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# Effect of statin treatment on the risk of cancer in patients with heart failure: A target trial emulation study

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## Abstract

**Purpose:** A recent observational study suggested statins could reduce cancer diagnosis in patients with heart failure (HF). The findings need to be validated using robust epidemiological methods. This study aimed to evaluate the effect of statin treatment on the risk of cancer in patients with HF.

**Methods:** We conducted two target trial emulations using primary care data from IQVIA Medical Research Database-UK (2000 to 2019) with a clone-censor-weight design. The first emulated trial addressed the treatment initiation effect: initiating within 1 year versus not initiating a statin after the HF diagnosis. The second emulated trial addressed the cumulative exposure effect: continuing a statin for  $\leq 3$  years, 3–6 years, and  $> 6$  years after initiation. The study outcomes were any incident cancer and site-specific cancer diagnoses. Weighted pooled logistic regression models were used to estimate 10-year risk ratios (RR). 95% confidence intervals (CIs) were estimated using non-parametric bootstrapping.

**Results:** The first emulated trial showed that, compared to no statin, statins did not reduce the cancer risk in patients with HF (RR, 1.05; 95% CI, 0.94–1.15). The second emulated trial showed that, compared to treatment  $\leq 3$  years, statins with longer durations did not reduce the cancer risk (3–6 years: RR, 0.94; 95% CI, 0.70–1.33.  $> 6$  years: RR, 0.97; 95% CI, 0.79–1.26). No significant risk difference was observed on any site-specific cancer diagnoses.

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**Conclusions:** The results from the target trial emulations suggest that statin treatment is not associated with cancer risk in patients with HF.

#### KEYWORDS

cancer, causal inference, heart failure, statin, target trial emulation

#### Key Points

- This study applied target trial emulation frameworks with clone-censor-weight designs to investigate the effects of statin treatment on the risk of cancer in patients with heart failure (HF).
- Using IQVIA Medical Research Database-UK data, two trial emulations were conducted.
- In the first trial emulation, initiation of statin treatment did not reduce the risk of cancer in patients with HF.
- In the second trial emulation, continuation of statin treatment with longer durations did not reduce the risk of cancer in patients with HF.

#### Plain Language Summary

We wanted to confirm if statins, a type of medication, really help reduce the risk of cancer in people with heart failure. A previous study suggested they might, but we needed to use strong scientific methods to check if this is true. To do this, we used information from medical records of people in the UK from 2000 to 2019. We designed two ‘emulated’ trials to mimic what would happen if real trials were conducted. In the first ‘trial’, we looked at people who started taking statins within 1 year of being diagnosed with heart failure, comparing them to those who did not start taking statins. In the second ‘trial’, we looked at people who continued taking statins for different lengths of time (less than 3 years, 3–6 years, and more than 6 years) after starting. After analyzing the data, we found that taking statins did not actually lower the risk of cancer in people with heart failure. Whether they started taking statins or continued taking them for a longer time, it did not make a significant difference in the likelihood of developing cancer. This was true for different types of cancer as well. In conclusion, our study suggests that taking statins does not appear to be connected to an increased or decreased risk of cancer in people with heart failure.

## 1 | INTRODUCTION

The effect of statins on cancer development is controversial. While numerous observational studies have reported lower risks for cancer associated with statin use,<sup>1–3</sup> analyses of data from randomised controlled trials (RCTs) have not shown such an effect.<sup>4</sup> The discrepancies between the effect estimates from observational studies and RCTs may be due to bias inflicted by inappropriate study designs. The target trial emulation framework is a promising new paradigm for establishing causal inference with observational data.<sup>5,6</sup> By explicitly emulating a target trial, observational study design can benefit from clarifying the causal question of interest, transparent reporting of study design, and, most importantly, minimised self-inflicted bias (e.g., immortal-time bias and selection bias).<sup>5,6</sup> Several different study designs and methods have been proposed to be used to fit the target trial emulation framework, such as clone-censor-weight, sequential trials, active comparator, or prevalent new-user designs.<sup>7–10</sup> Previous target trial emulations have successfully replicated the results from RCTs of the effects of statin use on various endpoints, including cancer outcomes.<sup>7–9,11</sup>

Cancer and heart failure (HF) are two major causes of morbidity and mortality with a complex inter-relationship including shared risk

factors and overlapping pathophysiology.<sup>12,13</sup> Epidemiological research has shown that the cancer incidence is higher in patients with HF than the general population even after controlling for other risk factors.<sup>14</sup> Given the impact on survival of newer pharmacological treatment for HF, it is of increasing clinical interest to identify strategies to reduce the burden of comorbid cancer in this population.<sup>12</sup> Statins are commonly prescribed in patients with heart failure with risk factors or pre-existing coronary heart disease, and have been proposed to have potential anti-cancer effects in this patient group due to their anti-inflammatory and mevalonate-inhibition effects.<sup>15,16</sup> Recent evidence from an observational study has suggested that statins may reduce the risk of cancer and cancer-related mortality in an Asian population with HF.<sup>16</sup> While it is plausible that there may be specific interactions between statins and HF in regulating certain tumorigenic pathways, this finding warrants further validation in different settings and by applying the target trial emulation framework to minimise potential sources of bias in the study designs.

