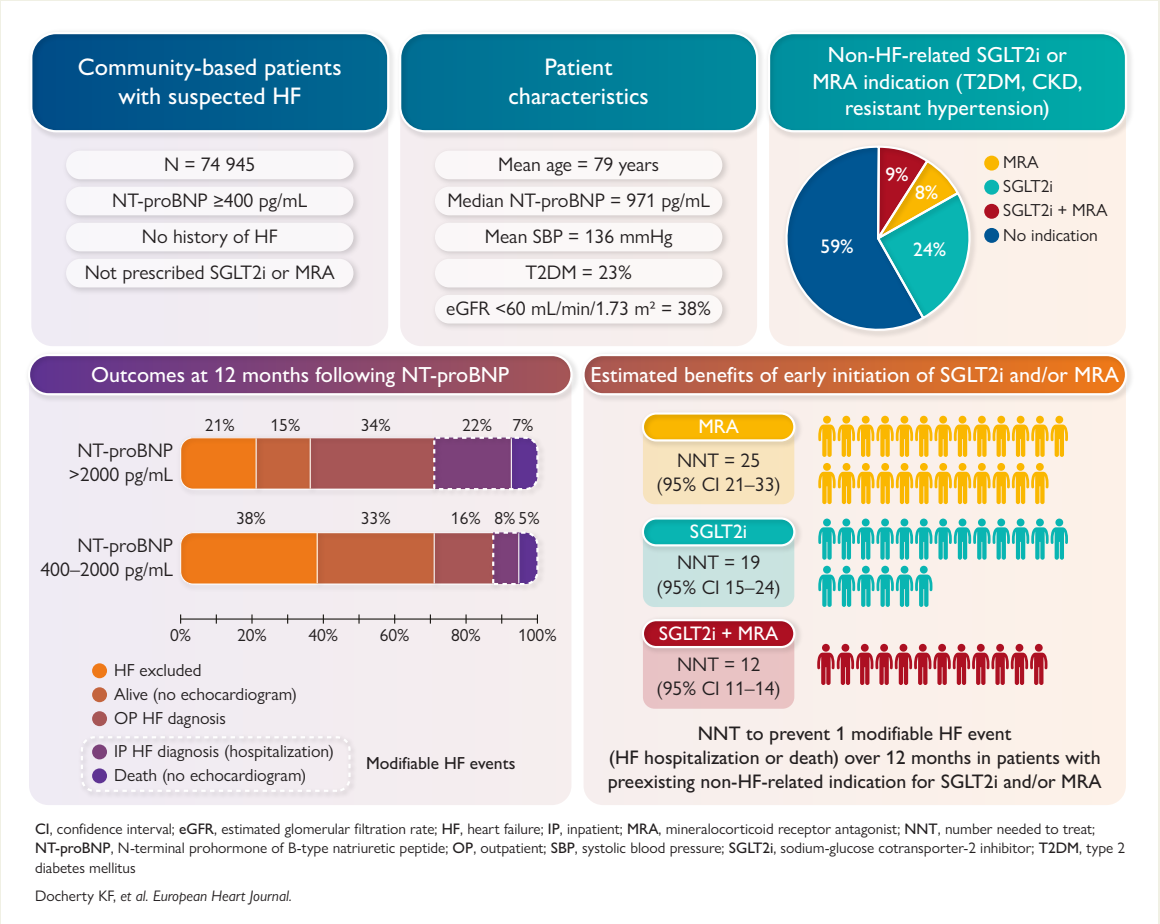
What is the potential effect of early initiation of disease-modifying therapy in community-based patients with suspected heart failure (HF) at the point of detection of elevated natriuretic peptide levels?

Key Finding

Patients without a history of HF and who were not prescribed an SGLT2i or MRA, were followed up for 12 months if NT-proBNP was ≥400 pg/mL. If both an SGLT2i and MRA were commenced in those with a preexisting non-HF-related indication, it was estimated that for every 1000 patients treated, 84 would avoid either a HF hospitalization or death at 12 months.

Take Home Message

A non-HF-related indication for an SGLT2 inhibitor and/or MRA is an opportunity to immediately initiate disease-modifying therapy in patients with suspected HF. This easy-to-implement strategy could have a substantial and clinically meaningful effect on reducing early adverse outcomes.



CI, confidence interval; **eGFR**, estimated glomerular filtration rate; **HF**, heart failure; **IP**, inpatient; **MRA**, mineralocorticoid receptor antagonist; **NNT**, number needed to treat; **NT-proBNP**, N-terminal prohormone of B-type natriuretic peptide; **OP**, outpatient; **SBP**, systolic blood pressure; **SGLT2i**, sodium-glucose cotransporter-2 inhibitor; **T2DM**, type 2 diabetes mellitus

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The estimated benefit of the early initiation of disease-modifying therapy in community-based patients with suspected heart failure. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; IP, inpatient; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OP, outpatient; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, Type 2 diabetes mellitus.

Keywords Heart failure • Hypertension • Diabetes • Chronic kidney disease • Natriuretic peptides

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Introduction

Unfortunately, patients presenting with suspected heart failure (HF) in the community frequently experience delays in both diagnostic echocardiography and the initiation of disease-modifying therapy.[1–4] These delays may contribute to preventable HF hospitalizations and deaths.[4,5] Two classes of drugs, sodium-glucose cotransporter 2 inhibitors (SGLT2is) and mineralocorticoid receptor antagonists (MRAs), reduce the risk of HF hospitalization and death across the entire spectrum of ejection fraction in patients with HF.[6–8] Both treatments also lead to rapid and substantial reductions in morbidity and mortality and are generally well-tolerated and safe.[9–14] Whilst it could be argued that all patients with a high likelihood of having HF (e.g. by virtue of an elevated natriuretic peptide level) could be started on these treatments whilst awaiting investigation (echocardiography) and treatment for HF, this approach would lead to unnecessary treatment of some patients who later have HF excluded. However, SGLT2is are also recommended treatments for Type 2 diabetes and chronic kidney disease (CKD) and MRAs for chronic kidney disease and resistant hypertension, although many patients with these conditions are not prescribed an SGLT2i or an MRA.[15–21] Diabetes, CKD, and hypertension are also common comorbidities in patients with HF and greatly elevate risk in patients with HF. If an SGLT2i, an MRA, or both were introduced at the time of suspected development of HF in patients with one or more of Type 2 diabetes, CKD, or resistant hypertension, these treatments would not only be appropriate but also anticipated to have a substantial potential benefit in particularly high-risk patients during a period of significant vulnerability while awaiting diagnostic work-up.

