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Long term trends in natriuretic peptide testing for heart failure in UK primary care: a cohort study

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Aims Heart failure (HF) is a malignant condition with poor outcomes and is often diagnosed on emergency hospital admission. Natriuretic peptide (NP) testing in primary care is recommended in international guidelines to facilitate timely diagnosis. We aimed to report contemporary trends in NP testing and subsequent HF diagnosis rates over time.

Methods and results Cohort study using linked primary and secondary care data of adult (≥45 years) patients in England 2004–18 ($n = 7\,212\,013$, 48% male) to report trends in NP testing (over time, by age, sex, ethnicity, and socioeconomic status) and HF diagnosis rates. NP test rates increased from 0.25 per 1000 person-years [95% confidence interval (CI) 0.23–0.26] in 2004 to 16.88 per 1000 person-years (95% CI 16.73–17.03) in 2018, with a significant upward trend in 2010 following publication of national HF guidance. Women and different ethnic groups had similar test rates, and there was more NP testing in older and more socially deprived groups as expected. The HF detection rate was constant over the study period (around 10%) and the proportion of patients without NP testing prior to diagnosis remained high [99.6% ($n = 13\,484$) in 2004 vs. 76.7% ($n = 12\,978$) in 2017].

Conclusion NP testing in primary care has increased over time, with no evidence of significant inequalities, but most patients with HF still do not have an NP test recorded prior to diagnosis. More NP testing in primary care may be needed to prevent hospitalization and facilitate HF diagnosis at an earlier, more treatable stage.

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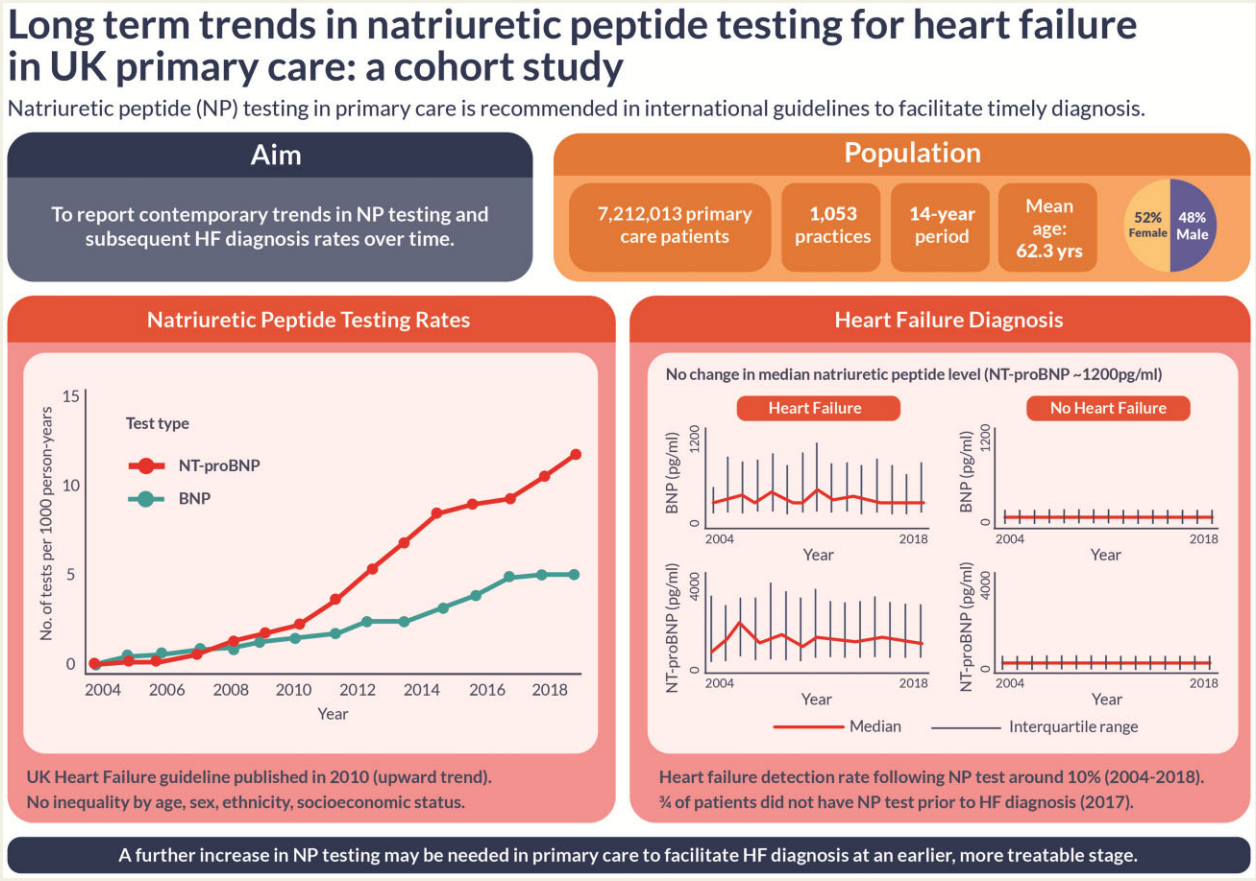
Graphical Abstract



BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Keywords Heart failure • Diagnosis • Natriuretic peptide • Testing

Background

Heart failure (HF) is a malignant condition affecting over 40 million people worldwide and has a worse prognosis than most cancers.[1,2] Timely diagnosis is key to allow initiation of evidence-based treatments which can improve quality of life and prolong survival.[3] Natriuretic peptides (NP) are produced by the heart in response to fluid overload and NP measurement is a key step in the HF diagnostic pathway. International HF guidelines, including those of the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA), recommend that patients presenting to primary care with HF symptoms (breathlessness, fatigue, ankle swelling) have an NP blood test to determine whether referral for specialist assessment is required.[4–7]

Across Europe, survival rates following a HF diagnosis remain low and there has been little improvement over the last two decades.[8–10] This differs from cancer where prognosis for many cancer types has greatly increased in recent years.[11] Investment in cancer diagnostic and treatment services, including rapid referral pathways for patients with symptoms, is associated with improved outcomes for some cancers.[12] The same investment has not been seen in HF services and a high proportion of people with new-onset HF are diagnosed on emergency hospital admission.[13]