Therefore, we applied the target trial emulation framework<sup>5</sup> to investigate the effect of statin treatment in patients with HF on the risk of developing cancer using observational data from the United Kingdom. We conducted two emulated target trials to

thoroughly evaluate the effect of statin treatment on the risk of cancer. In the first emulated trial, we estimated the overall effect of statin initiation within the first year versus no statin initiation after HF on the risk of cancer; in the second emulated trial, we explored the cumulative exposure-response effect of statin on cancer by comparing different durations of statin treatment after HF on the risk of cancer. This cumulative exposure-response effect is considered the key to establishing a causal effect for the drug-cancer relationship.<sup>17</sup>

## 2 | METHODS

### 2.1 | Data source

We used de-identified routine primary care data from the IQVIA Medical Research Data (IMRD)-UK (formerly known as THIN database) for this study. The IMRD-UK database is a nationwide database of primary care records in the United Kingdom that contains around 6% of the total UK population. Previous studies have demonstrated the validity of the database for pharmacoepidemiologic studies and generalisability to the UK population.<sup>18,19</sup> The IMRD-UK database includes data on demographic information, lifestyle information (including smoking, and alcohol consumption), medical diagnosis and procedures (recorded in read codes), prescribing information and biochemistry tests.

### 2.2 | Study design

This study was an observational study using the target trial emulation design. We emulated two hypothetical target pragmatic trials: (1) comparing the effect of statin initiation within 1 year versus non-statin use on the risk of incident cancer diagnosis in patients with new-onset HF; (2) comparing the effects of different durations of statin treatment ( $\leq 3$  years, 3–6 [ $>3$  and  $\leq 6$ ] years, and  $>6$  years) on the risk of incident cancer diagnosis in patients with new-onset HF to explore any cumulative exposure-response effect. In the first emulated trial, all HF patients identified in the database were replicated into two copies (cloned) and two identical patient cohorts were assigned to statin treatment strategy cohort and no statin treatment strategy cohort. In the second emulated trial, statin initiators were replicated into three copies and assigned to statin treatments with different durations. The detailed designs of the target trial emulation frameworks are presented and explained in Tables S1 and S2.

### 2.3 | Study population

The study population consisted of all patients who had their first HF diagnosis between 1 January 2000 and 25 September 2019. All HF diagnoses were ascertained using the list of read codes adapted from Conrad et al. (shown in Table S3).<sup>20</sup> Patients were excluded if they have ever had a prior history of cancer (except non-melanoma skin cancer), liver failure, human immunodeficiency virus (HIV)

infection, or had received a prescription for a statin medication within 180 days prior to the HF diagnosis. Lastly, any patients with less than one-year of up-to-standard registration history with the current GP practice were also excluded. All patient information, including statin use status, outcome and covariates, was updated at monthly intervals of the follow-up. In the first emulated trial, all eligible patients were included; in the second emulated trial, patients who initiated statin treatment within 12 months after the index HF diagnosis were included with patients who developed the new-onset cancer before statin initiation being excluded.

### 2.4 | Treatment strategy

In the first emulated trial, we compared the treatment strategies of initiating statin treatment within 1 year versus non-statin treatment after the HF diagnosis. The one-year grace period allowed the inclusion of more statin initiators over this period after time zero (i.e., date of the HF diagnosis) with the consideration of real-life delay in treatment initiation.<sup>5,16</sup> All patients in the two identical patient cohorts were followed from the index HF diagnosis until the first cancer diagnosis, death, transfer out of practice, end date of data collection from the GP practice, 10 years since the HF diagnosis, deviation from the assigned treatment strategy, or end of the study period, whichever occurred first.

In the second emulated trial, we compared the treatment strategies of initiating statins after the HF diagnosis and receiving it for different durations, that is,  $\leq 3$  years, 3–6 ( $>3$  and  $\leq 6$ ) years, and  $>6$  years. These cut-off points were chosen based on the data reported in the previous study<sup>16</sup> and the statistical power in our cohort. All patients in the different treatment strategy cohorts were followed from the date of statin initiation until the first cancer diagnosis, death, transfer out of the practice, end date of data collection from the GP practice, 10 years since the statin initiation, deviation from the assigned treatment strategy, or end of the study period, whichever occurred first.

### 2.5 | Study outcomes and covariates

The primary study outcome was an incident cancer diagnosis, which was identified as any first-ever cancer diagnosis except for non-melanoma skin cancer in the database, using read codes. Benign neoplasms or in situ tumours were not included. This approach has been demonstrated with high validity for identifying cancer cases.<sup>21</sup> The secondary study outcomes were site-specific cancers, including lung cancer, prostate cancer, female breast cancer, colorectal cancer, haematological cancer and gastric/oesophageal cancer.

The baseline covariates evaluated included: age, sex, smoking status (current smoker, ex-smoker, and non-smoker), BMI ( $\text{kg}/\text{m}^2$ ) in categories (underweight [ $<18.5$ ], normal weight [ $18.5$ – $24.9$ ], overweight [ $25$ – $29.9$ ], and obese [ $\geq 30$ ]), socioeconomic status measured as Townsend score quintiles, comorbidities including hypertension,

dyslipidaemia, coronary heart disease, cardiac arrhythmia, peripheral vascular disease, stroke, diabetes, inflammatory bowel disease, chronic obstructive pulmonary disease, rheumatoid arthritis, depression, and chronic kidney disease; recent use of medications including aspirin, non-steroidal anti-inflammatory drugs (excluding aspirin), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, anticoagulant agents, metformin, antidepressant agents, and proton-pump inhibitors. Time-varying covariates that were updated at monthly intervals included the same variables as the baseline measurements except for age, sex and Townsend score. The demographic information and comorbidities were defined as the most recent record within 3 years prior to the baseline, and drug use records were defined as any prescription within 180 days prior to the baseline. Figure S3 illustrates the study design for patient selection and covariate measurements.