In this retrospective cohort study, we used a large, contemporary epidemiological dataset to estimate the potential benefit of the early initiation of disease-modifying therapy on outcomes in community-based patients with suspected HF.

Methods

Data sources

The Clinical Practice Research Datalink (CPRD) is an anonymized patient database comprising 46.5 million patient records with current patients representing ~24% of the UK population with a similar distribution of age, sex, and ethnicity as the general UK population (Supplementary data online). We linked primary care CPRD Aurum records (December 2023 build) to hospital admission records on an individual patient basis using the Hospital Episodes Statistics (HES), a dataset that records all hospital admissions in England. Approval for this study was granted by the CPRD Research Data Governance Committee (24_004778).

Patient population

Patients aged ≥18 years were included if they had no prior documented diagnosis of HF (either a primary care diagnosis or a record of a HF hospitalization) and had a community-measured N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥ 400 pg/mL between 1 January 2015 and 31 March 2022. The first recorded NT-proBNP during the study period was considered as the index measurement. An NT-proBNP concentration of ≥400 pg/mL was chosen as this is the rule-out value recommended in the National Institute for Health and Care Excellence (NICE) guidelines in patients with signs or symptoms of suspected HF.[22] In England, the only authorized primary care indication for the measurement of NT-proBNP concentrations is in patients presenting with signs and/or symptoms of suspected *de novo* HF. Patients were eligible for inclusion if they had been registered with their general practice for at least 12 months and if their data were labelled as eligible for HES linkage. Patients without a recorded estimated glomerular filtration rate (eGFR) in the 12 months before NT-proBNP measurement and those prescribed either an SGLT2 inhibitor or an MRA before or at the time of NT-proBNP measurement were excluded from the study.

Baseline characteristics

Baseline characteristics for included patients were extracted from primary care and hospitalization diagnostic codes using Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) and International Classification of Diseases, 10th revision (ICD-10), respectively. The absence of a diagnostic code for any comorbidity was considered as evidence that the patient did not have that comorbidity. For systolic blood pressure, body mass index (BMI), eGFR, potassium, and haemoglobin, values recorded in the 12 months leading up to NT-proBNP measurement were used. Records relating to medications of interest [diuretics, renin–angiotensin system (RAS) inhibitors, and beta-blockers] were selected using CPRD product codes if a patient had a recorded prescription in the 12 months before NT-proBNP measurement.

Outcome definitions

The outcomes of interest in this study were the occurrence of a HF diagnosis (the first event recorded either as an outpatient or as a hospitalization with HF documented in any diagnostic position) and death from any cause. Patients entered the study at the date of the detection of an NT-proBNP ≥ 400 pg/mL and were followed for the occurrence of these outcomes for 12 months (*Figure 1*). The diagnostic codes used to define these events are detailed in Supplementary data online, *Table S1*. Codes relating to hospital admissions were derived from the ICD-10, and those relating to primary care diagnoses were derived from primary care SNOMED-CT codes.

Definition of indication for disease-modifying therapy

A patient's eligibility for the initiation of an SGLT2i, an MRA, or both at the time of NT-proBNP measurement was assessed using their documented comorbidities and systolic blood pressure and biochemistry values recorded within the 12 months before NT-proBNP measurement. Eligibility for the initiation of an SGLT2 inhibitor was defined as the presence of Type 2 diabetes and/or CKD [defined as eGFR 20–44 mL/min/1.73 m^2, or eGFR 45–90 mL/min/1.73 m^2 with a history of diabetes or urinary albumin to creatinine ratio (uACR) ≥ 22.6 mg/mmol]. Eligibility for the initiation of an MRA was defined as having Type 2 diabetes, an eGFR between <90 and ≥25 mL/min/1.73 m^2, potassium ≤ 5.0 mmol/L and a uACR ≥ 3 mg/mmol, and/or resistant hypertension [defined as systolic blood pressure ≥ 130 mmHg on ≥3 anti-hypertensives (a RAS inhibitor; a loop, thiazide, thiazide-like, or potassium-sparing diuretic; calcium channel blocker; beta-blocker; alpha blocker; central alpha-2 agonist; or a vasodilator) with an eGFR ≥ 30 mL/min/1.73 m^2 and potassium ≤ 5.0 mmol/L].

Statistical analysis

Baseline characteristics are presented as frequencies (%) for categorical data and means (standard deviations) and medians [interquartile ranges (IQRs)] for normally and non-normally distributed data, respectively. The frequency and proportions of patients with missing data are displayed. The incidences of outcomes of interest were calculated as event rates per 100 patients followed up for 2 weeks, 6 weeks, 6 months, and 12 months following measurement of NT-proBNP and are displayed graphically using Kaplan–Meier curves according to NT-proBNP concentration (400–2000 pg/mL or >2000 pg/mL).

The estimated treatment effects of SGLT2i and MRA expressed as hazard ratios (HRs) with 95% confidence intervals (CIs) were extracted from published meta-analyses of large, randomized placebo-controlled trials in patients with HF across the full spectrum of ejection fraction.[6,8] Treatment effect estimates for HF hospitalization and all-cause mortality as individual outcomes and the composite of time-to-first cardiovascular death or HF hospitalization were identified (see Supplementary data online, *Table S2*). Assuming that the benefits of these medications are