In the UK, approximately one million people are living with HF and 200 000 are newly diagnosed each year, with 80% of new diagnoses occurring on hospitalization.[13,14] In patients with symptoms and signs of HF, the addition of an NP test can aid general practitioner's (GP) decision-making, with a low NP level being particularly helpful to rule out HF.[15] Since 2003, the National Institute for Health and Care Excellence (NICE) has recommended NP testing in primary care to guide referral for specialist diagnostic assessment, with a strengthened recommendation in 2010 which included time limits for specialist review based on NP level [6 weeks for N-terminal pro B-type natriuretic peptide (NT-proBNP) ≥400 pg/mL or B-type natriuretic

peptide (BNP) ≥100 pg/mL and 2 weeks if NT-proBNP >2000 pg/mL or BNP >400 pg/mL].[4] However, there is evidence that this guidance is not followed in practice and outcomes for people with HF remain poor, particularly if baseline NP level is high.[8,13,16] The British Heart Foundation recently published a report highlighting the importance of earlier diagnosis of HF in primary care to improve morbidity and mortality.[17] Our main aim was to report trends in NP testing in UK primary care over time, and by individual patient factors, and HF diagnosis rate.

Methods

Design and setting

An open retrospective cohort study was conducted including persons registered with a general practice contributing to the Clinical Practice Research Datalink (CPRD) Gold and Aurum databases between 1 January 2004 and 31 December 2018. Calendar years prior to this were excluded due to too few ($n < 10$) NP tests being recorded.

Big data sources

CPRD Gold and Aurum are longitudinal research databases of electronic patient records drawn from general practices using Vision and Egton Medical Information Systems clinical computer systems, respectively. The combined databases contain data from over 1400 general practices in the UK, or 15.7% of the whole general practice population and have been shown to be representative of the UK population in terms of age and sex.[18–20] The database includes demographic and clinical information such as age, sex, ethnicity, diagnostic codes, and laboratory results including NP tests. Patient records from CPRD were linked to hospital inpatient records (Hospital Episodes Statistics; HES)[21] and deprivation (Index of Multiple Deprivation; IMD)[22] data.

Participants

Patients were eligible for inclusion if their records met CPRD quality measures and were registered at practices with continuous data reporting during the study period. The cohort excluded patients aged under 45 years since types of HF affecting children and younger people are pathologically distinct from HF found in middle-aged and older adults.

Outcome measures

NP tests and HF diagnoses were identified in CPRD using clinical coding lists (Supplementary material online, *Tables S1* and *S2*) derived from the NHS terminology and classifications browser and the Quality and Outcomes Framework (QOF) guidance. HF diagnoses from primary care were also validated through data linkage with HES using clinical (International Classification of Diseases, 10th revision) codes.

Statistical analysis

The total number of NP tests per 1000 person-years at risk and associated 95% confidence intervals (CIs) were reported overall, by calendar year (2004–18), and by NP test subtype (BNP and NT-proBNP). To allow for changes in the age and sex distributions over time, the rates were directly standardized by age and sex to mid-2018 England Office for National Statistics (ONS) population estimates.[23] To assess the potential impact of national chronic HF guidance in 2010,[4] a weighted linear regression model was fitted to the standardized test rates, where weights were inversely proportional to the variance of the rates. An interaction term between year of test and time period (2004–10 vs. 2011–18) was used to compare regression slopes before and after guidelines were introduced. Temporal trends were also explored by the age group (45–54, 55–64, 65–74, 75–84, ≥85 years), sex, ethnicity, and deprivation (IMD quintiles). Patients whose IMD score was missing (0.1%) were excluded from comparisons by deprivation.

Annual crude and age/sex directly standardized (2018 England population) HF incidence rates were estimated to assess the underlying trend in newly diagnosed HF. To assess whether length of time from NP testing to diagnosis had improved since 2004, the cumulative HF detection rate was estimated using a survival method (Nelson-Aalen cumulative hazard), stratified by 5-year intervals (2004–08, 2009–13, 2014–18). Trends in positive predictive values (PPVs) were also used to assess test performance over time. PPVs were estimated by the percentage of tests with NP level above the recommended NICE thresholds (NT-proBNP ≥400 pg/mL or BNP ≥100 pg/mL), where a HF diagnosis was confirmed within 6 months. The calendar year 2018 was excluded from the evaluation of test performance due to the considerable number of persons with <6-months follow-up data. Visual comparison of CIs was mainly used to determine clinical significance of differences, rather than formal significance tests, since the large sample size would detect small non-clinically relevant differences in most instances.

Statistical analysis was undertaken with Stata 15.0 (StataCorp LLC, College Station, TX, USA).

Results

The cohort included 253 general practices from CPRD GOLD database and 800 from CPRD Aurum over the observation period (see flow diagram of included and excluded participants in Supplementary material online, *Figure S1*). There were 332 984 NP tests recorded for a total of 7 212 013 persons aged 45 years and over, across 48 354 892 person-years of follow-up. The average age of the cohort was 62.3 years [standard deviation (SD) 12.3] and 51.6% were women, with no significant changes over the follow-up period.

A total of 257 862 patients underwent an NP test—206 276 (80%) patients had a single NP test; 37 371 (14.5%) two tests and 14 215 (5.5%) three or more tests. The mean age at testing was 72.9 years (SD 11.2) and 56.6% were women.

Natriuretic peptide testing over time

From 2004 to 2018, absolute numbers of tests increased from 712 to 48 832 per year. *Table 1* presents the age- and sex-specific NP test rate per 1000 person-years by calendar year. The overall crude test rates increased from 0.24 per 1000 person-years in 2004 to 16.24 in 2018, with similar age- and sex-standardized rates of 0.25 (95% CI 0.23–0.26) in 2004 and 16.88 (95% CI 16.73–17.03) in 2018. The slope of the trend line increased significantly after the publication of the 2010 NICE chronic HF guideline.[4] In the pre-2010 period, the number of tests increased by 0.54 tests per 1000 person-years (95% CI 0.47–0.62), whereas a larger increase of 1.65 tests per 1000 person-years (95% CI 1.47–1.83) was seen in the post-2010 period (difference in slopes: 1.11 (95% CI 0.91–1.30), P for interaction <0.001). NT-proBNP tests accounted for two-third of the total number of tests performed, with age-/sex-standardized test rate per 1000 person-years increasing from 0.10 (95% CI 0.09–0.11) in 2004 to 11.71 (95% CI 11.59–11.84) in 2018; and BNP test rate increasing from 0.15 (95% CI 0.13–0.16) to 5.17 (95% CI 5.08–5.25) over the same time period (*Figure 1* and Supplementary material online, *Tables S3–S6*).