## 2.6 | Target trial emulation and statistical analysis

We used a clone-censor-weight method to emulate two target trials.<sup>5,7,22,23</sup> Details of the application of this method are described in Methods in Data S1 and Figures S1–S2. In brief, in the first emulated trial comparing the effect of statin treatment versus no statin treatment, we replicated each eligible patient at baseline (the index HF diagnosis) to two same copies, and the two identical patient cohorts were assigned to the two treatment strategies, that is, 'statin treatment' or 'no statin treatment' (the cloning step). Patient clones were artificially censored if they deviated from the assigned treatment strategy, that is, a patient clone who was assigned to the 'statin treatment' strategy was censored at the end of the one-year grace period if they had not yet initiated the statin treatment; and a patient clone who was assigned to the 'no statin treatment' strategy was censored if they initiated the statin treatment anytime during the follow-up (the censoring step). We then estimated the inverse probability of censoring weight (IPCW) based on the patient's probability of being uncensored at that time interval using pooled logistic regression models,<sup>24</sup> conditional on time since baseline (in its linear and quadratic terms), baseline covariates, and time-varying covariates. The uncensored patient cohorts were reweighted with the IPCWs to account for potential selection bias introduced by the artificial censoring. The IPCWs were estimated separately for the statin treatment arm and no statin treatment arm to allow any different patterns of treatment deviation and interactions between the treatment and covariates.<sup>25</sup> To account for the competing risk of death, we estimated another IPCW based on the probability of being alive at each time interval. The final weight was calculated as the product term between IPCWs for treatment deviation and death. To avoid undue influence of outliers, weights were truncated at the 99.5th percentile (the weighting step). We then fitted another weighted pooled logistic regression model accounting for the IPCWs as the outcome model to estimate the effect of statin treatment on the risk of cancer. The outcome model included a treatment indicator, time since baseline (in its linear

and quadratic terms), and their product terms to calculate time-discrete hazards.<sup>8</sup> We estimated the 10-year absolute risk, risk differences and risk ratios. The 95% confidence intervals for the absolute risks were calculated using non-parametric bootstrapping with 200 full samples (2.5th and 97.5th percentile of the survival differences across the bootstrap samples). We also used the odds ratio from this pooled logistic regression model to approximate the hazard ratio given that the event rate of the outcome is rare during each follow-up interval.<sup>26</sup> Robust variance estimators were used to estimate the 95% confidence intervals (CIs) for the hazard ratio.

Similar procedures were conducted in the second emulated trial, in which the effects of different durations of statin treatment were estimated. At the baseline (redefined as the date of statin initiation), we replicated three data sets of patients who have initiated statin treatment within the 1-year grace period after HF into three same copies and assigned three identical patient cohorts into three durations of statin treatment. We considered statin prescriptions as continuous if without a 180-day gap, that is, statin discontinuation was defined as having a 180-day gap between two consecutive prescriptions or the last statin prescription that is at least 180-day before other causes of censoring. The exact date of discontinuation was defined as the theoretical last day of the statin prescription before the gap, and statin treatment duration was calculated from the date of initiation until discontinuation or other censoring events.<sup>27</sup> Patient clones were artificially censored if they deviated from the assigned treatment strategy, that is, a patient clone who was assigned to statin treatment for  $\leq 3$  years was censored start of year 3 if the patient used statin over 3 years; a patient clone who was assigned to statin treatment for 3–6 years was censored any time of discontinuation within 3 years if the patient did not use statin over 3 years or censored at the start of year 6 if the patient used statin over 6 years; and a patient clone who was assigned to statin treatment for  $> 6$  years was censored any time of discontinuation within 6 years if the patient did not use statin over 6 years. IPCWs were estimated from pooled logistic regression models based on the probability of patient replicates receiving treatment with the assigned treatment durations. Lastly, same as the first emulated trial, we estimated the IPCW for death and calculated the final weight, and the same outcome model was used.

All data were summarised as mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables and number of subjects (%) for categorical variables. Missing data were analyzed as a separate data class. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

## 2.7 | Sensitivity analysis

We conducted three sensitivity analyses to check the robustness of our results. First, we addressed the missing data by conducting a complete case analysis. Second, we addressed the missing data by conducting Multiple Imputation with Chained Equations to produce 20 imputed data sets. The multiple imputation models included all variables (statin use status, all baseline and time-varying covariates at

that month, GP practice, and outcome status). The inverse probability of weights and effect estimates were calculated in each imputed data set and combined using Rubin's rules to obtain the overall estimate and its 95% CIs. Third, we conducted the analysis with weights truncated at the 99.9th percentile, rather than the 99.5th percentile.