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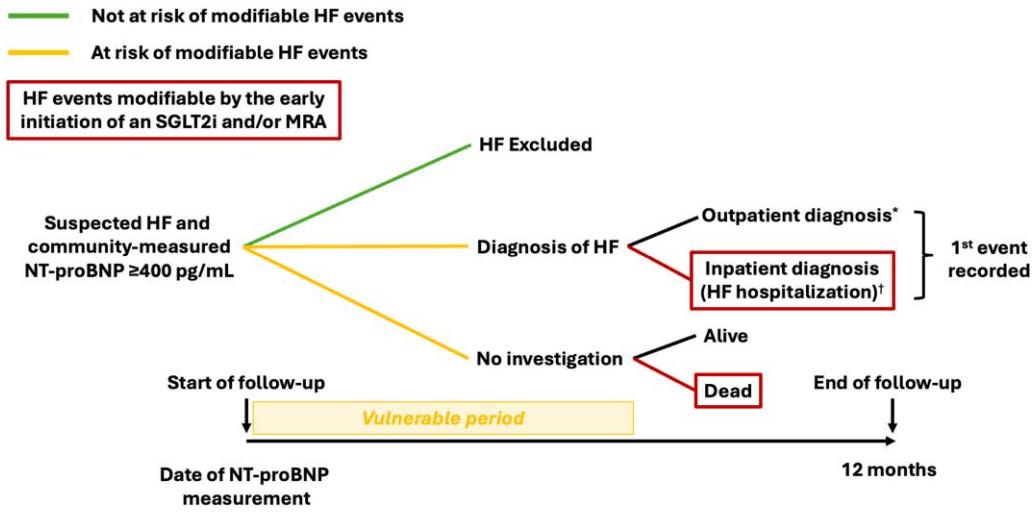

Figure 1 Study flowchart and the definition of HF events modifiable by the early initiation of an SGLT2i and/or MRA. *HF hospitalizations or deaths that occurred following an outpatient diagnosis of HF were not included in the modelling analysis. †Deaths that occurred following a HF hospitalization were not included in the modelling analysis. HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

independent of each other and additive, we estimated the combined effect of an SGLT2i and an MRA using the putative placebo method.[23,24] The combined HR was calculated as the product of the individual HRs of active treatment vs placebo, with 95% CIs calculated from the square root of the sum of squared standard errors of the logarithmic HRs. For modelling, we defined outcomes potentially modifiable by the early initiation of disease-modifying treatment within 12 months of NT-proBNP measurement as a HF hospitalization that was the first recorded HF diagnostic event, death from any cause in patients who did not have a non-fatal HF failure event (either a hospitalization or an outpatient diagnosis) and did not undergo echocardiography at any point, and a time-to-first composite of the two (*Figure 1*). For analyses using the composite of HF hospitalization or all-cause mortality, the published effects of an SGLT2i and an MRA on the composite of time-to-first cardiovascular death or HF hospitalization were used as published estimates for a composite including all-cause mortality were not available (see Supplementary data online, *Table S2*). The HRs and 95% CIs were applied to observed event rates among patients with a pre-existing indication for an SGLT2i and/or MRA to estimate treated event rates and 95% CIs. The number of events estimated to be prevented by treatment was calculated at 2 weeks and 6 weeks based on guidance for expedited (NT-proBNP > 2000 pg/mL) and routine (NT-proBNP 400–2000 pg/mL) echocardiography, respectively, and 12 months following detection of an NT-proBNP ≥ 400 pg/mL.[22,25] The absolute benefit was expressed as the number of events prevented per 1000 patients treated and the number needed to treat (NNT) to prevent one event at each time point. All analyses were performed in the overall population with an indication for treatment and according to NT-proBNP concentration of 400–2000 pg/mL or >2000 pg/mL. Statistical analyses were performed using R 4.4.0.

Results

Patient characteristics

In the 74 945 patients without a prior diagnosis of HF included in the study who had a community-measured NT-proBNP ≥ 400 pg/mL between 1 January 2015 and 31 March 2022, the median (Q1 – Q3) NT-proBNP concentration was 971 (581–1999) pg/mL; 56 227 (75%) and 18 718 (25%) had an NT-proBNP of 400–2000 pg/mL and >2000 pg/mL, respectively. The patient characteristics are presented overall and by NT-proBNP concentration in *Table 1*. The mean age was 79 years (SD 10), and 46% were men. Mean systolic blood pressure and eGFR measured within 12 months of NT-proBNP were 136 mmHg (SD 18) and 66 mL/min/1.73 m^2 (SD 21), respectively, and 38% had an eGFR of <60 mL/min/1.73 m^2. The most common comorbidity was hypertension (78%). A history of atrial fibrillation, ischaemic heart disease, and diabetes was recorded in 35%, 30%, and 23% of patients, respectively. In the year before NT-proBNP measurement, 31% were prescribed a loop diuretic, 49% a RAS inhibitor, and 42% a beta-blocker. Of those prescribed a loop diuretic prior to detection of an elevated NT-proBNP, 37% of the diuretic prescriptions were started in the 30 days prior to measurement of NT-proBNP.

Echocardiography

Echocardiography was recorded in 53% of patients in the 12 months following detection of an NT-proBNP ≥ 400 pg/mL and 53% in both those with an NT-proBNP of 400–2000 pg/mL and an NT-proBNP >2000 pg/mL. The median (IQR) time to echocardiography was 7 weeks (4–12) and 7 weeks (5–13) and 5 weeks (3–9) in those with an NT-proBNP of 400–2000 pg/mL and >2000 pg/mL, respectively. Echocardiography was performed within 2 weeks in 8% of those with an NT-proBNP >2000 pg/mL and within 6 weeks in 22% of all patients.

Heart failure diagnoses

A HF diagnosis within 12 months of detection of an NT-proBNP ≥ 400 pg/mL was recorded in 24 082 (32%) (*Table 2*; Supplementary data online, *Figure S1*). Of those, a diagnosis was first recorded as an outpatient in 15 398 (64%) and during a HF hospitalization in 8684 (36%). The median time to a HF diagnosis was 6 weeks (2–15) and 5 weeks (2–11) and 7 weeks (1–24) in those diagnosed as an outpatient and during a hospitalization, respectively. Patient characteristics

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Table 1 Characteristics of patients with elevated N-terminal pro-B-type natriuretic peptide levels ≥400 pg/mL

