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ORIGINAL ARTICLE

Use of heart failure medical therapy before and after a cancer diagnosis: A longitudinal study

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Abstract

Aims We aim to evaluate change in the use of prognostic guideline-directed medical therapies (GDMTs) for heart failure (HF) before and after a cancer diagnosis as well as the matched non-cancer controls, including renin-angiotensin-system inhibitors (RASIs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs).

Methods and results We conducted a longitudinal study in patients with HF in the UK Clinical Practice Research Datalink between 2005 and 2021. We selected patients with probable HF with reduced ejection fraction (HFrEF) based on diagnostic and prescription records. We described the longitudinal trends in the use and dosing of GDMTs before and after receiving an incident cancer diagnosis. HF patients with cancer were matched with a 1:1 ratio to HF patients without cancer to investigate the association between cancer diagnosis and treatment adherence, persistence, initiation, and dose titration as odds ratios (ORs) with 95% confidence intervals (CIs) using multivariable logistic regression models. Of 8504 eligible HFrEF patients with incident cancer, 4890 were matched to controls without cancer. The mean age was 75.7 (±8.4) years and 73.9% were male. In the 12 months following a cancer diagnosis, patients experienced reductions in the use and dosing of GDMT. Compared with the non-cancer controls, patients with cancer had higher risks for poor adherence for all three medication classes (RASIs: OR = 1.51, 95% CI = 1.35–1.68; beta-blockers: OR = 1.22, 95% CI = 1.08–1.37; MRAs: OR = 1.31, 95% CI = 1.08–1.59) and poor persistence (RASIs: OR = 2.04, 95% CI = 1.75–2.37; beta-blockers: OR = 1.35, 95% CI = 1.12–1.63; MRAs: OR = 1.49, 95% CI = 1.16–1.93), and higher risks for dose down-titration for RASIs (OR = 1.69, 95% CI = 1.40–2.04) and beta-blockers (OR = 1.31, 95% CI = 1.05–1.62). Cancer diagnosis was not associated with treatment initiation or dose up-titration. Event rates for HF hospitalization and mortality were higher in patients with poor adherence or persistence to GDMTs.

Conclusions Following a cancer diagnosis, patients with HFrEF were more likely to have reduced use of GDMTs for HF.

Keywords Cancer; Heart failure; Longitudinal study; Pharmacological treatment

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Introduction

Co-occurrence of HF and cancer is common due to their intersections at multiple levels. In recent years, there has been emerging evidence supporting the association between HF and cancer, and HF might also be an independent risk factor for cancer development.[1–3] Global disease statistics estimated the global incidence rate of cancer was around 2.3 per 1000 population in the general population.[4] The estimated incidence rate of HF varied from 1 to 20 per 1000 population depending on the population by different study.[5] A recent study in Italy showed that among an older population (mean age 76 years), the incidence rate of cancer was 21 per 1000 patient-years for patients with HF, compared with 12 per 1000 patient-years for the non-HF controls.[3] Evidence shows that patients with HF and cancer have a higher

all-cause or cancer-related mortality risk than those with cancer or HF alone.[3,6] However, guideline recommendations for HF management remain unmodified for people with HF who develop cancer.[7,8] The co-existence of HF and cancer can further complicate the clinical management of both conditions. The presence of HF at the time of diagnosis is recognized to limit treatment options available for patients with cancer.[9] Some patients may be unable to withstand well the oncological surgery, radiotherapy, or medical treatment,[10] especially if the treatment is potentially cardiotoxic, for example, anthracycline-based chemotherapy or radiotherapy.[8,11] Over past years, the introduction of new cancer treatments with different cardiotoxicity profiles may have introduced new opportunities or risks for patients with concurrent HF and cancer.[12,13] However, less is known regarding the impact of a cancer diagnosis on the management of HF.

Modern management of heart failure with reduced ejection fraction (HFrEF) involves administration of guideline-directed medical therapy (GDMT) for HF with a combination of renin-angiotensin-system inhibitors (RASIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and more recently, sodium-glucose cotransporter-2 inhibitors (SGLT-2Is).[8] Previous randomized controlled trials have demonstrated the dose-dependent benefits of medical therapies for HFrEF on patient outcomes.[14,15] This requires introduction of drugs and careful dose uptitration over a period of weeks to months.[16,17] For patients with HF, continuing guideline-recommended HF treatments may be more challenging following a cancer diagnosis. This may be because of common systemic side effects of the HF medications, complications related to cancer treatment or cancer progression (neutropenic sepsis-related hypotension and renal impairment), and issues related to polypharmacy and drug interactions. Together, these may lead to dose reduction, interruption, or even cessation of HF treatments, with potential impact on cardiovascular outcomes. This issue is even more concerning if the HF patient eventually needs cardiotoxic cancer treatments (benefits of the anticancer treatment may outweigh the risk of cardiotoxicity), given the evidence showing that patients with pre-existing cardiac dysfunction are at higher risk for developing cancer therapy related cardiac dysfunction (CTRCD).[18,19] As the prognosis of many cancers has improved a lot over recent decades,[20] treatment of co-existing HF becomes even more important.

To our knowledge, studies investigating the use of GDMT in patients with HF who develop cancer are lacking.[10,21] In this context, we conducted the study using a large electronic healthcare database in the United Kingdom to investigate any changes on the use and dosing of GDMT in patients with HF before and after a cancer diagnosis. We identified patients with HFrEF based on the diagnosis records and prescription records of GDMT for HFrEF. We also compared patterns of GDMT use between patients with cancer and patients without cancer.

Methods

Data source

In this longitudinal study, we used Clinical Practice Research Database (CPRD) primary-care electronic health records (GOLD and Aurum) accessed through the CALIBRE platform.[22–24] The primary care records were additionally linked to Hospital Episode Statistics (HES) admitted-patient care records, Office for National Statistics (ONS) death records, and patient-level Index of Multiple Deprivation (IMD) data. The study was approved by the CPRD Research Data Governance process (protocol number: 21_000695).