Table 1 Crude and standardized natriuretic peptide test rates (number of tests per 1000 person-years) by age, sex, and year

Age group (years)	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Men															
45–54	0.03	0.10	0.11	0.22	0.37	0.49	0.66	0.90	1.27	1.55	1.99	2.42	2.69	3.12	3.29
55–64	0.09	0.34	0.50	0.70	1.34	1.53	2.01	2.91	4.15	4.94	6.05	6.82	7.49	8.33	8.67
65–74	0.31	0.96	1.30	2.05	3.07	4.06	5.13	6.97	9.44	11.35	13.48	15.22	16.83	18.81	19.57
75–84	0.64	2.28	2.64	4.24	5.85	8.02	10.22	14.25	19.73	23.25	27.94	30.06	33.40	36.01	38.60
≥85	0.98	2.10	3.05	4.50	7.33	10.37	11.41	17.53	24.73	31.17	36.60	41.13	44.18	47.10	51.44
Women															
45–54	0.04	0.13	0.19	0.30	0.52	0.62	0.83	1.12	1.59	2.06	2.78	3.34	3.87	4.27	4.78
55–64	0.10	0.34	0.48	0.79	1.19	1.58	1.83	2.91	4.40	5.32	6.75	7.62	8.80	9.37	10.40
65–74	0.33	1.05	1.47	2.06	3.21	4.09	5.12	7.37	10.24	11.89	14.89	16.90	18.61	20.87	22.23
75–84	0.69	2.08	2.85	4.13	6.13	7.74	10.01	14.73	20.90	25.12	30.90	34.00	36.52	40.04	43.80
≥85	0.78	2.17	2.48	4.34	6.51	8.33	11.12	15.10	21.69	26.84	32.33	36.97	39.87	43.72	48.96
Total (both sexes)	0.24	0.75	0.98	1.50	2.29	2.94	3.73	5.32	7.50	9.04	11.11	12.48	13.70	15.02	16.24
Standardized rate[a] (95% CI)	0.25 (0.23–0.26)	0.77 (0.73–0.80)	1.01 (0.97–1.05)	1.55 (1.51–1.60)	2.37 (2.32–2.43)	3.07 (3.01–3.13)	3.88 (3.81–3.95)	5.55 (5.47–5.63)	7.81 (7.72–7.91)	9.40 (9.29–9.51)	11.52 (11.40–11.64)	12.93 (12.81–13.06)	14.23 (14.10–14.37)	15.64 (15.50–15.78)	16.88 (16.73–17.03)

CI, confidence interval.
[a]Directly standardized by age and sex to Office for National Statistics mid-year 2018 England population estimates.

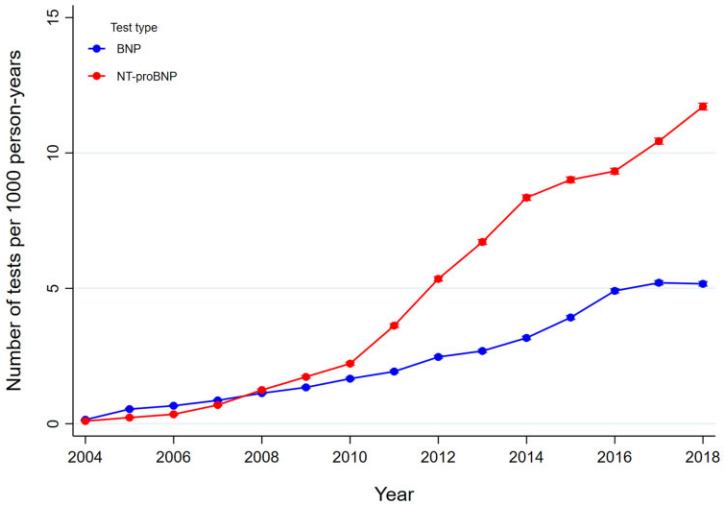


Figure 1 Standardized natriuretic peptide test rates (number of tests per 1000 person-years) by test type and year.

Individual patient factors

The upward trend in NP testing was observed in all age groups with test frequency greatest in older people (*Figure 2* and Supplementary material online, *Table S7*). The patterns were broadly similar across sexes (Supplementary material online, *Table S8*). For example, in 2018 among men aged 45–54 years there were 3.29 per 1000 person-years (95% CI 3.13–3.45) rising to 51.44 (95% CI 49.54–53.38) at age ≥85 and in women from 4.78 (95% CI 4.59–4.98) among those aged 45–54, compared to 48.96 (95% CI 47.56–50.39) in those aged ≥85 (Supplementary material online, *Table S9*).

The number of patients with unrecorded ethnicity decreased from 41% to 21% over the follow-up period with very low associated NP test rates, ranging from 0.02 per 1000 person-years (95% CI 0.01–0.03) in 2004 to 1.44 (95% CI 1.34–1.54) in 2018. NP trends across known ethnic groups were similar with standardized test rate in those of white ethnicity in 2018 of 20.68 (95% CI 20.49–20.88) compared to 22.81 (95% CI 22.05–23.59) in the combined minorities group (*Figure 3* and Supplementary material online, *Table S10*).

Test rates increased at all levels of deprivation with standardized rates being highest in the most deprived quintile and lowest in the most affluent [in 2018: standardized rate ratio of 1.42 (20.95 (95% CI 20.49–21.42) vs. 14.74 (95% CI 14.47–15.01)] (*Figure 3* and Supplementary material online, *Table S11*).

Heart failure diagnosis rates

The number of new cases of HF (confirmed in primary or secondary care) increased by 25% from 13 538 in 2004 to 16 910 in 2017, with a corresponding age and sex-standardized HF incidence rate of 4.71 per 1000 person-years to 5.49 per 1000 person-years (*Table 2*). The majority of these new cases were not linked to an NP test in the 6 months prior to diagnosis, decreasing from 99.6% (13 484) in 2004 to 76.7% (12 978) in 2017, and of these, most did not have an NP test recorded at any time prior to diagnosis [100% (13 484) in 2004, 78.8% (10 223) in 2017].