	Overall (*n* = 74 945)	NT-proBNP 400–2000 pg/mL (*n* = 56 227)	NT-proBNP > 2000 pg/mL (*n* = 18 718)
Age (years)	79 (10)	79 (10)	81 (10)
Sex			
Men	34 432 (46%)	24 982 (44%)	9450 (50%)
Women	40 513 (54%)	31 245 (56%)	9268 (50%)
Ethnicity			
Asian	2161 (3%)	1767 (3%)	394 (2%)
Black	840 (1%)	669 (1%)	171 (<1%)
Mixed	223 (<1%)	181 (<1%)	42 (<1%)
Other	337 (<1%)	274 (<1%)	63 (<1%)
White	64 094 (86%)	48 324 (86%)	15 770 (84%)
Missing	7290 (10%)	5012 (9%)	2278 (12%)
Systolic blood pressure (mmHg)	136 (18)	136 (18)	134 (19)
Missing	5595 (7%)	4319 (8%)	1276 (7%)
BMI category			
Normal/underweight	13 341 (18%)	9365 (17%)	3976 (21%)
Overweight	14 206 (19%)	10 522 (19%)	3684 (20%)
Obese	15 791 (21%)	12 827 (23%)	2964 (16%)
Missing	31 607 (42%)	23 513 (42%)	8094 (43%)
Smoking status			
Current	5278 (7%)	3882 (7%)	1396 (7%)
Prior	28 059 (37%)	21 214 (38%)	6845 (37%)
Never	13 106 (17%)	10 040 (18%)	3066 (16%)
Missing	28 502 (38%)	21 091 (38%)	7411 (40%)
eGFR (mL/min/1.73 m^2)	66 (21)	68 (20)	60 (21)
eGFR category			
<15 mL/min/1.73 m^2	418 (<1%)	130 (<1%)	288 (2%)
15–29 mL/min/1.73 m^2	2906 (4%)	1632 (3%)	1274 (7%)
30–44 mL/min/1.73 m^2	9121 (12%)	6100 (11%)	3021 (16%)
45–59 mL/min/1.73 m^2	16 385 (22%)	11 720 (21%)	4665 (25%)
60–89 mL/min/1.73 m^2	36 825 (49%)	28 866 (51%)	7959 (43%)
≥90 mL/min/1.73 m^2	9290 (12%)	7779 (14%)	1511 (8%)
Serum potassium (mmol/L)	4.5 (0.5)	4.5 (0.5)	4.5 (0.5)
uACR category			
<3 mg/mmol	8642 (12%)	6827 (12%)	1815 (10%)
3–29 mg/mmol	5523 (7%)	3866 (7%)	1657 (9%)
≥30 mg/mmol	1674 (2%)	1052 (2%)	622 (3%)
Missing	59 106 (79%)	44 482 (79%)	14 624 (78%)
Median (IQR) NT-proBNP (pg/mL)	971 (581–1999)	736 (523–1131)	3493 (2544–5755)
Haemoglobin (g/dL)	12.7 (2.1)	12.8 (2.0)	12.4 (2.1)

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Table 1 *Continued*

	Overall (*n* = 74 945)	NT-proBNP 400–2000 pg/mL (*n* = 56 227)	NT-proBNP > 2000 pg/mL (*n* = 18 718)
Prior conditions			
Atrial fibrillation	26 479 (35%)	17 847 (32%)	8632 (46%)
Chronic obstructive pulmonary disease	13 375 (18%)	10 195 (18%)	3180 (17%)
Diabetes	17 080 (23%)	12 720 (23%)	4360 (23%)
Type 2 diabetes	16 928 (23%)	12 606 (22%)	4322 (23%)
Dyslipidaemia	26 490 (35%)	20 336 (36%)	6154 (33%)
Hypertension	58 164 (78%)	43 536 (77%)	14 628 (78%)
Ischaemic heart disease	22 274 (30%)	16 604 (30%)	5670 (30%)
Myocardial infarction	7104 (9%)	5085 (9%)	2019 (11%)
Cancer (prior 5 years)	10 228 (14%)	7481 (13%)	2747 (15%)
Drugs in year prior			
Loop diuretic	22 942 (31%)	15 932 (28%)	7010 (37%)
Any diuretic	32 121 (43%)	23 157 (41%)	8964 (48%)
RAS inhibitor (ACE inhibitor or ARB)	36 498 (49%)	27 611 (49%)	8887 (47%)
Beta-blocker	31 618 (42%)	22 735 (40%)	8883 (47%)

Data are mean (standard deviation) or *n* (%) unless otherwise specified.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAS, renin–angiotensin system; uACR, urinary albumin to creatinine ratio.

Table 2 Heart failure diagnoses within 12 months of detection of N-terminal pro-B-type natriuretic peptide ≥ 400 pg/mL

	2 weeks		6 weeks		12 months	
	n/*N* (%)	Rate per 100 patients	*n*/*N* (%)	Rate per 100 patients	*n*/*N* (%)	Rate per 100 patients
HF diagnosis						
Overall (NT-proBNP ≥ 400 pg/mL)	7209/74 945 (10%)	10.2	12 588/74 945 (17%)	18.9	24 082/74 945 (32%)	47.2
NT-proBNP 400–2000 pg/mL	3010/56 227 (5%)	5.5	5749/56 277 (10%)	11.0	13 513/56 227 (24%)	31.7
NT-proBNP > 2000 pg/mL	4199/18 718 (22%)	25.7	6839/18 718 (37%)	49.0	10 569/18 718 (56%)	127.5
Outpatient HF diagnosis						
Overall (NT-proBNP ≥ 400 pg/mL)	4513/74 945 (6%)	6.2	8301/74 945 (11%)	12.0	15 398/74 945 (21%)	27.6
NT-proBNP 400–2000 pg/mL	2114/56 227 (4%)	3.8	4107/56 227 (7%)	7.7	8968/56 227 (16%)	19.9
NT-proBNP > 2000 pg/mL	2399/18 718 (13%)	13.8	4194/18 718 (22%)	26.8	6430/18 718 (34%)	60.2
HF hospitalization diagnosis						
Overall (NT-proBNP ≥ 400 pg/mL)	2696/74 945 (4%)	3.7	4287/74 945 (6%)	6.0	8684/74 945 (12%)	13.9
NT-proBNP 400–2000 pg/mL	896/56 227 (2%)	1.6	1642/56 227 (3%)	3.0	4545/56 227 (8%)	9.2
NT-proBNP > 2000 pg/mL	1800/18 718 (10%)	10.2	2645/18 718 (14%)	16.0	4139/18 718 (22%)	31.4

The numbers and proportions of patients with a heart failure diagnosis at 2 weeks, 6 weeks, and 12 months following detection of N-terminal pro-B-type natriuretic peptide ≥ 400 pg/mL and the first recorded clinical setting of that diagnosis are displayed overall and by N-terminal pro-B-type natriuretic peptide concentration (400–2000 pg/mL or >2000 pg/mL). Event rates displayed are the rates per 100 patients followed up for the time specified. NT-proBNP, N-terminal pro-B-type natriuretic peptide; HF, heart failure.