### 3 | RESULTS

#### 3.1 | First emulated trial: Statin treatment versus no statin treatment

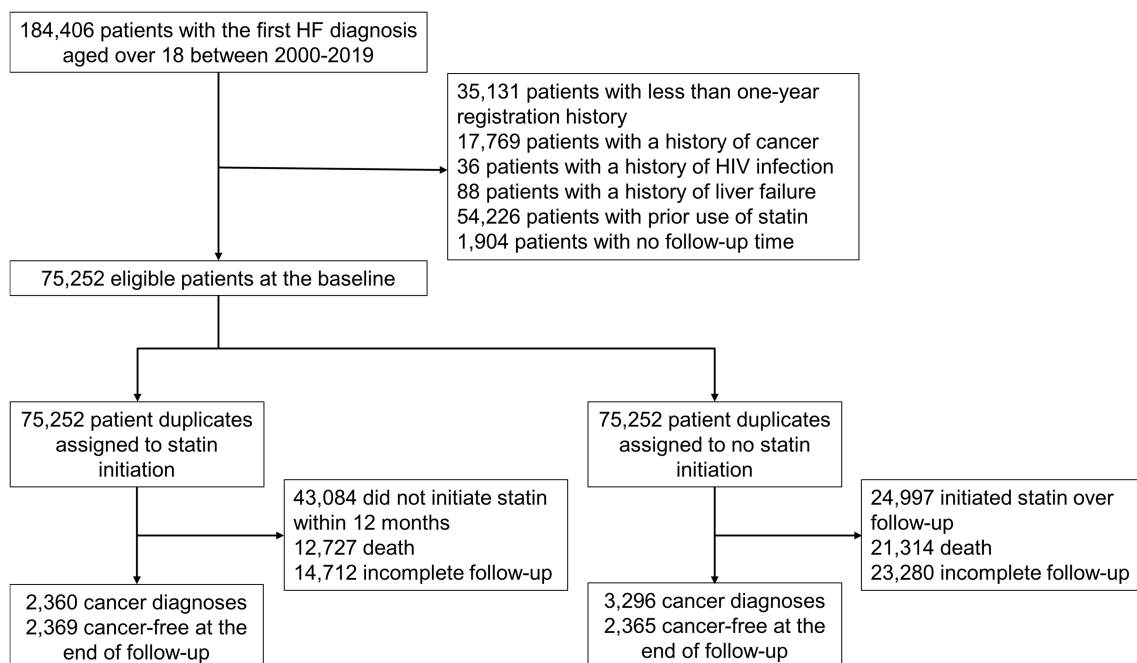
184 406 patients with newly diagnosed HF were identified from the database during the study period. Of these, 75 252 patients met the eligibility criteria and were included in the analysis of the first emulated trial. The eligible patients were duplicated and assigned to statin treatment and non-statin treatment strategy cohorts. The median follow-up time was 3.0 (IQR, 1.0 to 6.1) years. 15 545 (20.6%) patients initiated statin treatment, with 59 707 (79.4%) patients not prescribed statins over a one-year grace period following the HF diagnosis. Over the 10-year follow-up time, there were 2360 cases of cancer diagnosis in the statin treatment group and 3296 cases of cancer diagnosis under the non-statin treatment group. Other reasons for end-of-follow-up, including treatment deviation, death and administrative censoring, were described in Figure 1 and the patterns of censoring over the follow-up period were illustrated in Figure S5A. Full baseline characteristics of the patients before and after censoring due to treatment deviation over the one-year grace period and after weighting were shown in Table 1.

Table S4 shows the unweighted baseline characteristics of patients after the 1-year grace period. Patients who initiated statin during the grace period tended to be younger, more men, more smokers, had more dyslipidaemia and CHD, and used fewer anticoagulants and diuretics. After weighting, there was a good balance for all covariates at the end of the grace period between the two treatment groups. Distributions of the inverse probability weights are summarised in Table S5.

The weighted 10-year absolute risk for all cancer types was 17.3% (95% CI, 15.9% to 18.6%) under the statin treatment arm and 16.5% (95% CI, 15.4% to 17.5%) under the no statin treatment arm. The 10-year absolute risk difference was 0.8% (95% CI, -1.0% to 2.4%), and the risk ratio was 1.05 (95% CI, 0.94 to 1.15). The approximated hazard ratio was 0.99 (95% CI, 0.90 to 1.09), which was consistent with the risk ratio, (Table 2, Figure 2A) showing that statin treatment after HF was not associated with a lower risk of a cancer diagnosis than no statin treatment. When we stratified the cancer diagnoses by cancer sites, no significant risk difference was observed between statin and no statin arms in any site-specific cancer (Table S6). The absolute risk differences ranged from -0.5% (95% CI, -0.9% to 0.1%) for haematological cancer to 0.9% (95% CI, -0.2% to 1.8%) for lung cancer.

#### 3.2 | Second emulated trial: Statin treatment ≤3 year versus 3–6 years and >6 years

In the second emulated trial, we explored the potential dose-response relationship between statin treatment and the risk of cancer diagnosis.



**FIGURE 1** Selection of eligible patients for emulating a target trial of comparing statin treatment versus no statin treatment after HF on the risk of cancer.