Study population and patient cohorts

The study period was from 1 January 2005 to 31 December 2021. The study population included all patients with an HF diagnosis in their medical history and aged over 18 years at the time of first HF diagnosis. The validated search strategy for HF was adopted from a study by Conrad et al.[25] To describe the patterns of GDMT use before and after a cancer diagnosis, a cohort of patients with any type of cancer was selected from the HF population based on the following criteria: (1) had a first-ever cancer diagnosis in CPRD (except for non-melanoma skin cancer) based on the SNOMED/Read/ICD-10 codes between 1 January 2005 to 31 December 2020 (1-year before end of the study period), and the cancer diagnosis occurred at least 1 year after the HF diagnosis; (2) had at least one-year registration history with the current GP practice prior to the cancer diagnosis; (3) had at least one-year follow-up available after the cancer diagnosis (cancer survivors). As the study required data linkage, patients without available linked data from the ONS or HES datasets were excluded. Patients were also required to have received at least one prescription of a RASI [angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and angiotensin receptor/neprilysin inhibitor (ARNI)], and a beta-blocker with an indication for HF (bisoprolol, carvedilol, and nebivolol) during the year prior to the cancer diagnosis. This criterion was applied to restrict the study population to patients who were more likely to have HFrEF.[26] All eligible patients were followed from the cancer diagnosis until the earliest of date of death, the date a patient's care was transferred out of a CPRD practice, or the last date of the study period.

To compare the GDMT use among patients with versus without cancer, we further built a control cohort of patients with HF and without a cancer diagnosis. Patients in the control cohort were matched by sex, age at HF diagnosis (±3 years), year of HF diagnosis (±3 years), and GP practice. A hypothetical cancer diagnosis date was assigned to each control patient based on the cancer diagnosis of their matched counterparts (i.e., based on the time between HF di-

agnosis and cancer diagnosis), provided they are still in the risk set at the assigned index date. Then, the same eligibility criteria as the cancer cohort were then applied to the matched control patients to select the eligible control patients. Patients with cancer without a matched control were excluded from further analyses. Finally, we randomly selected one matched control for each patient with a cancer diagnosis to build the final control cohort.

Study outcomes

The study outcome was changes in the use of GDMT for HF up to 36 months after a cancer diagnosis, that is, RASIs [angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and angiotensin receptor/neprilysin inhibitor (ARNI)], beta-blockers with an indication for HF (bisoprolol, carvedilol, and nebivolol), and MRAs. Details of the methods for handling the GDMT prescription records are described in Method S1. Of interest, 15% of prescription records had missing daily doses, which we imputed with the guideline-recommended dose number and frequency. We did not separately investigate the use of ARNI due to the low number of users in our cohort (<300 patients), nor SGLT-2Is due to the retrospective study period. We looked 1 year back from the cancer diagnosis to establish a pre-diagnostic trend in medication use. We measured the use of GDMT in proportion of medication users, received dosage, and the number of GDMT used in combination. For each measurement, the received dose was compared with the guideline-recommended target dose as described in *Table* S1. The dosage of each prescription was then classified as non-use, <50% of target dose (low-off target), 50–99% target dose (high-off target), and on target dose.

Within the matched cohorts, we further evaluated detailed patterns of the use of HF medical therapies. For each medication class of interest, we measured medication adherence, persistence, up-titration, down-titration, and initiation during the 12 months following the index date (defined as the cancer diagnosis for patients with cancer or the matched hypothetical cancer date for patients without cancer). Medication adherence was evaluated by calculating the proportion of days covered (PDC), that is, the sum of days covered by prescriptions over a period divided by the number of days in the period; and poor adherence was defined as having a PDC $<$ 80%.[27] Medication persistence was evaluated by calculating the gap between consecutive prescriptions, and poor persistence was defined as occurring when there was a refill gap of ≥90 days.[28] Dose titration was evaluated by comparing the percentage of target dose 1 year after the index date to that at the index date; and up-titration and down-titration were defined as dose class (as defined above) escalation or de-escalation, respectively. Medication initiation was defined as receiving any new prescription within 1 year following the index date. Adherence and persistence were assessed among those who were medication users on the index date; dose titration was assessed among those who were medication users on both the index date and 1 year after the index date; initiation was only assessed among those who were non-users on the index date.

We described the crude proportion of patients who experienced one-year all-cause mortality, cardiovascular mortality, cancer mortality, and hospitalization for HF (HHF) following the treatment adherence and persistence assessment for each GDMT. Cause of death was ascertained from ONS death records using ICD-10 codes. The one-year assessment period was from 1 year to 2 years after the cancer diagnosis, after assessing treatment adherence and persistence.

Covariates

The baseline study covariates measured at the index date included age, sex, calendar year of study entry stratified by the publications of European Society of Cardiology (ESC) guidelines (2005–2008, 2009–2012, 2013–2016, and 2017–2020), IMD, duration of HF (i.e., the time since the first HF diagnosis to the index date), recent hospitalization (defined as within 180 days before the index date); lifestyle information (the most recent record within 3 years before the index date), including body mass index (BMI) and smoking status; co-morbidities including atrial fibrillation, coronary heart disease, hypertension, peripheral vascular disease, stroke, asthma/chronic obstructive pulmonary disease, chronic kidney disease, dementia, depression, and type II diabetes; recent use of GDMTs and other cardiovascular medications (defined as within 180 days before the index date), including diuretics, nitrates, anticoagulants, antiplatelet agents, and statins; and the total number of any medications (defined as the number of different prescribed medicinal products at the index date).

Statistical analysis

All continuous variables were summarized as means [standard deviation (SD)] or medians [interquartile range (IQR)], and all categorical variables were summarized as numbers of subjects (%). The use and dosing of the GDMTs were described as the proportion of patients within each dosage group for each medication class at each time. The trends were constructed by indexing the medication usage data from 1 year prior to the cancer diagnosis up to 3 years after the cancer diagnosis as per the following time points: −12 months (12 months before cancer diagnosis), −9 months, −6 months, −3 months, 0 months (the date of cancer diagnosis), 3 months (after date of cancer diagnosis), 6 months, 9 months, 12 months, 18 months, 24 months and 36 months. Sankey diagrams were constructed to describe the individual-level longitudinal tra-

jectories between time points. A similar trend was constructed to describe the combined use of medications of different classes. In the one-to-one matched cohort, we repeated the descriptive trends, and we further analysed the use of GDMTs measured in 12-month persistence, adherence, titration, and initiation using multivariable logistic regressions to estimate the adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Missing data in covariates (BMI, smoking status, and IMD) were categorized as a separate data group.