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Table 3 Estimated effect of the early initiation of a sodium-glucose cotransporter 2 inhibitor, mineralocorticoid receptor antagonist, or both at the time of detection of an elevated N-terminal pro-B-type natriuretic peptide

	2 weeks				6 weeks				12 months			
	Observed event rate per 100 patients	Treated event rate per 100 patients	Events prevented per 1000 patients (95% CI)	NNT (95% CI)	Observed event rate per 100 patients	Treated event rate per 100 patients	Events prevented per 1000 patients (95% CI)	NNT (95% CI)	Observed event rate per 100 patients	Treated event rate per 100 patients	Events prevented per 1000 patients (95% CI)	NNT (95% CI)
Indication for SGLT2i ($n = 24\,606$)												
HF hospitalization	4.5	3.2	12 (9–14)	80 (68-102)	7.1	5.1	20 (15–23)	51 (43–64)	16.7	12.0	46 (36–55)	22 (19–28)
All-cause mortality	0.8	0.7	<1	1620 (926–12 954)	2.5	2.3	2 (0–3)	497 (284–3973)	21.2	19.5	17 (2–29)	59 (34–472)
HF hospitalization or all-cause mortality	5.2	4.0	11 (9–14)	85 (70–108)	8.9	6.8	20 (16–24)	50 (41–63)	24.1	18.6	55 (43–67)	19 (15–24)
Indication for MRA ($n = 12\,256$)												
HF hospitalization	3.3	2.4	8 (6–10)	117 (98–152)	5.4	4.0	14 (10–16)	72 (60–93)	13.7	10.2	35 (27–42)	29 (24–37)
All-cause mortality	0.3	0.3	<1	2274 (1551–4263)	1.2	1.0	1 (0–2)	576 (393–1079)	12.6	10.7	18 (10–27)	53 (37–100)
HF hospitalization or all-cause mortality	3.6	2.7	8 (6–10)	123 (101–166)	6.2	4.8	14 (10–17)	71 (58–96)	17.8	13.7	41 (30–49)	25 (21–33)
Indication for SGLT2i and MRA ($n = 6372$)												
HF hospitalization	3.9	2.1	18 (15–20)	56 (50–64)	6.2	3.3	29 (25–32)	35 (32–40)	15.6	8.3	72 (63–81)	14 (13–16)
All-cause mortality	0.4	0.3	<1	1085 (789–1820)	1.6	1.3	3 (2–4)	282 (205–472)	16.0	12.5	34 (20–47)	29 (21–49)
HF hospitalization or all-cause mortality	4.2	2.5	17 (14–19)	59 (52–68)	7.3	4.3	29 (25–33)	34 (30–40)	20.7	12.3	84 (72–95)	12 (11–14)

Event rates for the composite outcome of time-to-first heart failure hospitalization or death from any cause, and the individual components of the composite, represent the number of events per 100 patients over that period (2 weeks, 6 weeks, and 12 months since N-terminal prohormone of B-type natriuretic peptide measurement) in patients with a pre-existing non-heart failure-related indication for an sodium-glucose cotransporter 2 inhibitor, mineralocorticoid receptor antagonist, or both. The estimates for treatment with a sodium-glucose cotransporter 2 inhibitor or mineralocorticoid receptor antagonist alone on the composite outcome are based on a hazard ratio of 0.77 (95% confidence interval 0.72–0.82) and 0.77 (95% confidence interval 0.72–0.83), respectively (see Supplement Supplementary data online, *Table S2*). The effect of combination treatment is modelled on a hazard ratio of 0.59 (95% confidence interval 0.54–0.65).
CI, confidence interval; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

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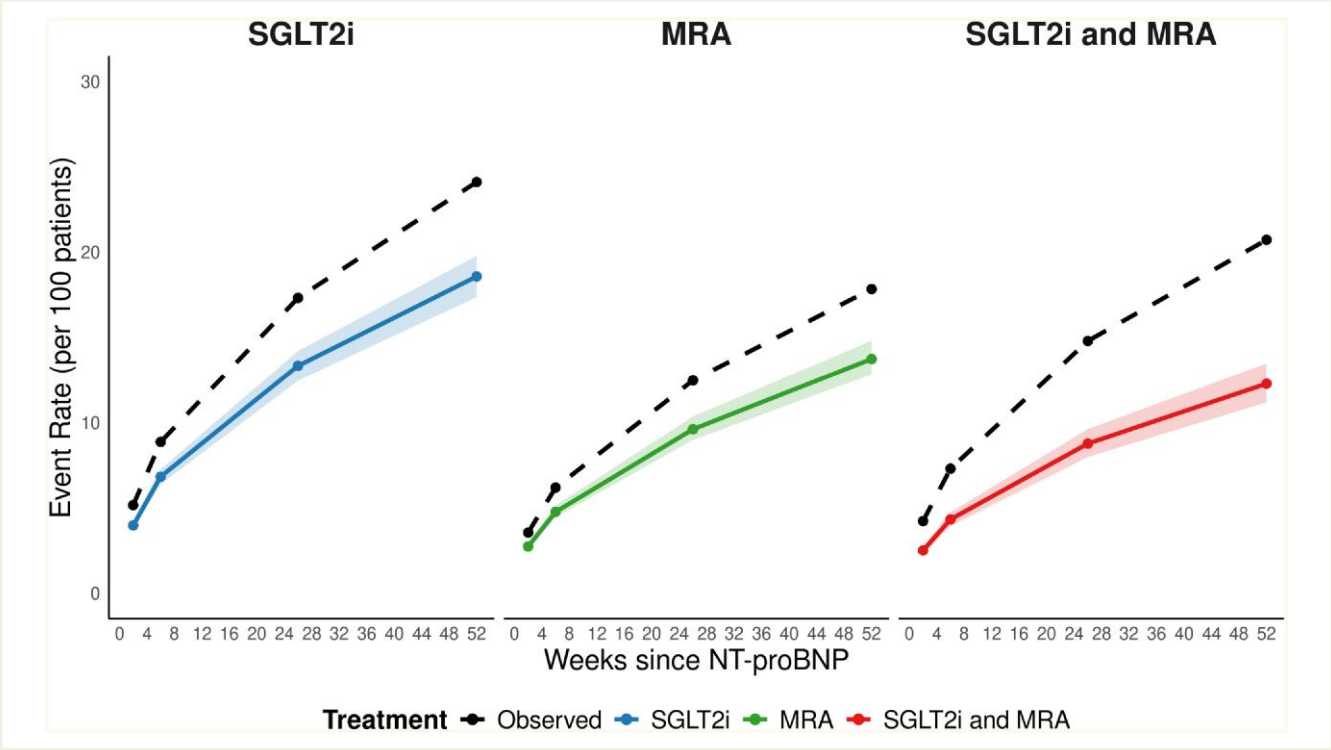