**TABLE 1** Baseline characteristics of patients with HF in the study cohorts, for all patients at cohort entry and patients remained uncensored after the one-year grace period after weighting.<sup>a</sup>

	All patients (n = 75 252)	Statin—After 1 year (n = 67 130)	Non-statin—After 1 year (n = 69 369)	SMD
<b>Age (years) (SD)</b>	74.6 (14.1)	73.6 (25.7)	74.2 (18.5)	−0.03
<b>Sex, (% male)</b>	37 622 (50.0)	33 483 (49.9)	35 314 (50.9)	−0.02
<b>BMI, kg/m<sup>2</sup> (%)</b>				0.04
Underweight (<18.5)	1932 (2.6)	1545 (2.3)	1601 (2.3)	
Normal weight (18.5–24.9)	19 356 (25.7)	16 684 (24.9)	17 203 (24.8)	
Overweight (25–29.9)	20 952 (27.8)	19 297 (28.8)	19 727 (28.4)	
Obese (≥30)	17 005 (22.6)	16 467 (24.5)	16 304 (23.5)	
Missing	16 007 (21.3)	13 137 (19.6)	14 534 (21.0)	
<b>Smoking status (%)</b>				0.03
Current smoker	12 431 (16.5)	11 038 (16.4)	11 906 (17.2)	
Ex-smoker	20 684 (27.5)	18 429 (27.5)	19 144 (27.6)	
Non-smoker	34 399 (45.7)	31 079 (46.3)	31 072 (44.8)	
Missing	7738 (10.3)	6583 (9.8)	7246 (10.5)	
<b>Townsend score (%)</b>				0.02
1 (affluent)	13 261 (17.6)	11 607 (17.3)	12 050 (17.4)	
2	13 963 (18.6)	12 407 (18.5)	12 730 (18.4)	
3	13 813 (18.4)	12 038 (17.9)	12 756 (18.4)	
4	13 022 (17.3)	11 886 (17.7)	12 282 (17.7)	
5 (deprived)	9309 (12.4)	8381 (12.5)	8858 (12.8)	
Missing	11 884 (15.8)	10 810 (16.1)	10 693 (15.4)	
<b>Comorbidities (%)</b>				
Hypertension	37 219 (49.5)	34 496 (51.4)	35 051 (50.5)	0.02
Dyslipidaemia	15 447 (20.5)	15 024 (22.4)	14 527 (20.9)	0.03
CHD	18 082 (24.0)	15 842 (23.6)	18 358 (26.5)	−0.07
PVD	6157 (8.2)	6299 (9.4)	6021 (8.7)	0.02
Cardiac arrhythmia	17 777 (23.6)	18 175 (27.1)	16 390 (23.6)	0.08
Stroke	3286 (4.4)	3455 (5.2)	3540 (5.1)	0.00
Diabetes mellitus	7240 (9.6)	7803 (11.6)	7233 (10.4)	0.04
Depression	6353 (8.4)	5842 (8.7)	5890 (8.5)	0.01
CKD	4696 (6.2)	4711 (7.0)	4304 (6.2)	0.03
IBD	290 (0.4)	235 (0.4)	259 (0.4)	0.00
COPD	6831 (9.1)	5941 (8.9)	6419 (9.3)	−0.01
RA	851 (1.1)	691 (1.0)	834 (1.2)	−0.02
<b>Recent medications (%)</b>				
NSAIDs	10 253 (13.6)	9621 (14.3)	9973 (14.4)	0.00
Aspirin	21 554 (28.6)	22 410 (33.4)	20 914 (30.2)	0.07
ACEIs	25 607 (34.0)	25 298 (37.7)	24 242 (35.0)	0.06
ARBs	6200 (8.2)	6055 (9.0)	5839 (8.4)	0.02
Beta-blockers	19 304 (25.7)	19 450 (29.0)	17 831 (25.7)	0.07
CCBs	15 717 (20.9)	15 430 (23.0)	14 827 (21.4)	0.04
Diuretics	45 636 (60.6)	42 419 (63.2)	42 347 (61.1)	0.04
Anticoagulants	11 932 (15.9)	12 293 (18.3)	10 984 (15.8)	0.07
Metformin	3293 (4.4)	3762 (5.6)	3468 (5.0)	0.03
Antidepressants	11 712 (15.6)	10 582 (15.8)	10 609 (15.3)	0.01
PPIs	18 477 (24.6)	17 141 (25.5)	16 710 (24.1)	0.03



TABLE 1 (Continued)