Sensitivity analysis

We conducted several sensitivity analyses to evaluate the robustness of our findings. Firstly, during a hospital stay patients may have continued to receive GDMT, of which the prescriptions cannot be captured by the primary care database. Therefore, we repeated the analyses by treating the time during a hospitalization as the time being exposed to the previous GDMT. Secondly, we addressed the missing data in the outcome analyses using multiple imputation by chained equations to produce 20 imputed datasets. Rubin's rules were applied to combine the results from the analyses on each imputed dataset to produce the OR estimates and 95% CIs. Thirdly, we explored long-term outcomes in medication use by extending the outcome-defining period from 12 months to 18 months, 24 months, and 36 months. Patients who were censored before the end of the outcome-defining periods were excluded from each corresponding analysis. Fourthly, we stratified the study period by the calendar years covered by different ESC guidelines to explore changes in prescribing practice over time. Fifthly, we stratified the study cohort by sex. Sixthly, we additionally measured and controlled for high-dose furosemide (defined as receiving furosemide treatment ≥80 mg for at least 30 days in 1 year before index date)[3] and electronic frailty index using a validated approach within CPRD[29] as surrogate markers for disease severity. Seventhly, we used an alternative definition for poor persistence as having a 30-day gap between prescriptions.

Exploratory analysis

We repeated the analysis in the patients without concurrent RASI and a beta-blocker with an indication for HF during the year prior to the cancer diagnosis, who were less likely to have HFrEF and excluded in the main analysis, to enhance the granularity and generalizability of our findings.

Results

Patient cohort and baseline characteristics

After applying the inclusion and exclusion criteria, a total of 8504 out of 1 026 340 patients diagnosed with cancer and HFrEF were included in the descriptive analyses. Of these, 4890 patients with cancer were matched to patients with HF and no cancer diagnosis (controls), leaving 9780 patients in the one-to-one matched cohort (*Figure 1*). The five most common types of cancer were prostate cancer (18.0%), colorectal cancer (9.5%), breast cancer (8.1%), bladder cancer (7.2%), and malignant melanoma (7.1%) in the cohort for the descriptive analyses (n = 8504) (Table S2). The mean age of patients in the total cohort of patients with cancer was 76.1 (SD, 9.4) years, and 71.2% of patients were male sex. The mean time from the index HF diagnosis to cancer diagnosis was 6.2 (SD, 5.8) years. The baseline characteristics of the matched cohort of patients with cancer were largely similar to the total unmatched cohort of patients with cancer, except that the matched patients had a shorter duration of HF with a mean of 4.6 (SD, 3.9) years (*Table 1*).

Trends in medication use and dosing

The trends for the use and dosing of each class of GDMT and their combinations before and after the cancer diagnosis are

Figure 1 Study cohort selection.