Figure 2 Modelled event rates of the effect of the early initiation of disease-modifying therapy in patients with suspected heart failure. Event rates for the composite outcome of time-to-first heart failure hospitalization or death from any cause are presented and represent the number of events per 100 patients over that period (2 weeks, 6 weeks, 6 months, and 12 months since NT-proBNP measurement) in patients with a pre-existing non-HF-related indication for an SGLT2i, MRA, or both. Shaded areas represent the 95% confidence intervals. The observed rates are plotted in the dashed line. The estimates for treatment with an SGLT2i or MRA alone are based on a HR of 0.77 (95% CI 0.72–0.82) and 0.77 (0.72–0.83), respectively. The effect of combination treatment is plotted and estimated based on a HR of 0.59 (0.54–0.65). NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; HR, hazard ratio.

according to the clinical setting of HF diagnosis are presented in Supplementary data online, *Table S3*.

The proportion of patients with an NT-proBNP > 2000 pg/mL in whom the diagnosis of HF was first documented during a HF hospitalization was higher (22%) than that of those with an NT-proBNP of 400–2000 pg/mL (8%) (*Table 2*). The corresponding proportions for an outpatient diagnosis were 34% and 16%, respectively. Of the 15 398 outpatient HF diagnoses recorded, 54% were made within 6 weeks of detection of an elevated NT-proBNP ≥ 400 pg/mL. Of the outpatient diagnoses in those with an NT-proBNP of >2000 pg/mL, 37% were documented within 2 weeks of NT-proBNP measurement (*Table 2*). In those with an NT-proBNP of >2000 pg/mL without a documented outpatient diagnosis of HF, 10% and 14% had a hospitalization for HF within 2 and 6 weeks of NT-proBNP measurement, respectively. The corresponding proportion of those with an NT-proBNP of 400–2000 pg/mL was 3% at 6 weeks.

Mortality

Of the 74 945 patients, 9447 (13%) died within 12 months of NT-proBNP measurement (see Supplementary data online, *Table S4*, and *Figure S1*). The crude annualized mortality rate was 2.5-fold higher in those with an NT-proBNP of >2000 pg/mL (26.4 per 100 patient-years) than those with a value of 400–2000 pg/mL (10.3 per 100 patient-years). Among those with a documented diagnosis of HF, the proportions who died were 11% and 26% following an outpatient diagnosis and a HF hospitalization as their diagnostic event, respectively. Following a HF hospitalization as the diagnostic event, 32% of those with an NT-proBNP > 2000 pg/mL had died at 12 months, as compared with 21% of those with an NT-proBNP of 400–2000 pg/mL who were hospitalized as a first event (see Supplementary data online, *Table S4*, and *Figure S1*). The corresponding proportions for those with an outpatient diagnosis were 16% (NT-proBNP > 2000 pg/mL) and 7% (NT-proBNP 400–2000 pg/mL). Compared with patients who underwent echocardiography and did not have a subsequent documented diagnosis of HF, the risk of mortality was fivefold higher (HR 5.56, 95% CI 5.20–5.94) and two-fold higher (HR 2.10, 95% CI 1.95–2.25) in those who were diagnosed with HF following a HF hospitalization and as an outpatient, respectively (see Supplementary data online, *Figure S2*). The HR for death following a hospitalization as compared with an outpatient diagnosis of HF was 2.68 (95% CI 2.52–2.86).

Of those without a documented diagnosis of HF following detection of an NT-proBNP ≥ 400 pg/mL (see Supplementary data online, *Table S5*), 5% of those who underwent echocardiography (i.e. had a diagnosis of HF excluded) and 16% of those who did not have an echocardiogram had died at 12 months (see Supplementary data online, *Table S4*). Of those who did not have an echocardiogram, 31% of those with an NT-proBNP > 2000 pg/mL had died within 12 months of NT-proBNP measurement as compared with 13% of those with an NT-proBNP of 400–2000 pg/mL. Those who died without

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undergoing echocardiography were three times more likely to die within 12 months of NT-proBNP than those who had HF excluded (HR 3.31, 95% CI 3.12–3.52) (see Supplementary data online, *Figure S2*).