Figure 4 presents the summary NP levels over the study period by test subtype. Minor fluctuations in both NT-proBNP and BNP levels were observed in the early years but were relatively constant over the past decade, with median (interquartile range) of NT-proBNP in those with HF confirmed within 6 months, of 1345 pg/mL (488–3790) in 2008 to 1206 pg/mL (486–2915) in 2017, compared to levels of those without HF confirmed over this follow-up period, ranging from 127 pg/mL (59–322) in 2008 to 124 pg/mL (57–288) in 2017 (Supplementary material online, *Table S12*).

The percentage of NP tests with a subsequent confirmed HF diagnosis within 6 months has remained at around 10% over the last decade (*Figure 5* and *Table 3*). Similarly, the proportion of patients diagnosed with HF, among those above the NP thresholds recommended by UK guidelines, has not increased significantly over the period, with PPV ranging from 28.1% (95% CI 26.1–30.2) in 2008 to 29.5% (95% CI 28.6–30.3) in 2017 (*Table 3*).

Discussion

Main findings

Our study found NP testing in UK primary care increased overall between 2004 and 2018, particularly following publication of a national HF guideline in 2010.[4] We did not identify any inequalities in relation to sex or ethnicity, and found testing was positively associated with age and deprivation, with more testing observed in older age groups and those from more deprived areas where higher rates of HF are expected.[24] However, testing in primary care remained limited with less than one in four patients having an NP test in the six months prior to HF diagnosis by the end of the study period. Neither the proportion of NP tests with a subsequent HF diagnosis (around 10%) nor the PPV (around 28%) significantly changed over time. The median level for NT-proBNP associated with a subsequent HF diagnosis has remained around 1200 pg/mL over the past decade.

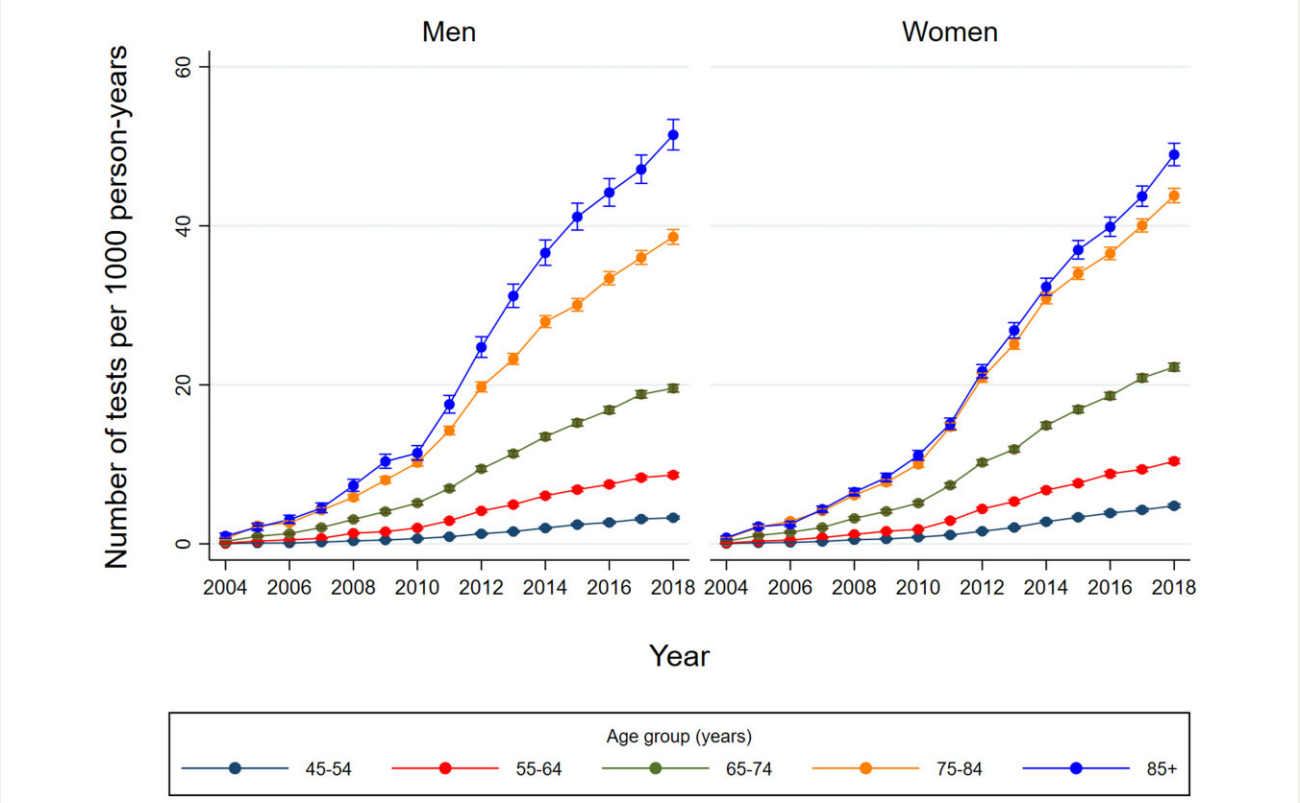


Figure 2 Standardized natriuretic peptide test rates (number of tests per 1000 person-years) by age group, sex, and year.

Strengths and limitations

UK national guidance from NICE has recommended NP testing in patients with suspected HF since 2003, with updated guidance in 2010 and 2018, and, for the first time, our study reports rates of NP testing throughout this period.[4,5] The results are based on a large representative sample of real-world data, generalisable to the UK population. This research is reliant on the accuracy of coding by GPs during the consultation. Clinical coding has improved significantly over time and the introduction of the HF QOF indicator in 2006 required robust evidence of HF in the GP record.[25] The benefit of CPRD and similar general practice databases is that they provide an insight into real-life clinical practice. The emergence of two distinct HF types, HFrEF and HFpEF, have only been coded very recently in GP records therefore analysis of trends by HF type were not possible in this study.[26]

Our study was designed to explore temporal trends in NP testing, and by individual patient factors (age, sex, ethnicity, socioeconomic status) and did not consider the potential influence of medications prescribed or comorbid conditions such as obesity and atrial fibrillation, which may be relevant to both HF diagnosis and NP result interpretation. NP tests are only performed in general practice for the purpose of diagnosing or monitoring HF, hence potential confounders are likely to have a consistent effect on NP testing over the time period but may warrant further research.