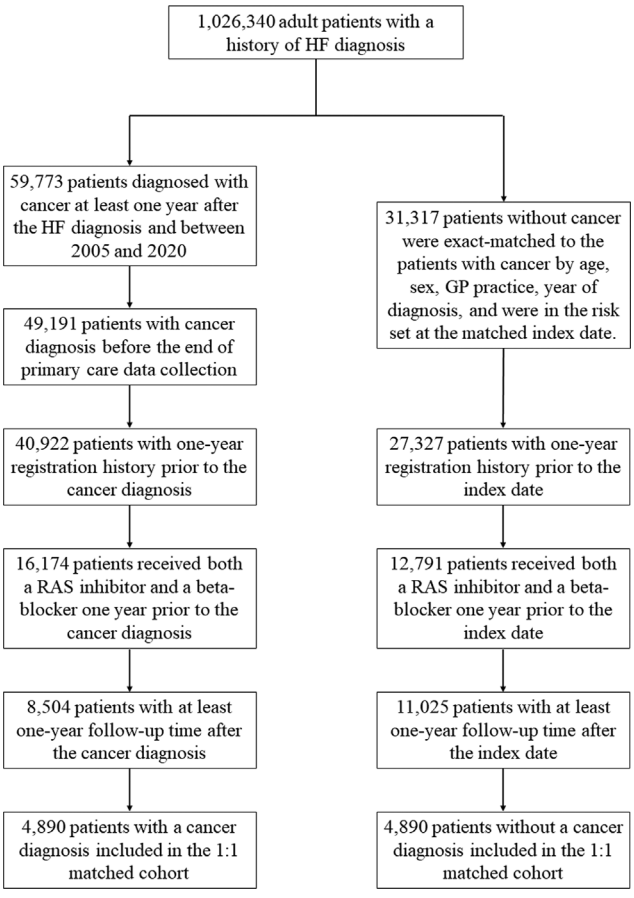

Table 1 Baseline characteristics of patients with heart failure

	Patients with cancer (n = 8504)	Matched patients with cancer (n = 4890)	Matched patients without cancer (n = 4890)
Age, years (mean, SD)	76.1 (9.4)	75.7 (8.4)	75.7 (8.4)
Male sex (%)	6056 (71.2)	3614 (73.9)	3614 (73.9)
BMI, kg/m^2 (%)[a]			
Underweight (<18.5)	83 (1.0)	43 (0.9)	46 (0.9)
Normal weight (18.5–24.9)	1403 (16.5)	781 (16.0)	736 (15.1)
Overweight (25–29.9)	2600 (30.6)	1492 (30.5)	1513 (30.9)
Obese (≥30)	3008 (35.4)	1778 (36.4)	1685 (34.5)
Missing	1410 (16.6)	796 (16.3)	910 (18.6)
Smoking status (%)[a]			
Current smoker	855 (10.1)	511 (10.5)	429 (8.8)
Ex-smoker	4008 (47.1)	2355 (48.2)	2212 (45.2)
Non-smoker	2831 (33.3)	1595 (32.6)	1751 (35.8)
Missing	810 (9.5)	429 (8.8)	498 (10.2)
IMD (%)			
1 (most deprived)	1773 (20.9)	1051 (21.5)	974 (19.9)
2	1811 (21.3)	1032 (21.1)	1045 (21.4)
3	1636 (19.2)	948 (19.4)	937 (19.2)
4	1620 (19.1)	922 (18.9)	945 (19.3)
5 (least deprived)	1616 (19.0)	915 (18.7)	947 (19.4)
Missing	48 (0.6)	22 (0.5)	42 (0.9)
Index year (%)			
2005–2008	773 (9.1)	307 (6.2)	290 (5.9)
2009–2012	1829 (21.5)	1020 (20.9)	1001 (20.5)
2013–2016	2782 (32.7)	1693 (34.6)	1731 (35.4)
2017–2020	3120 (36.7)	1870 (38.2)	1868 (38.2)
Duration of HF (years) (mean, SD)	6.2 (5.8)	4.6 (3.9)	4.6 (3.9)
Recent hospitalization (%)[b]			
Any hospitalization	3001 (35.3)	1692 (34.6)	714 (14.6)
HHF	1313 (15.4)	737 (15.1)	357 (7.3)
Co-morbidities (%)			
Atrial fibrillation	3921 (46.1)	2214 (45.3)	2169 (44.4)
CHD	5108 (60.1)	2891 (59.1)	2866 (58.6)
Hypertension	5465 (64.3)	3161 (64.6)	3037 (62.1)
PVD	839 (9.9)	454 (9.3)	405 (8.3)
Stroke	788 (9.3)	463 (9.5)	430 (8.8)
Asthma/COPD	1890 (22.2)	1123 (23.0)	976 (20.0)
CKD stage 3–5	3314 (39.0)	1835 (37.5)	1736 (35.5)
Dementia	181 (2.1)	108 (2.2)	128 (2.6)
Depression	1497 (17.6)	841 (17.2)	841 (17.2)
Type 2 diabetes mellitus	2626 (30.9)	1503 (30.7)	1449 (29.6)
Recent GDMT (%)[b]			
RASI	8199 (96.4)	4708 (96.3)	4725 (96.6)
Beta-blocker	8261 (97.1)	4749 (97.1)	4764 (97.4)
MRA	2116 (24.9)	1237 (25.3)	1295 (26.5)
Recent other cardiovascular medications (%)[b]			
Anticoagulants	3319 (39.0)	1853 (37.9)	1755 (35.9)
Antiplatelets	4466 (52.5)	2618 (53.5)	2666 (54.5)
Diuretics	5318 (62.5)	2945 (60.2)	2899 (59.3)
Nitrates	1890 (22.2)	1012 (20.7)	1069 (21.9)
Statins	6381 (75.0)	3713 (75.9)	3690 (75.5)
High-dose furosemide[c]	1225 (14.4)	704 (14.4)	609 (12.5)
Frailty index			
Fit	1253 (14.7)	776 (15.9)	934 (19.1)
Mild frailty	3612 (42.5)	2105 (43.1)	2153 (44.0)
Moderate frailty	2640 (31.0)	1491 (30.5)	1344 (27.5)
Severe frailty	999 (11.8)	518 (10.6)	459 (9.4)
No. of medications (mean, SD)	9.4 (4.5)	9.4 (4.5)	8.9 (4.6)

[a]The most recent measurement within 3 years prior to the index date.
[b]Within 180 days prior to the index date.
[c]Furosemide treatment with 80 mg or more daily dose for at least 30 days within 1 year before the index date.
BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GDMT, guideline-directed medical therapy; HF, heart failure; HHF, hospitalization with a heart failure diagnosis; IMD, Index of Multiple Deprivation; MRA, mineralocorticoid receptor antagonist; PVD, peripheral vascular disease; RASI, renin-angiotensin-system inhibitor; SD, standard deviation.

illustrated in *Figure 2*, and the longitudinal trajectories of individual-level changes are illustrated by Sankey diagrams in *Figure* S1.

Within the cohort with cancer for the descriptive analyses, there were reductions in the usage of RASIs and beta-blockers after the cancer diagnosis. The percentage of RASI users reduced from 89% at 12 months prior to the cancer diagnosis to 86% at the cancer diagnosis, 75% at 12 months, and 74% at 36 months after the cancer diagnosis. The corresponding percentages of patients who received the target dose of RASIs at those time points were 26%, 25%, 20%, and 21% (*Figure 2A*, *Figure* S1A) For beta-blockers, the percentage of users changed from 85% at 12 months prior to diagnosis to 88% at the diagnosis, 84% at 12 months after diagnosis, and 80% at 36 months after diagnosis. The percentage of patients who received the target dose of beta-blockers did not change: 16% at 12 months prior to diagnosis, 17% at diagnosis, 16% at 12 months after diagnosis, and 16% at 36 months after diagnosis (*Figure 2B*, *Figure* S1B).

There was little change in the proportion of MRA users before and after the cancer diagnosis. The percentage of MRA users ranged from 20% to 21%, and the percentage of patients on the target dose of MRAs ranged from 13% to 14% throughout all time points (*Figure 2C*, *Figure* S1C).

Combination use of GDMT declined after the cancer diagnosis. The percentage of patients who did not receive any RASI, beta-blocker, or MRA increased with time from 5% at diagnosis to 9% at 12 months after diagnosis and 10% at 36 months after diagnosis. The percentage of patients who received triple therapy decreased from 18% at 12 months before and at diagnosis to 16% at 12 months after diagnosis and 15% at 36 months after diagnosis. Most patients used two classes of the GDMTs (ranging from 66% to 55% at different times of measurement) (*Figure 2D*, *Figure* S1D).

Figure 2 Trends in use and dosing of GDMTs for HF before and after the cancer diagnosis, (A) RASIs; (B) beta-blockers; (C) MRAs; (D) number of GDMT combinations. The daily dose of each medication was measured as percentage of the guideline recommended daily dose; the number of GDMT combinations measured the concurrent use of a RASI, beta-blocker, and MRA. The trends were indexed with measurements from 12 months before cancer to 36 months after cancer. The measurements at the cancer diagnosis were marked with red border.