Estimating the effect of the early initiation of disease-modifying therapy

A non-HF-related indication for an SGLT2, MRA, or both was present in 41% of patients at the time of detection of an elevated NT-proBNP level and for an SGLT2i in 33%, an MRA in 16%, and both in 9% (see Supplementary data online, *Figure S3*, and *Table S6*). The estimated reductions in events resulting from the early initiation of these disease-modifying therapies at the time of detection of an elevated NT-proBNP are displayed in *Table 3* and *Figure 2*. An estimated 84 (95% CI 72–95) HF hospitalizations or deaths (considering only deaths from any cause that occurred in those without a documented HF diagnosis who did not undergo echocardiography at 12 months) would be prevented per 1000 patients treated if an SGLT2i and an MRA were started in those with a pre-existing indication at the point of detection of an NT-proBNP ≥400 pg/mL. This equated to an NNT to prevent one event of 12 (95% CI 11–14) over 12 months. In those with an indication for an SGLT2i alone, the equivalent reduction in events per 1000 patients was 55 (95% CI 43–67), and the NNT was 19 (95% CI 15–24). For an MRA, 41 events (95% CI 30–49) could be prevented with an NNT of 25 (95% CI 21–33). In those with an NT-proBNP of >2000 pg/mL treated with both an SGLT2i and MRA, the estimated reduction in HF hospitalizations or deaths per 1000 patients was 147 (95% CI 126–166), equating to a NNT of 7 (95% CI 6–8). The data for the individual components of the composite outcome and the results at 2 and 6 weeks following NT-proBNP measurement are presented in *Table 3* and *Figure 2* and by NT-proBNP level in Supplementary data online, *Table S7*, and *Figure S4*.

Discussion

This large, retrospective, observational population-wide analysis of community-based patients with suspected HF and elevated NT-proBNP levels ≥ 400 pg/mL has several key findings. First, one in three patients with an elevated NT-proBNP measured in the community who were subsequently diagnosed with HF had the diagnosis made as a result of a hospitalization for HF, a potentially preventable event. A diagnosis of HF during hospital admission was associated with a substantial risk of subsequent mortality compared with patients who were diagnosed with HF as an outpatient. This relative risk of mortality following hospitalization was as pronounced in those with an NT-proBNP between 400 and 2000 pg/mL as in those with NT-proBNP > 2000 pg/mL. Second, 41% of patients with suspected HF had a pre-existing non-HF indication for an SGLT2i, an MRA, or both, i.e. at least one of Type 2 diabetes, CKD, or resistant hypertension and one of the benefits of these treatments is reduction in incident HF. Finally, our modelling study estimated that the early initiation of an SGLT2i, an MRA, or both in individuals with a non-HF-related indication at the time of the detection of elevated NT-proBNP levels could substantially reduce the risk of adverse outcomes in patients with suspected HF awaiting echocardiography (*Structured Graphical Abstract*).

In the weeks following detection of an elevated NT-proBNP, patients with suspected HF were at a high risk of adverse events. Of all the hospitalizations that occurred as the first recorded diagnosis of HF in the 12 months following NT-proBNP measurement, 31% occurred within 2 weeks and 49% within 6 weeks of detection of an elevated NT-proBNP ≥ 400 pg/mL. Despite this, less than a quarter of patients had undergone echocardiography by 6 weeks, highlighting that many patients with suspected HF faced delays in diagnostic echocardiography.[4] Furthermore, the strikingly high mortality rate in those who did not undergo echocardiography with NT-proBNP concentrations > 2000 pg/mL, in whom 37% of deaths occurred within 6 weeks of NT-proBNP measurement, suggests that many patients with suspected HF died prior to confirmatory investigation and the initiation of life-saving therapy. This diagnostic inertia means that many patients with HF remain untreated with disease-modifying therapy for weeks and months whilst awaiting confirmatory echocardiography, placing them at risk of hospitalization and an elevated risk of subsequent mortality that is associated with this event relative to an outpatient diagnosis of HF.

Two in five patients had an indication for one of an SGLT2, an MRA, or both at the time of detection of an elevated NT-proBNP, regardless of a subsequent diagnosis of HF or not. Both SGLT2i and MRA have robust evidence that they prevent the development of HF in patients with diabetes and CKD; therefore, their low utilization in this cohort in patients with these indications, along with the high prevalence of uncontrolled hypertension, could reasonably be hypothesized to have contributed to the observed incidence of HF. Our modelling suggests that if an SGLT2i, an MRA, or both were belatedly started at the point of detection of an elevated NT-proBNP in those with a non-HF-related indication such as Type 2 diabetes, CKD, or resistant hypertension, this could have a clinically meaningful effect on improving outcomes, even in a relatively short period of time. The potential absolute benefit of this strategy in terms of the numbers of events prevented per 1000 patients is substantial; the number of patients needed to be treated with the combination of an SGLT2i and MRA to prevent one HF hospitalization or death prior to echocardiography in the overall population was estimated to be 12 (95% CI 11–14) and 7 (95% CI 6–8) in those with an NT-proBNP > 2000 pg/mL. We believe that his approach of starting combined therapy is safe in patients with suspected HF, and this is supported by recent randomized clinical trial evidence demonstrating the safety of the combined initiation of an SGLT2i and a non-steroidal MRA in patients with Type 2 diabetes and CKD, a substantial proportion of whom also had hypertension.[26] Furthermore, our proposed strategy limits the initiation of therapy to those with a pre-existing indication rather than starting in all patients with an elevated NT-proBNP. Therapy can therefore be continued even if a diagnosis of HF is ultimately not made, in which case the patients still stand to benefit from the primary preventative benefit of these medications, particularly in light of their elevated NT-proBNP, which is associated with a higher risk of the development of HF, as well as other benefits such as reduction in end-stage kidney disease.[27,28]

Limitations

There are several limitations of this analysis that should be considered. The analysis period includes the COVID-19 pandemic and periods of lockdown, during which many HF diagnostic services were limited. Although this likely resulted in an elevated rate of hospitalizations and mortality in patients with suspected HF, it may serve to highlight the importance of prompt investigation and initiation of disease-modifying therapy in these patients. We cannot discount that those with highest NT-proBNP concentrations may have not had echocardiography requested due to frailty, comorbid conditions, or expectation of limited life expectancy. Therefore, events in these patients may not necessarily have been modifiable by the early initiation of HF therapy,