	All patients (n = 75 252)	Statin—After 1 year (n = 67 130)	Non-statin—After 1 year (n = 69 369)	SMD
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Dyslipidaemia	15 447 (20.5)	15 024 (22.4)	14 527 (20.9)	0.03
CHD	18 082 (24.0)	15 842 (23.6)	18 358 (26.5)	−0.07
PVD	6157 (8.2)	6299 (9.4)	6021 (8.7)	0.02
Cardiac arrhythmia	17 777 (23.6)	18 175 (27.1)	16 390 (23.6)	0.08
Stroke	3286 (4.4)	3455 (5.2)	3540 (5.1)	0.00
Diabetes mellitus	7240 (9.6)	7803 (11.6)	7233 (10.4)	0.04
Depression	6353 (8.4)	5842 (8.7)	5890 (8.5)	0.01
CKD	4696 (6.2)	4711 (7.0)	4304 (6.2)	0.03
IBD	290 (0.4)	235 (0.4)	259 (0.4)	0.00
COPD	6831 (9.1)	5941 (8.9)	6419 (9.3)	−0.01
RA	851 (1.1)	691 (1.0)	834 (1.2)	−0.02
<b>Recent medications (%)</b>				
NSAIDs	10 253 (13.6)	9621 (14.3)	9973 (14.4)	0.00
Aspirin	21 554 (28.6)	22 410 (33.4)	20 914 (30.2)	0.07
ACEIs	25 607 (34.0)	25 298 (37.7)	24 242 (35.0)	0.06
ARBs	6200 (8.2)	6055 (9.0)	5839 (8.4)	0.02
Beta-blockers	19 304 (25.7)	19 450 (29.0)	17 831 (25.7)	0.07
CCBs	15 717 (20.9)	15 430 (23.0)	14 827 (21.4)	0.04
Diuretics	45 636 (60.6)	42 419 (63.2)	42 347 (61.1)	0.04
Anticoagulants	11 932 (15.9)	12 293 (18.3)	10 984 (15.8)	0.07
Metformin	3293 (4.4)	3762 (5.6)	3468 (5.0)	0.03
Antidepressants	11 712 (15.6)	10 582 (15.8)	10 609 (15.3)	0.01
PPIs	18 477 (24.6)	17 141 (25.5)	16 710 (24.1)	0.03



Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PVD, peripheral vascular disease; RA, rheumatoid arthritis; SD, standard deviation; SMD, standardised mean difference.

<sup>a</sup>The first column shows the baseline characteristics of all patients included in the cohort at the cohort entry, the second and third columns show the baseline characteristics of the patients under statin and no statin arms after the one-year grace period who remained uncensored, after weighted by the IPCWs.

**TABLE 2** Estimated treatment effect of statin treatment versus non-statin treatment on the risk of cancer in patients with HF.

	Treatment strategies	
	Non-statin (n = 75 252)	Statin (n = 75 252)
<b>Total cancer</b>		
Number of cases, n (%)	3296 (4.4%)	2360 (3.1%)
Follow-up time, patient-years	179 131	125 802
10-year absolute risk, % (95% CI)	16.5 (15.4 to 17.5)	17.3 (15.9 to 18.6)
10-year risk difference, % (95% CI)	Reference	0.8 (−1.0 to 2.4)
10-year risk ratio (95% CI)	Reference	1.05 (0.94 to 1.15)
Hazard ratio (95% CI)	Reference	0.99 (0.90 to 1.09)

Abbreviation: CI, confidence interval.

15545 patients who initiated statin in the first emulated trial were selected and included in this analysis. These statin initiators were replicated into three copies of the cohort. The three replicated copies were assigned to statin treatment of  $\leq 3$  years, 3–6 years, and over 6 years (Figure S4). The patterns of censoring over the follow-up period were illustrated in Figure S5B.

The weighted 10-year absolute risk for total cancer was 16.9% (95% CI, 13.0% to 20.0%) under statin treatment of  $\leq 3$  years, 15.9% (95% CI, 12.2% to 20.3%) under statin treatment of 3–6 years, and 16.4% (95% CI, 15.1% to 18.1%) under statin treatment of  $> 6$  years. Using statin treatment of  $\leq 3$  years as the reference group, the 10-year absolute risk difference was  $-1.0\%$  (95% CI,  $-5.7\%$  to  $5.0\%$ ) for statin treatment of 3–6 years and  $-0.4\%$  (95% CI,  $-3.9\%$  to  $3.6\%$ ) for statin treatment  $> 6$  years. Estimates in risk ratios and hazard ratios showed consistent results with the risk differences (Table 3, Figure 2B). Statin treatment after HF with a longer duration was therefore not associated with a lower risk of a cancer diagnosis. When we stratified the cancer diagnoses by cancer sites, the absolute risk differences ranged from  $-2.4\%$  (95% CI,  $-7.3\%$  to  $4.1\%$ ) for female breast cancer to  $1.1\%$  (95% CI,  $-0.5\%$  to  $2.7\%$ ) for prostate cancer. No significant risk difference or trend indicating a cumulative exposure-response relationship for statin treatment was observed in any site-specific cancer (Table S7).

### 3.3 | Sensitivity analysis

Results from the sensitivity analyses are summarised in Figure S6. Analyses with complete cases only, multiple imputation, and weights untruncated at 99.9th percentile showed consistent results to the main analysis for both emulated trials. The hazard ratios ranged from 0.98 (95% CI, 0.88 to 1.09) to 1.00 (95% CI, 0.89 to 1.12) in the first emulated trial; and the hazard ratios ranged from 1.08 (95% CI, 0.86–1.34) to 0.96 (95% CI, 0.75 to 1.22) in the second emulated trial.