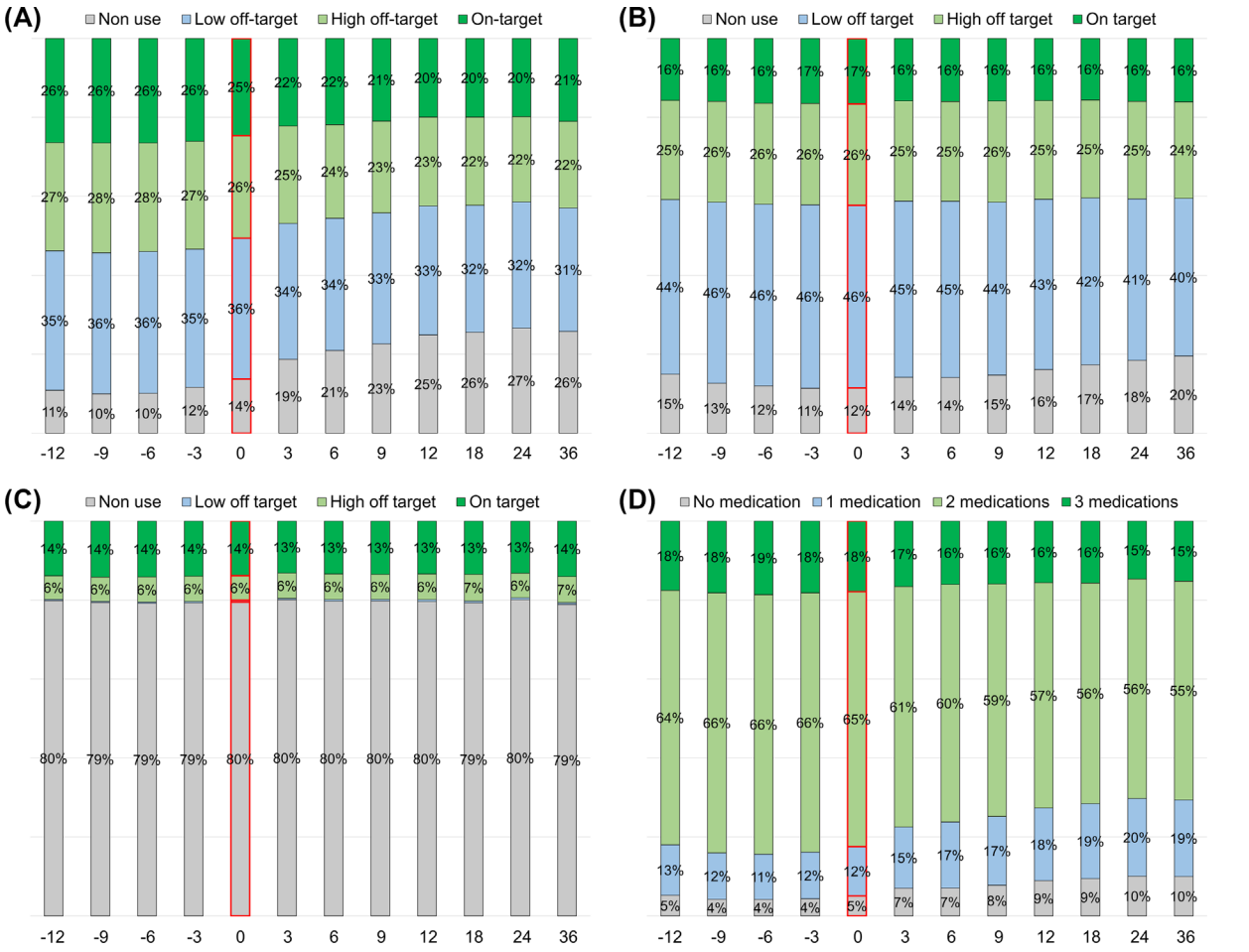

Table 2 Associations between cancer diagnosis and adherence, persistence, up-titration, down-titration, and initiation of GDMTs among the matched patient cohorts

	Cohort	No. of patients	No. of outcomes (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
RASIs					
12-month poor adherence[a]	Non-cancer	4347	775 (17.8)	1 (Reference)	1 (Reference)
Cancer	4215	1111 (26.4)	**1.65 (1.49–1.83)**	**1.51 (1.35–1.68)**	
12-month poor persistence[a]	Non-cancer	4347	294 (6.7)	1 (Reference)	1 (Reference)
Cancer	4215	588 (14.0)	**2.24 (1.93–2.59)**	**2.04 (1.75–2.37)**	
12-month up-titration	Non-cancer	3851	161 (4.2)	1 (Reference)	1 (Reference)
Cancer	3445	155 (4.5)	1.08 (0.86–1.35)	0.96 (0.76–1.22)	
12-month down-titration	Non-cancer	3851	206 (5.4)	1 (Reference)	1 (Reference)
Cancer	3445	309 (9.0)	**1.74 (1.45–2.09)**	**1.69 (1.40–2.04)**	
12-month initiation	Non-cancer	543	315 (58.0)	1 (Reference)	1 (Reference)
Cancer	675	360 (53.3)	0.83 (0.66–1.04)	0.90 (0.69–1.17)	
Beta-blockers					
12-month poor adherence[a]	Non-cancer	4425	656 (14.8)	1 (Reference)	1 (Reference)
Cancer	4327	816 (18.9)	**1.34 (1.19–1.49)**	**1.22 (1.08–1.37)**	
12-month poor persistence[a]	Non-cancer	4425	209 (4.7)	1 (Reference)	1 (Reference)
Cancer	4327	297 (6.9)	**1.49 (1.24–1.78)**	**1.35 (1.12–1.63)**	
12-month up-titration	Non-cancer	4019	179 (4.5)	1 (Reference)	1 (Reference)
Cancer	3838	227 (5.9)	**1.35 (1.10–1.65)**	1.21 (0.99–1.50)	
12-month down-titration	Non-cancer	4019	163 (4.1)	1 (Reference)	1 (Reference)
Cancer	3838	218 (5.7)	**1.42 (1.16–1.75)**	**1.31 (1.05–1.62)**	
12-month initiation	Non-cancer	465	300 (64.5)	1 (Reference)	1 (Reference)
Cancer	563	350 (62.2)	0.90 (0.70–1.17)	0.92 (0.69–1.22)	
MRAs					
12-month poor adherence[a]	Non-cancer	1127	311 (27.6)	1 (Reference)	1 (Reference)
Cancer	1032	352 (34.1)	**1.36 (1.13–1.63)**	**1.32 (1.08–1.60)**	
12-month poor persistence[a]	Non-cancer	1127	135 (12.0)	1 (Reference)	1 (Reference)
Cancer	1032	182 (17.6)	**1.57 (1.23–2.00)**	**1.50 (1.16–1.93)**	
12-month up-titration	Non-cancer	916	18 (2.0)	1 (Reference)	1 (Reference)
Cancer	795	22 (2.8)	1.42 (0.76–2.67)	1.36 (0.77–2.41)	
12-month down-titration	Non-cancer	916	29 (3.2)	1 (Reference)	1 (Reference)
Cancer	795	22 (2.8)	0.87 (0.50–1.53)	0.68 (0.40–1.16)	
12-month initiation	Non-cancer	3763	313 (8.3)	1 (Reference)	1 (Reference)
Cancer	3858	312 (8.1)	0.97 (0.82–1.14)	0.86 (0.72–1.02)	