The diagnostic test performance of NP in routine data was hindered by lack of reference standard for those individuals not referred for echocardiography; however, by assuming clinical guidelines were followed, the data enabled estimation of PPVs, based on NP levels measured, reflecting test accuracy in the real world. CPRD data have been utilized previously in the test performance evaluation of other diagnostic biomarkers such as cancer antigen 125 for the detection of ovarian cancer.[27]

Comparison with existing literature

Laboratory testing has an increasing role in clinical practice. A recent analysis of CPRD data identified a two-fold increase in general laboratory testing since 2004 which may partially explain the upturn in NP testing.[28] The authors suggest increased primary care access to testing, patient expectations of having a test and GP use of testing to both inform decision-making and potentially reduce litigation may all explain the increase in test use. Policy changes may also be responsible for an increase in primary care investigations. There was a large rise in test use following the UK Cancer Plan in 2000 and NICE guideline updates in 2005 and 2015 for patients with symptoms suggestive of cancer.[29] These influential policy documents emphasized the importance of prompt investigation to facilitate diagnosis at an earlier, curable stage.[11,12] The evidence on the value and importance of NP testing in all patients with suspected HF has increased over time and then has been incorporated into international guidelines.[4–7,15] The NICE chronic HF guideline update in 2010,[4] and subsequent commissioning of referral pathways reliant on an NP test result, is likely to have contributed to the sustained rise in NP testing seen in our study.

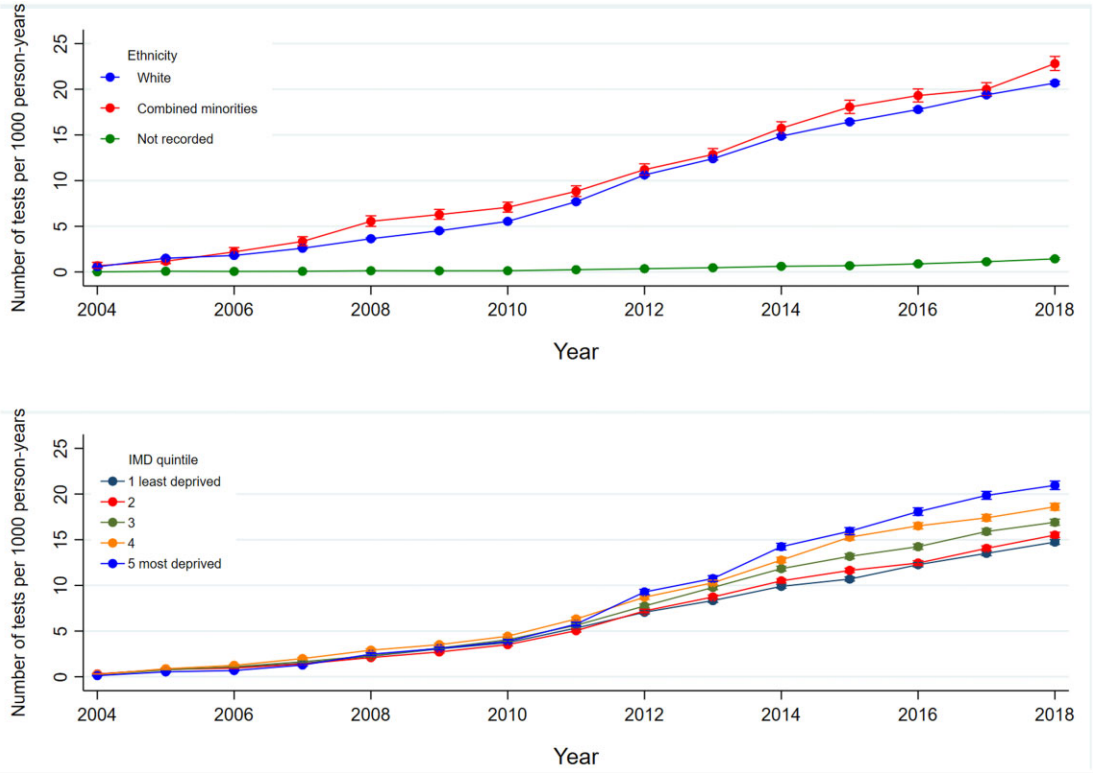


Figure 3 Standardized natriuretic peptide test rates (number of tests per 1000 person-years) by ethnicity, deprivation, and year.

Table 2 **Crude and standardized heart failure incidence rates by year of diagnosis**

Year of diagnosis	Persons with newly diagnosed HF, *n* (%)				Person-years	Crude HF incidence rate per 1000 person-years (95% CI)	Standardized HF incidence rate[a] per 1000 person-years (95% CI)
	NP test up to 6 months before diagnosis	NP test over 6 months before diagnosis	No previous NP test	Total			
2004	54 (0.4)	0 (0)	13 484 (99.6)	13 538	2 996 810	4.52 (4.44–4.59)	4.71 (4.63–4.79)
2005	208 (1.6)	23 (0.2)	12 440 (98.2)	12 671	3 055 572	4.15 (4.08–4.22)	4.34 (4.27–4.42)
2006	259 (2.2)	50 (0.4)	11 518 (97.4)	11 827	3 122 718	3.79 (3.72–3.86)	3.95 (3.88–4.02)
2007	385 (3.4)	86 (0.8)	10 932 (95.9)	11 403	3 188 246	3.58 (3.51–3.64)	3.74 (3.67–3.81)
2008	577 (4.8)	208 (1.7)	11 204 (93.5)	11 989	3 261 068	3.68 (3.61–3.74)	3.84 (3.77–3.91)
2009	769 (6.2)	301 (2.4)	11 407 (91.4)	12 477	3 307 657	3.77 (3.71–3.84)	3.95 (3.88–4.02)
2010	886 (7.0)	432 (3.4)	11 295 (89.6)	12 613	3 331 742	3.79 (3.72–3.85)	3.97 (3.90–4.04)
2011	1300 (10.0)	535 (4.1)	11 152 (85.9)	12 987	3 340 117	3.89 (3.82–3.96)	4.08 (4.01–4.15)
2012	1967 (14.0)	798 (5.7)	11 266 (80.3)	14 031	3 366 428	4.17 (4.10–4.24)	4.36 (4.29–4.43)
2013	2380 (14.5)	1179 (7.2)	12 895 (78.4)	16 454	3 322 194	4.95 (4.88–5.02)	5.18 (5.10–5.26)
2014	2866 (18.3)	1574 (10.1)	11 190 (71.6)	15 630	3 279 287	4.77 (4.70–4.84)	4.98 (4.90–5.06)
2015	3238 (19.9)	1920 (11.8)	11 132 (68.3)	16 290	3 266 330	4.99 (4.91–5.06)	5.22 (5.14–5.30)
2016	3538 (21.4)	2339 (14.1)	10 671 (64.5)	16 548	3 255 828	5.08 (5.01–5.16)	5.34 (5.26–5.42)
2017	3932 (23.3)	2755 (16.3)	10 223 (60.5)	16 910	3 253 999	5.20 (5.12–5.28)	5.49 (5.40–5.57)