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and the estimated benefit of the initiation of disease-modifying therapy may be overestimated. Data on urinary albumin concentrations were not available in all patients; therefore, our estimates of the number of patients with pre-existing indications for an SGLT2i and/or MRA may be underestimated. Conversely, due to the expansion in the indications for these medications during the analysis period, the proportion of patients with an indication who are untreated is now likely lower in contemporary practice than that observed in the present study. Eligibility for SGLT2i and MRA treatment was calculated based on blood pressure, potassium, and kidney function data that were recorded in the 12 months prior to NT-proBNP measurement. These data may therefore not reflect the clinical status and eligibility for treatment at the time of NT-proBNP measurement. Furthermore, prescription records are not necessarily reflective of adherence to therapy, and therefore, the apparent existence of resistant hypertension may reflect non-adherence. Patients included in this analysis differed in key characteristics from those enrolled in the clinical trials contributing to the meta-analyses (e.g. they were older and had a lower prevalence of diabetes). However, the meta-analyses found no evidence of heterogeneity of treatment effect according to these characteristics, supporting the applicability of these treatment effect estimates to the population studied.[6,8] The modelling technique employed to calculate the estimated effect of the combined initiation of an SGLT2i and MRA relies on that the treatment effect of each drug is independent and additive to the other. However, given their independent mechanisms of action, we believe this to be the case. For the purposes of the modelling analysis, we considered the treatment effect of classes of drugs estimated from meta-analyses, not individual drugs; in the case of MRAs, individual drugs have specific indications for the treatment of CKD or resistant hypertension. Data on ejection fraction and other echocardiographic parameters are not available in CPRD. We are therefore unable to provide further information relating to the ejection fraction phenotypes of HF. Treatment with an SGLT2i, an MRA, or both was only assumed to have benefit to the point of outpatient or inpatient diagnosis of HF, on the basis that these treatments would be initiated at that point, although this is often not the case and the overall events prevented may be a conservative estimate. The estimated benefits of the proposed strategy presented are specific to the observed event rates in the cohort examined. The potential benefits of this approach in other healthcare systems with different clinical pathways and event rates (e.g. the use of a lower rule-out NT-proBNP value of 125 pg/mL) may differ from those presented. We lacked data on prescriber-related reasons for non-prescription of an SGLT2i and/or MRA in those with a pre-existing indication, such as concerns regarding frailty, advanced age, polypharmacy, or other comorbidities affecting prognosis. Therefore, the number of patients who would be eligible for treatment with an SGLT2i and/or MRA in clinical practice may be lower than that estimated in the present analysis. Our modelling assumes that all patients with an indication for therapy would stay on treatment with no discontinuations for treatment-related adverse events. Although the treatment effect estimates used in the modelling are reflective of discontinuation rates in the clinical trials, the rates in clinical practice may differ. Therefore, the results presented may overestimate the potential benefits of the proposed strategy.

Conclusions

A substantial proportion of community-based patients with suspected HF experience events that are potentially modifiable in the months following detection of an elevated NT-proBNP. The early initiation of an SGLT2i and an MRA in patients with a pre-existing non-HF-related indication may reduce the risk of these events, resulting in substantial and clinically meaningful absolute reductions in event rates.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

K.F.D. reports that his employer, the University of Glasgow, has been remunerated by AstraZeneca for his work on clinical trials, and he has received speakers' fees from AstraZeneca, Boehringer Ingelheim, Pharmacosmos, and Translational Medicine Academy; has served on advisory boards or performed consultancy for Abbott, FIRE-1, Us2.ai, and Bayer AG; has served on a Clinical Endpoint Committee for Bayer AG; and has received research grant support (paid to his institution) from AstraZeneca, Roche Diagnostics, Novartis, and Boehringer Ingelheim. B.H. is an employee of Health Data Sciences who received funding from AstraZeneca for analysis and data processing relating to this manuscript. He reports research funding from ELPEN, Novo Nordisk, Insmed, Novartis, and Sanofi. A.B.-G. reports that he has lectured and/or participated in advisory boards for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, and Vifor. R.T.C. reports speakers' fees from CircleCVI and research funding from AstraZeneca, SQ Innovations, and Roche Diagnostics (all paid to his institution). A.D.H. reports receiving payments from Bayer for travel outside the submitted work. P.S.J. reports speakers' fees from AstraZeneca and ProAdWise Communications; advisory board fees from AstraZeneca and Bayer AG; research funding from AstraZeneca, Boehringer Ingelheim, Analog Devices Inc., and Roche Diagnostics. P.S.J.'s employer, the University of Glasgow, has been remunerated for clinical trial work from AstraZeneca, Bayer AG, Novartis, Novo Nordisk; he is a Director of Global Clinical Trial Partners Ltd. L.K. reports speakers' honorarium from Astra Zeneca, Boehringer Ingelheim, Novartis, and Novo Nordisk. M.S. reports speakers' honorarium from Astra Zeneca, Boehringer Ingelheim, Novartis, and Novo Nordisk and travel support from Bayer. S.D.S. reports receiving research grants from Alexion, Alnylam, Applied Therapeutics, AstraZeneca, Bellerophon, Bayer, BMS, Boston Scientific, Cytokinetics, Edgewise, Eidos/BridgeBio, Gossamer, GSK, Ionis, Intellia, Lilly, NIH/NHLBI, Novartis, Novo Nordisk, Respicardia, Sanofi Pasteur, Tenaya, Theracos, and US2.AI and has consulted for Abbott, Action, Akros, Alexion, Alnylam, Amgen, Arena, AskBio, AstraZeneca, Bayer, BMS, Cardior, Cardurion, Corvia, Cytokinetics, GSK, Lilly, Novartis, Novo Nordisk, Roche, Theracos, Quantum Genomics, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProthera, Moderna, American Regent, Sarepta, Lexicon, AnaCardio, Akros, Valo, Synhale, and Recordati. M.V. reports receiving research grant support from American Regent, Amgen, AstraZeneca, Boehringer Ingelheim, Roche Diagnostics, Galmed, Novartis, Bayer AG, Occlutech, Pharmacosmos, and Impulse Dynamics; consulting fees from Alnylam Pharmaceuticals, American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, BMS, Boehringer Ingelheim, Chiesi, Cytokinetics, Esperion, Fresenius Medical Care, Idorsia Pharmaceuticals, Lexicon Pharmaceuticals, Merck, Milestone

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Data Availability

Access to Clinical Practice Research Datalink (CPRD) data, including UK Primary Care Data, and linked data such as Hospital Episode Statistics, is subject to protocol approval via CPRD's Research Data Governance (RDG) Process.

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Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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