Note: Odds ratios with statistical significance were highlighted in bold.
CI, confidence interval; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; RASI, renin-angiotensin-system inhibitor.
[a]Grace periods of the duration of prescriptions were removed when defining the outcomes.

The trends for the use and dosing of each class of GDMT and their combinations within the one-to-one matched cohort are illustrated in Figures S2–S5. The matched patients with cancer generally showed similar trends in the usage of individual medication classes and the combination of medications compared with the unmatched total patients with cancer. The pre-cancer baseline use of GDMTs was similar between matched cancer patients and controls. After the cancer diagnosis, the matched controls showed less decline in medication use and dosing than their matched counterparts with cancer, although a reduction was observed for the use of RASIs and beta-blockers over time.

Treatment adherence, persistence, dose titration, and initiation

Patients with cancer were more likely to have poor adherence and poor persistence in all three medication classes (RASIs, beta-blockers, and MRAs) within 1 year following the cancer diagnosis. The percentages of patients with and without cancer who had 12-month poor adherence were 26.4% versus 17.8% for RASIs, 18.9% versus 14.8% for beta-blockers, and 34.1% versus 27.6% for MRAs, respectively. After adjusting for the covariates, the OR for the associations between cancer diagnosis and poor adherence was 1.51 (95% CI, 1.35–1.68) for RASIs, 1.22 (95% CI, 1.08–1.37) for beta-blockers, and 1.31 (95% CI, 1.08–1.59) for MRA. The percentages of patients with and without cancer who had 12-month poor persistence were 14.0% versus 6.7% for RASIs, 6.9% versus 4.7% for beta-blockers, and 17.6% versus 12.0% for MRAs, respectively. After adjusting for the covariates, the OR for the associations between cancer diagnosis and poor persistence was 2.04 (95% CI, 1.75–2.37) for RASIs, 1.35 (95% CI, 1.12–1.63) for beta-blockers, and 1.49 (95% CI, 1.16–1.93) for MRAs (*Table 2*).

Among the medication users who also remained on treatment 12 months after the cancer diagnosis, patients with cancer were more likely to experience dose down-titration within 12 months for RASIs and beta-blockers. The percentages of medication users with and without cancer who had 12-month dose down-titration were 9.0% and 5.4%, respectively, for RASIs, and 5.7% and 4.1%, respectively, for beta-blockers. The ORs after multivariable adjustments were 1.69 (95% CI, 1.40–2.04) for RASIs and 1.31 (95% CI, 1.05–1.62) for beta-blockers. No association was found between cancer and dose up-titration for RASIs or beta-blockers or any dose titration for MRAs (*Table 2*).

We found no association of cancer diagnosis with treatment initiation among medication non-users at the cancer diagnosis for any of these medication classes (*Table 2*).

The patients with cancer who had poor adherence and persistence to each GDMT had higher event rates for all-cause mortality, cardiovascular mortality, cancer mortality, and HHF within 1 year compared with the patients with cancer with good adherence and persistence (Table S3).

Sensitivity analysis

The results from the sensitivity analyses were consistent with the main analysis when we repeated the outcome analyses by recalculating the duration of prescriptions by considering in-hospital use of medications (Table S4) or addressing the missing data with multiple imputation (Table S5). When we extended the outcome-defining period from 12 months to 18 months, 24 months, and 36 months, the comparative risks of poor adherence, poor persistence, and dose down-titration tended to become closer to null in patients who survived longer after the cancer diagnosis (Table S6, Figure S6). When we stratified the patients by the calendar year of study entry, there was no clear change in trends in GDMT use after cancer diagnosis from the period 2005–2008 to 2017–2020 (Table S7, Figure S7). In the analysis stratified by sex, men were more likely to experience changes to RASI and beta-blocker treatments than women (Table S8, Figure S8). Additionally, adjusting for the frailty index and high-dose furosemide did not materially change our results (Table S9). Changing the definition of poor persistence to having a 30-day gap did not change the results (Table S10).

Exploratory analysis

In the exploratory analysis nested in patients with HF but without at least one RASI and beta-blocker prescription in a year prior to the cancer diagnosis (likely HFpEF), the baseline patient characteristics were presented in Table S11, similar results on the impact of cancer on the use of medications were obtained from the regression analyses, although many did not reach statistical significance due to lower statistical power (Table S12, Figure S9).