CI, confidence interval; HF, heart failure.
[a]Directly standardized by age and sex to Office for National Statistics mid-2018 England population estimates.

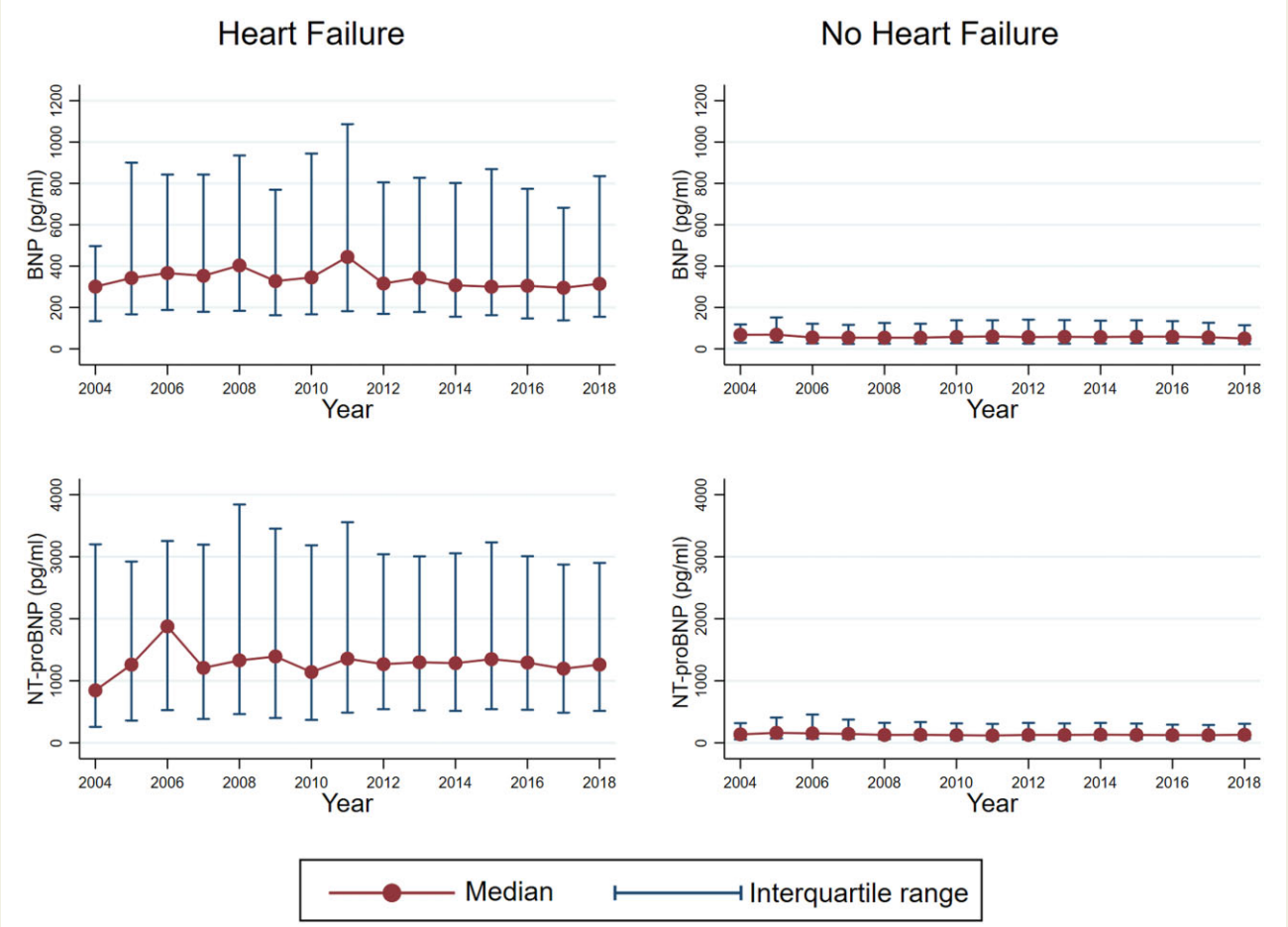


Figure 4 Median (interquartile range) natriuretic peptide levels (pg/mL) by test subtype, heart failure diagnosis, and year. BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Earlier HF guidelines in the UK, Europe, and North America recommended NP testing to aid decision-making where it was available, only in specified groups or when the diagnosis was uncertain. The updated recommendation of NP testing for all symptomatic patients may have taken several years to result in a change in practice following guideline publication.[4–7]

Across Europe, NP testing has increased in recent years.[30] The Cardiac Marker guideline uptake in Europe (CARMAGUE) study was a web-based questionnaire survey of HF biomarker testing, with responses from 266 laboratories across 33 countries. It found there was a rise in the number of laboratories offering NP testing (increasing from 67% in 2013 to 77% in 2019 of the laboratories surveyed), with NT-proBNP being the preferred test. There is limited data on NP testing specifically in the primary care population. A study in the Netherlands aimed to evaluate the use of community NP testing between 2005 and 2013, across nine practices with 21 000 registered patients.[31] The rate of NP testing increased from 2.5 to 14.0 per 1000 person-years across the study period, with a peak in 2009 of 15.6 per 1000 person-years following a GP training initiative. Our results show a similar trend, as NP test rates increased from 0.25 per 1000 person-years in 2004 to 16.88 per 1000 person-years in 2018, with a significant upward trend in 2010 following publication of national HF guidance. In the Dutch study, a total of 2269 tests were conducted across the 9-year study period and all practices used a single hospital laboratory. Our study included a much larger number of tests (332 984) from 1053 practices over a 14-year period.