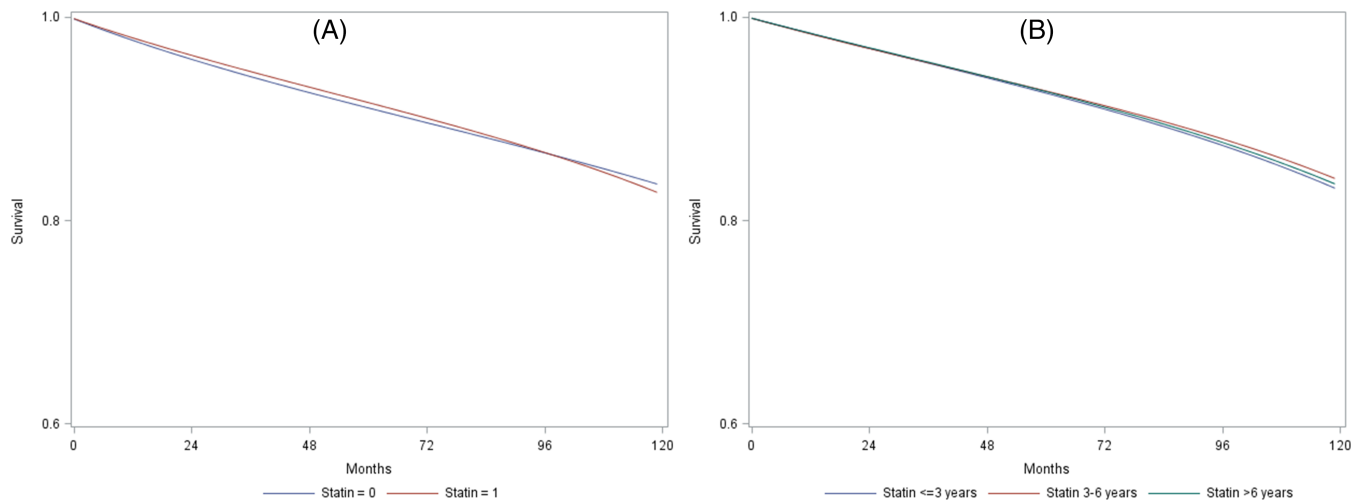
## 4 | DISCUSSION

In this study, we applied a target trial emulation framework and evaluated the effect of statin treatment on the risk of developing a new cancer diagnosis in patients with HF. We found that statin treatment after HF diagnosis was not associated with a lower risk of cancer diagnosis, regardless of the treatment duration. We found no association between statin treatment and the risk of site-specific cancers.

### 4.1 | Comparison with previous studies

Although the statin-associated cancer risk has been continuously investigated over decades, there is a paucity of data on the population with HF. Our finding of the null association between statin and risk of cancer diagnosis is discordant with the recent study by Ren et al. which suggested a protective effect of statin treatment on cancer incidence in patients with HF,<sup>16</sup> but is consistent with a previous target trial emulation study by Dickerman et al.<sup>8</sup> and a systematic review of randomised controlled trials<sup>4</sup> on statins and cancer risk in a general population mostly without HF.

There are a number of noticeable differences between these studies. Compared to Dickerman et al., our study and Ren et al. attempt to address a different question. We focused on testing the specific interaction between statin and HF on cancer development, based on the recent evidence that HF might be an independent risk factor for cancer.<sup>12,28,29</sup> Moreover, although both our study and Dickerman et al. are emulating target trials, different designs for trial emulation are used, that is, clone-censor-weight versus sequential trial emulation. A unique strength of the clone-censor-weight approach used in our study is in evaluating the effect of treatment duration (our second emulated trial).<sup>30</sup> This analysis further strengthened the causal interpretation of statin on cancer risk in HF from our data.<sup>17</sup>



**FIGURE 2** Weighted cancer-free survival curves comparing A, statin treatment versus no statin treatment in patients with HF; B, statin treatment of different durations in patients with HF.

**TABLE 3** Estimated treatment effect of statins among the different durations on the risk of cancer in patients with HF.

	Treatment strategies		
	Statin duration ≤3 years (n = 15 545)	Statin duration 3–6 years (n = 15 545)	Statin duration >6 years (n = 15 545)
<b>Total cancer</b>			
Number of cases, n (%)	656 (4.2%)	742 (4.7%)	943 (6.1%)
Follow-up time, patient-years	42 655	51 509	61 333
10-year absolute risk, % (95% CI)	16.9 (13.0 to 20.0)	15.9 (12.2 to 20.3)	16.4 (15.1 to 18.1)
10-year risk difference, % (95% CI)	Reference	−1.0 (−5.7 to 5.0)	−0.4 (−3.9 to 3.6)
10-year risk ratio (95% CI)	Reference	0.94 (0.70 to 1.33)	0.97 (0.79 to 1.26)
Hazard ratio (95% CI)	Reference	0.95 (0.78 to 1.16)	0.98 (0.83 to 1.15)

Abbreviation: CI, confidence interval.

Compared to Ren et al., the discrepancies in results may be explained by the following reasons. First, the previous study by Ren et al. defined statin users as patients who used at least 90 days of statin at least 1 year before the start of follow-up.<sup>16</sup> This approach artificially selected prevalent users and adherers to statin treatment and might thereby introduce selection bias (so called the prevalent user bias and healthy user bias),<sup>5,6,8</sup> partially leading to the inverse association between statin and cancer outcomes.<sup>7</sup> In contrast, observational studies applying the target trial emulation framework like ours and Dickerman et al.<sup>8</sup> ensured all patients were followed up from treatment assignment and eligibility assessment (analysed like in trial settings) thus could minimise the bias.<sup>5,31</sup> Second, certain key confounders associating statin use and cancer, such as smoking and BMI, were not directly controlled for in Ren et al. The authors attempted to adjust for these variables by using proxies such as the diagnoses of chronic pulmonary disease and obesity<sup>16</sup> but this might not fully control the confounding via these pathways. Thirdly, the studies were conducted in different settings with different data sources. Ren et al. were

nested within an almost homogenous Asian population in Hong Kong hospital settings, while the current study and Dickerman et al. were based on a sample of the population from the United Kingdom primary care. As differences in response to statin treatment between Asian and Western populations have been reported,<sup>32,33</sup> it is also possible that statin may have differential effects on cancer outcomes between various ethnic groups. Differences in the healthcare systems may also lead to variations in recordings of clinical events.