Discussion

In this longitudinal study using UK-based primary care electronic health records, we conducted a comprehensive analysis of the use of GDMT for HF among patients with HFrEF (identified based on diagnosis and prescription records) who developed incident cancer. We found that use of GDMT was reduced in HF patients with incident cancer, both in terms of the usage and dosage of individual medication classes (particularly the RASIs) and the number of GDMT combinations. Despite similar baseline rates of GDMT, compared with matched HF patients without cancer, patients with an incident cancer diagnosis had higher risks for poor adherence and poor persistence to RASIs, beta-blockers, and MRAs, as

well as higher risks for dose down-titration for RASIs and beta-blockers as the direct results of the cancer diagnosis.

Our results provide valuable real-world data illustrating the challenge of maintaining pharmacological treatment for HF after a cancer diagnosis. The findings agreed with previously reported clinical experience, with several potential explanations suggested for treatment changes. Firstly, cancer progression or cancer treatments often lead to complications such as deteriorating renal function, hypotension, or atrial fibrillation.[10] In particular, among these three classes of GDMT, we found that interruptions of RASIs were more often than beta-blockers or MRAs. This might be due to certain complications of cancer or cancer treatment affecting the tolerability of patients to RASI treatments, for example, deterioration of renal function or atrial fibrillation, which has been linked to reduced usage of RASIs in previous studies.[27,30] Likewise, these complications may lead to clinically reasonable dose modifications,[31,32] reflected as the dose downtitration in our data. Although we observed more deviations from the guideline-recommended target dose, this may not necessarily mean suboptimal use of GDMTs as higher dose may not associate with better prognosis in these patients. Secondly, patients with cancer and heart failure have worse prognosis and shorter life expectancy.[3,6] Therefore, clinicians may consider the continuation of long-term treatment for HF less important, especially if the patients need aggressive cancer treatment or palliative care. In our data, we observed that patients with poor adherence and persistence to GDMTs are those with higher risk of cancer mortality, which may support this notion. Lastly, there may be other barriers to the optimization of GDMTs related to the patients, the healthcare providers, and the healthcare system,[33] for example, poor adherence to the prescribed medications by the patients, limited knowledge or clinical inertia of the clinicians, or limited access to cardio-oncology or other healthcare services.[34] The observed treatment changes after a cancer diagnosis are likely to result from a combination of these reasons. While the current study is limited by the retrospective nature in evaluating the factors driving the changes in GDMTs after cancer, further research should be conducted to investigate the reasons for the treatment changes at an individual level.

There is a strong bidirectional relationship between cancer and HF, with many cancer therapies also cardiotoxic and may lead to worse cardiovascular outcomes.[35,36] Such cancer treatments can cause CTRCD in patients without pre-existing cardiac conditions, but even mild baseline LV impairment is known to be a significant risk factor for subsequent decline in cardiac function.[37,38] There is also evidence that administration of RASI and beta-blocker in patients at risk of CTRCD may attenuate subsequent decline in cardiac function and hence cancer treatment discontinuation.[9,39,40] Therefore, this means that optimal use of HF medications that may also provide cardioprotection is even more critical in HF patients undergoing treatment for cancer. Despite the clear theoretical rationale, the role of co-morbid cancer or incident cancer on HF therapy is under-researched as patients with a cancer diagnosis are usually excluded from HF trials.[41] Our analysis presents novel results and addresses some of the missing evidence surrounding this clinical difficulty.

The current study provides data from a generalized population of patients with heart failure and a new cancer diagnosis. The risks of cardiotoxicity and potential drug interactions will vary between cancer types and cancer therapies.[6,42] Different cancer treatments are associated with different profiles of complications, toxicity, and other side effects, therefore may interact differently with HF and the GDMTs for HF. Future studies are needed to identify which patients are at highest risk of heart failure decompensation or treatment interruption, and the reasons for this. These studies might need to focus on a specific treatment for a specific cancer, for example, in women with breast cancer receiving radiotherapy as it is a well-known risk factor for worsening cardiac function.[11] Furthermore, with the introduction of new cancer treatments,[12,13] continuous research in this field is required to understand the optimal cancer treatment strategies in patients who are actively treated for their HF.

71.2% of patients included in this study were men. This could be due to our eligibility criteria for selecting patients with probable HFrEF, which is more common among male patients.[43] Also, women have worse prognosis of HF than men.[44] This may reduce the likelihood of women developing cancer after HF. The proportion of men and women in our study is similar to previous clinical trials or HF registries that exclusively included patients with HFrEF.[43,45] From our data, we identified that men were potentially more prone to treatment changes after cancer diagnosis. Further research is needed to investigate any sex-based differences in the use of GDMTs for HF in relation to the cancer diagnosis.

Our study has several implications for better medical management of HF after a cancer diagnosis and further research. Real-world adherence to GDMT for HF is known to be challenging even in the general HF population.[46] With the change in clinical focus following a new diagnosis of cancer, alongside cancer and treatment-related complications, changes in the use of GDMT in patients with cancer are almost inevitable under certain circumstances. Our data reinforce the need for targeted strategies for HF treatment optimization and patient and clinician education at the time of cancer diagnosis. Closer collaboration between cardiologists, oncologists, general practitioners, pharmacists, and specialist nurses is required to manage the cardiovascular health of patients with cancer to prevent cardiovascular complications including worsening HF.[35,47] In the United Kingdom, cardio-oncology services are growing in providing more integrated care for patients with cancer to better manage cardiovascular risks.[37] However, the scope of the cardio-oncology services should not only be limited to the prevention of cardiovascular diseases in-

duced by cardiotoxic cancer therapies, but also be on the better management of patients with cancer with pre-existing cardiovascular diseases.[47,48] Alternative approaches for establishing HF treatment regimens may also be worth considering in this scenario. For example, the strategies of more rapid and personalized up-titration and concurrent initiation of multiple drug classes of GDMT prior to cancer treatment initiation.[49,50]

Strengths and limitations

This is the first study investigating the use of GDMT for HF after a cancer diagnosis. Despite implementing stringent inclusion and exclusion criteria, the study is large in its sample size. Our analysis was further strengthened by the rich prescription information in the longitudinal datasets, such as the prescription quantity, duration, product strength, and daily dose, which allowed us to evaluate medication utilization patterns in depth from multiple aspects.