The overall proportion of people with HF who have an NP test prior to diagnosis is also important. A CPRD study following up patients after a HF diagnosis found that overall, from 2002 to 2014, only 9% of patients with HF had an NP test in their GP record within ±6 months of diagnosis, but in 2014 alone this increased to 23% of patients.[32] Our data reveal a similar trajectory, albeit at a slower rate (due to inclusion of pre-diagnosis tests only), increasing from 18% in 2014 to 23% in 2017.

Importantly, our study demonstrates that despite increased availability of NP testing in primary care, the proportion of tests that lead to a subsequent HF diagnosis within 6 months has stabilized at around 10% over the last decade, and the PPV for an NP test above the referral threshold set by NICE has remained around 28%. These findings are in marked contrast to some cancers where diagnostic detection rates and PPVs are much lower. In 2015, NICE introduced a

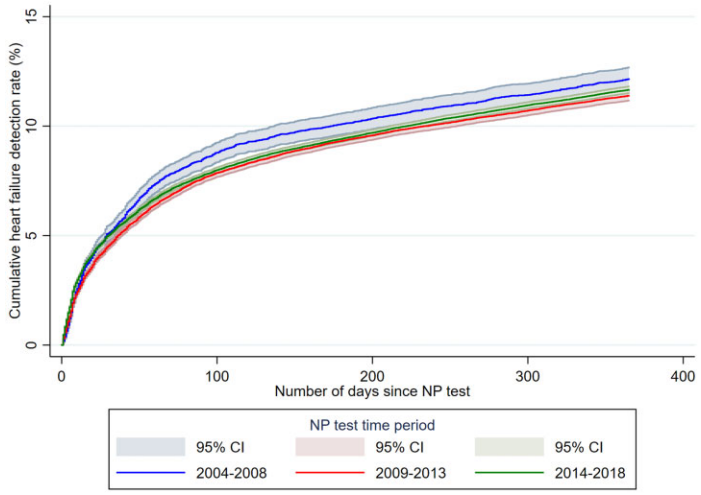


Figure 5 Cumulative heart failure detection rate in days following a natriuretic peptide test by 5-year calendar intervals.

Table 3 Diagnostic accuracy of natriuretic peptide tests in detection of heart failure

Year of NP test	Number of NP tests[a]	Number of HF diagnoses confirmed within 6 months of NP test	HF detection rate,[b] % (95% CI)	Positive predictive value,[c] % (95% CI)
2004	533	66	12.4 (9.7–15.5)	27.2 (21.0–34.1)
2005	1816	220	12.1 (10.6–13.7)	25.2 (22.1–28.5)
2006	2478	279	11.3 (10.0–12.6)	26.8 (23.9–29.9)
2007	3930	407	10.4 (9.4–11.4)	26.2 (23.8–28.7)
2008	6097	648	10.6 (9.9–11.4)	28.1 (26.1–30.2)
2009	7910	793	10.0 (9.4–10.7)	26.3 (24.5–28.1)
2010	10 035	980	9.8 (9.2–10.4)	25.0 (23.5–26.6)
2011	14 460	1428	9.9 (9.4–10.4)	26.8 (25.5–28.1)
2012	20 665	2096	10.1 (9.7–10.6)	27.8 (26.7–28.9)
2013	24 410	2484	10.2 (9.8–10.6)	28.5 (27.5–29.6)
2014	29 829	3061	10.3 (9.9–10.6)	28.4 (27.5–29.4)
2015	33 338	3413	10.2 (9.9–10.6)	28.3 (27.5–29.2)
2016	36 998	3722	10.0 (9.8–10.4)	28.4 (27.6–29.3)
2017	40 469	4156	10.3 (10.0–10.6)	29.5 (28.6–30.3)
2018	19 865	3416	–	–

BNP, B-type natriuretic peptide; CI, confidence interval; HF, heart failure; NP, natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide.
[a]Excludes tests occurring after HF diagnosis;.
[b]Number of HF cases per 100 NP tests performed;.
[c]Applying UK NICE guideline NP test thresholds (NT-proBNP ≥400 pg/mL, BNP ≥100 pg/mL); HF detection rate and positive predictive value are not calculated for 2018 due to insufficient follow-up data.

PPV threshold of just 3% for referral for cancer diagnosis.[12] As a result, there was a very substantial increase in testing and consequent fall in PPV values. For example, in colorectal cancer PPV for GP referral for diagnosis was 10.3% in 2000 and had dropped to 3.1% in 2018.[29] Recent analysis using data from 2014/15 to 2018/19 found the conversion rate (2-week referrals resulting in a cancer diagnosis) was 7.6% for cancer in England.[33] This also differs markedly from PPV of NP testing in the acute HF population presenting to hospital. Evidence from people with acute onset breathlessness being assessed in the emergency department suggests a PPV for NP testing of between 50% and 60%.[34] This reflects the higher prevalence of HF in this highly symptomatic population. In contrast, patients presenting to primary care have much milder symptoms and the overall prevalence of HF is lower. Confounding factors associated with elevated NP levels such as age, chronic kidney disease and atrial fibrillation can also lead to false positive cases at the lower NP threshold.

A large systematic review and economic evaluation from Canada summarising the latest evidence on NP testing in HF diagnosis concluded that NP testing improved diagnostic accuracy and was cost-effective in the primary care setting, and acceptable to patients.[35] However, in our study we found that whilst the number of newly diagnosed HF cases increased over time, we did not find a corresponding increase in the NP detection rates for HF. A recent report by the British Heart Foundation highlighted that almost 80% of patients with HF are diagnosed on emergency hospital admission.[13,17] This suggests there are missed opportunities in primary care to undertake NP testing for patients with suspected HF.[36] In alignment with this, recent studies have found poor adherence to NICE recommended timeframes.[13,16,37] One CPRD study that analysed routes to HF diagnosis with data from 2010 to 2013, found that only 1.2% of patients who had a previous myocardial infarction completed the referral pathway within 2 weeks (as per 2010 NICE guideline) and only 3.9% of patients completed the pathway within 6 weeks.[13]

Policy and practice

There is already evidence to demonstrate that patients with suspected HF have high mortality and hospitalization rates and that timely HF specialist involvement is associated with better outcomes.[16,38] However, the pathway to HF diagnosis is complex with patient, clinician, and disease factors determining both the mode of presentation and speed of diagnostic labelling. Our previous qualitative work found patients with a recent HF diagnosis often normalized their symptoms until they were severe enough to have a substantial impact on daily activities[39] and, in some cases, emergency admission from home via ambulance was facilitated by their family.[40] Similarly, primary care clinicians assessing patients with signs of overt HF may admit them directly to hospital for acute treatment rendering primary care NP testing for diagnosis redundant at this advanced stage of disease.