## 4.2 | Clinical implications and future directions

Together with the previous evidence, the current study does not support a causal effect of statin on cancer prevention in patients with HF. Clinicians should continue to prescribe statins for primary and secondary prevention of coronary heart disease and cerebrovascular disease in patients with HF, but not to reduce the risk of cancer in these patients based on current evidence. Similarly, in older patients

with chronic multimorbidity when discontinuation of statin treatment is considered appropriate,<sup>34</sup> the belief in cancer prevention with statin should not contribute to the hesitancy against statin deprescribing. Furthermore, our current data do not support conducting a large, randomised trial on statins for cancer prevention or treatment in patients with HF. If any trials are planned at all, they should be guided by further research considering specific cancer types in specific patient populations or ethnicities. Lastly, the real-world effects of statin treatment have been widely studied in observational studies, but many challenges underlying this topic have been overlooked. For example, the lack of an active comparator for statin increases the susceptibility of observational studies to immortal time bias and confounding bias.<sup>35</sup> Any relevant future research needs to be designed carefully concerning these challenges. The target trial emulation framework proposed by Hernan et al.<sup>5</sup> could be a potential solution to some of these problems in making causal inferences on statin treatment using observational data and should be considered when appropriate.

### 4.3 | Strengths and limitations

This study is strengthened by applying the target trial emulation framework with a clone-censor-weight approach—a method for investigating the causal effect of treatment and the duration of treatment using observational data.<sup>30</sup> We believe the clone-censor-weight approach is appropriate to answer our questions because in both emulated trials the treatment strategies are indistinctive at the baseline, using clone-censor-weight can effectively avoid any time-related bias that may be common in other study designs.<sup>30,36</sup> We emulated two pragmatic trials and consistently showed that neither statin treatment nor statin treatment with longer duration was associated with a lower risk of cancer in patients with HF. The current study also benefited from the availability of some essential confounder records for statin treatment and cancer outcomes reported by the GPs, such as BMI and smoking status. Lastly, we have conducted comprehensive analyses and provided the effect estimates in relative and absolute risk differences at each follow-up interval to facilitate clear interpretations of the results.

This study has limitations. First, despite the use of sophisticated epidemiological designs and statistical methods, we cannot rule out residual bias in the study, that is, the study was emulating trials, and selection bias due to informative censoring was adjusted by an inverse probability weighting based on measured confounders. Some potential confounders were not recorded or directly controlled for in this study, such as diet, ethnicity, inflammation biomarkers or physical activities. Alcohol consumption may also be a risk factor for certain types of cancer but the quality of the record in our database is insufficient for a meaningful analysis.<sup>37</sup> However, our results are consistent across two emulated trials with different settings, suggesting these unmeasured confounders are less likely to affect our conclusion. Second, the statin treatment is not directly indicated for HF but for the underlying aetiologies and risk factors associated with HF.<sup>38</sup> Nevertheless, factors influencing statin

prescriptions were well-controlled in our study, including CHD and dyslipidaemia. We also do not have data on ejection fraction to differentiate the aetiologies of HF. However, the ejection fraction in HF is not directly related to statin initiation<sup>39,40</sup> or cancer development.<sup>12,28,29</sup> Although patients with HF with reduced ejection fraction may receive different treatments and have different comorbidities that may affect the cancer risk than patients with preserved ejection fraction, most of these variables have been measured and controlled in our models. Third, we could not obtain data on cancer stage, molecular subtypes or cancer-specific mortality from our data source, which limited us from conducting more detailed analyses on this topic. Lastly, although we explored the association between statin treatment and certain site-specific cancers, the power of some of our analyses was low and limited us to conduct further analysis on uncommon cancer entities, especially in the second emulated trial. Results from these analyses need to be interpreted with caution.

### 4.4 | Conclusions

In summary, by emulating two target pragmatic trials using UK primary care data, we found statin treatment was not associated with a lower risk of new cancer diagnosis in patients with HF. Our study does not support the use of statin for reducing cancer risks in patients with HF.

#### AUTHOR CONTRIBUTIONS

CJ, WL and LW conceived the idea for the study. CJ, WL and LW designed the study. CJ did the data analysis and drafted the first version of the article under WL and LW's supervision. LW obtained data access. All authors were responsible for drafting the article or revising it critically for important intellectual content and approved the final version. LW is the guarantor.

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#### CONFLICT OF INTEREST STATEMENT

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#### DATA AVAILABILITY STATEMENT

No additional data are available.

#### ETHICS STATEMENT

The study protocol was approved by the THIN Scientific Review Committee (ref: 22SRC026). IMRD-UK is an anonymized electronic

healthcare record database and hence further ethics approval is not required.

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#### SUPPORTING INFORMATION

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

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