The study has limitations. Firstly, we evaluated the medication utilization using prescription data; however, we did not know whether the prescriptions were redeemed or whether the prescribed medications were consumed by the patients. Therefore, we are likely to have overestimated the actual pattern of GDMT utilization. However, previous studies suggested that the risk of misclassification of medication consumption using prescription records is low for GDMT for HF[27] and is likely to be non-differential between cancer and non-cancer patients.[28] Secondly, we do not have information on the ejection fraction of the HF diagnosis, and therefore we could not clearly differentiate patients with HFrEF from patients with other types of HF. However, we restricted the study patients to those who received both a RASI and a beta-blocker 1 year before cancer for treating HF as RASIs and beta-blockers are recommended for all patients with HFrEF if tolerated.[8] This approach was adapted from a previously validated method with a high positive predictive value for selecting patients who are likely to have HFrEF, or at least, with indications for the study medications.[26] Similarly, we do not have direct measurement of disease severity, but we included several surrogate markers for disease severity, such as frailty index, previous hospitalizations, and use of HF treatment, and no difference in results were found. Thirdly, we do not have data on in-hospital use of medications. However, we conducted a sensitivity analysis adding the duration of hospital stays to duration of prescriptions and found similar results. Furthermore, our data are not sufficiently large or updated to investigate the use of ARNI or SGLT-2Is separately. Lastly, we could not capture the reasons for treatment changes, so we could not analyse whether the changes in GDMT were inappropriate or justifiable.

Conclusions

In this study, we identified patterns of reduced use of GDMTs for HF after a cancer diagnosis. Among patients with HF, those who developed incident cancer were more likely to experience poor treatment adherence, poor persistence, and dose down-titration of the GMDT medications compared with patients without cancer following the cancer diagnosis. The reduced use of pharmacological therapies by patients with cancer are concerning, as the cancer diagnosis often leads to worsened cardiovascular prognosis, especially when the changes may be avoidable under certain circumstances. Our study provides evidence supporting the complexity of treating HF when co-morbid cancer develops.

Conflict of interest

CM is supported by the University College London Hospitals' National Institute for Health Research Biomedical Research Centre. ISM declares recent or current grant funding to institution from NIHR HTA, HDR UK, IMI, University of Oxford, BHF and RTI, institutional consultancy income from AstraZeneca, and personal consultancy/advisory board income from AstraZeneca, Amgen, and Amarin UK. MDF is supported by the UCL/UCLH NIHR Biomedical Research Centre and acknowledges grant support from CRUK, AstraZeneca, Boehringer Ingelheim, MSD, and Merck; is an advisory board member for Transgene; and has consulted for Achilles, Amgen, AstraZeneca, Bayer, Boxer, Bristol-Myers Squibb, Celgene, EQRx, Guardant Health, Immutep, Ixogen, Janssen, Merck, MSD, Nanobiotix, Novartis, Oxford VacMedix, Pharmamar, Pfizer, Roche, Takeda, UltraHuman. All other authors declared no conflict of interest.

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Data availability statement

The data used in this study were provided by CPRD under licence/by permission. All CPRD data are available via a CPRD Research Data Governance application.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The guideline-recommended target dose of RASIs, beta-blockers, and MRAs for treatment of HFrEF.
Methods S1. Methods for cleaning daily dose and duration of the GDMT prescription records.
Table S2. Summary of the cancer diagnosis by site, among all patients with cancer and the matched patients with cancer.
Figure S1. Sankey diagrams for the longitudinal trajectories of use and dosing of GDMT for HF before and after the cancer diagnosis, (A) RASI; (B) beta-blocker; (C) MRA; (D) number of GDMT combinations.
Figure S2. Trends in use and dosing of RASI before and after the cancer diagnosis within the one-to-one match cohort, (Top) patients with cancer; (Bottom) patients without cancer.
Figure S3. Trends in use and dosing of beta-blocker before and after the cancer diagnosis within the one-to-one match cohort, (Top) patients with cancer; (Bottom) patients without cancer.
Figure S4. Trends in use and dosing of MRA before and after the cancer diagnosis within the one-to-one match cohort, (Top) patients with cancer; (Bottom) patients without cancer.
Figure S5. Trends in the number GDMT combinations for HF used by patients before and after the cancer diagnosis within the one-to-one match cohort, (Top) patients with cancer; (Bottom) patients without cancer.
Table S3. Event rates for all-cause mortality, cardiovascular mortality, and hospitalization with a HF diagnosis among matched patients with cancer, stratified by adherence and persistence to GDMTs.
Table S4. Sensitivity analysis with the duration of hospitalization added into the duration of corresponding prescriptions.
Table S5. Sensitivity analysis with multiple imputation for missing data.
Table S6. Sensitivity analysis with varied outcome-defining periods.
Figure S6. Forest plots for adjusted odds ratios with 95% CIs from the sensitivity analysis with varied outcome-defining periods.
Table S7. Sensitivity analysis with stratifications by calendar year.
Figure S7. Forest plots for adjusted odds ratios with 95% CIs from the sensitivity analysis with stratifications by calendar year.
Table S8. Sensitivity analysis with stratifications by sex.
Figure S8. Forest plots for adjusted odds ratios with 95% CIs from the sensitivity analysis with stratifications by sex.
Table S9. Sensitivity analysis with additional adjustment for frailty index and high-dose furosemide, as surrogates for disease severity.
Table S10. Exploratory analysis: baseline characteristics of patients with heart failure without concurrent use of RASIs and beta-blockers prior to cancer (excluded from the main analysis).
Figure S9. Trends in use and dosing of GDMT for HF before and after the cancer diagnosis in patients with heart failure without concurrent use of RASIs and beta-blockers prior to cancer (excluded from the main analysis)., (A) RASI; (B) beta-blocker; (C) MRA; (D) number of GDMT combinations.
Table S11. Exploratory analysis: associations between cancer diagnosis and adherence, persistence, up-titration, down-titration, and initiation of GDMTs among the matched patient cohorts without concurrent use of RASIs and beta-blockers prior to cancer (excluded from the main analysis).

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