Our study found that around one in four patients who had an NP test above the referral threshold went on to have a HF diagnosis. This is a very high ratio compared to, for example, colorectal cancer, where 32 patients need specialist review to diagnose one cancer.[29] The higher threshold for referral recommended by NICE compared to ESC guidance (e.g. 400 vs. 125 mL for NT-proBNP) could also contribute to later detection of HF in the UK.[5,6] Other European countries may achieve more timely diagnosis in the community and outpatient settings by detecting slow onset HF and implementing management sooner, although data are limited. The ACC/AHA guidelines go further and recommend NP testing in patients with risk factors for HF to allow both preventative strategies and earlier initiation of HF management to avoid emergency presentation with decompensated HF.[7] This recommendation is based on the PONTIAC[41] and STOP-HF[42] trials which both showed serial NP testing improved prevention and early management of HF in at risk groups.

The median level of NT-proBNP among people subsequently diagnosed with HF in our study remained high at around 1200 pg/mL over the last decade indicating most testing occurs in patients with more advanced disease. This suggests progress has not been made in testing to achieve a timely diagnosis, and that many patients with subtle clinical symptoms and signs are not being tested. The NP tests in our study were prior to referral for diagnostic imaging and assessment so NP levels are likely to have increased further by the time of diagnosis.

Greater public awareness, a higher index of suspicion for HF in primary care and an increase in NP testing is required to allow diagnosis at an earlier, more treatable stage.[43] Investment in rapid referral and treatment pathways, including universal access to NP testing, increased echocardiography capacity and specific HF diagnostic clinics, is needed to achieve timely HF diagnosis. The UK Cancer Plan in 2000 shone a light on delayed diagnosis and poor outcomes in cancer and the same policy driven approach may be needed in HF.

Conclusion

NP testing in primary care has increased over time with no evidence of significant inequalities. Around a quarter of patients who have an NP test above the NICE referral threshold go on to have a HF diagnosis. The HF detection rate though remains static at around 10% and most people with a new diagnosis have not had an NP test, suggesting there are missed opportunities in the diagnostic pathway. Greater use of NP testing in primary care may be needed to prevent hospitalization and facilitate HF diagnosis at an earlier, more treatable stage.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Ethical approval

The protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the MHRA (ISAC protocol number 19_136; available from the authors on request). Ethics approval for observational research using the CPRD with approval from ISAC was granted by a National Research Ethics Service Committee (Trent MultiResearch Ethical Committee, REC reference number 05/MRE04/87).

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without access to this data. The NIHR recognizes and values the role of patient data, securely accessed, and stored, both in underpinning and leading to improvements in research and care. All authors had full access to the full data in the study and accept responsibility to submit for publication.

Copyright statement

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest: S.L.L.-F. reports grants from NIHR Oxford BRC and grants from NIHR ARC Oxford and Thames Valley, during the conduct of the study. N.R.J. reports personal fees from Oxon Epidemiology, outside the submitted work. C.J.T. reports speaker fees from Vifor and Novartis and non-financial support from Roche outside the submitted work. All other authors report no conflicts of interest.

Data availability

Data for this study were obtained on licence from CPRD and cannot be shared. Equivalent data can be obtained directly from CPRD with relevant ISAC approval.

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ENTRESTO is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction.[1,2]

Entresto®
sacubitril/valsartan

Patients on ENTRESTO experience fewer hospitalisations, reduced risk of CV death and improved QoL versus ACEi (enalapril)*[3–7]

QoL based on post hoc analysis[6,7]

Explore ENTRESTO further

Current, expert-led ESC guidelines recommend ENTRESTO as a first-line treatment option for eligible patients with symptomatic chronic HFrEF in combination with a BB, SGLT2i and MRA[8]

~2% **of the NHS budget is spent on HF†[9,10]**

~70% **of the cost of HF to the NHS is due to hospitalisation[9]**

Versus ACEi (enalapril), at a median follow-up of 27 months, **ENTRESTO** significantly **reduced the risk** of:[‡3]

Composite of death from CV causes or first hospitalisation for worsening HF	Death from CV causes	First hospitalisation for worsening HF
20% RRR (ARR=4.7%; p<0.001)	20% RRR (ARR=3.1%; p<0.001)	21% RRR (ARR=2.8%; p<0.001)

Starting ENTRESTO first-line could add 1 to 2 years to patients' lives vs ACEi[4]

Based on actuarial estimates from the PARADIGM-HF trial, and assuming that protective effects of ENTRESTO remain consistent with long-term use; extrapolated from available short-term follow-up data. Results were found in patients who were 45–75 years of age.[4]

The most commonly reported adverse reactions with ENTRESTO were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%); angioedema was reported in patients treated with ENTRESTO (0.5%; uncommon).[1,2]

For further safety information, please refer to the Summary of Product Characteristics[1,2]

ACEi, angiotensin converting enzyme inhibitor; ARR, absolute risk reduction; BB, beta blocker; CV, cardiovascular; DHSC, Department of Health and Social Care; EF, ejection fraction; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor agonist; QoL, quality of life; RCT, randomised controlled trial; RR, risk reduction; SGLT2i, sodium-glucose cotransporter 2.

*PARADIGM HF (N=8,442) was a double-blind RCT of patients with class II, III or IV HF and an EF of ≤40% randomised to receive either ENTRESTO (200 mg twice daily) or enalapril (10 mg twice daily) in addition to recommended therapy. Primary outcome was a composite of death from CV causes or hospitalisation for HF[1]; †NHS budget 2020–2021 based on DHSC departmental expenditure limit of £130.38 billion[10]; ‡N=8,399.

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