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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Statin associated lower cancer risk and related mortality in patients with heart failure

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Aims Patients with heart failure (HF) have an increased risk of incident cancer. Data relating to the association of statin use with cancer risk and cancer-related mortality among patients with HF are sparse.

Methods and results Using a previously validated territory-wide clinical information registry, statin use was ascertained among all eligible patients with HF ($n = 87\,102$) from 2003 to 2015. Inverse probability of treatment weighting was used to balance baseline covariates between statin nonusers ($n = 50\,926$) with statin users ($n = 36\,176$). Competing risk regression with Cox proportional-hazard models was performed to estimate the risk of cancer and cancer-related mortality associated with statin use. Of all eligible subjects, the mean age was 76.5 ± 12.8 years, and 47.8% was male. Over a median follow-up of 4.1 years (interquartile range: 1.6–6.8), 11 052 (12.7%) were diagnosed with cancer. Statin use (vs. none) was associated with a 16% lower risk of cancer incidence [multivariable adjusted subdistribution hazard ratio (SHR) = 0.84; 95% confidence interval (CI), 0.80–0.89]. This inverse association with risk of cancer was duration dependent; as compared with short-term statin use (3 months to <2 years), the adjusted SHR was 0.99 (95% CI, 0.87–1.13) for 2 to <4 years of use, 0.82 (95% CI, 0.70–0.97) for 4 to <6 years of use, and 0.78 (95% CI, 0.65–0.93) for ≥6 years of use. Ten-year cancer-related mortality was 3.8% among statin users and 5.2% among nonusers (absolute risk difference, -1.4 percentage points [95% CI, -1.6% to -1.2%]; adjusted SHR = 0.74; 95% CI, 0.67–0.81).

Conclusion Our study suggests that statin use is associated with a significantly lower risk of incident cancer and cancer-related mortality in HF, an association that appears to be duration dependent.

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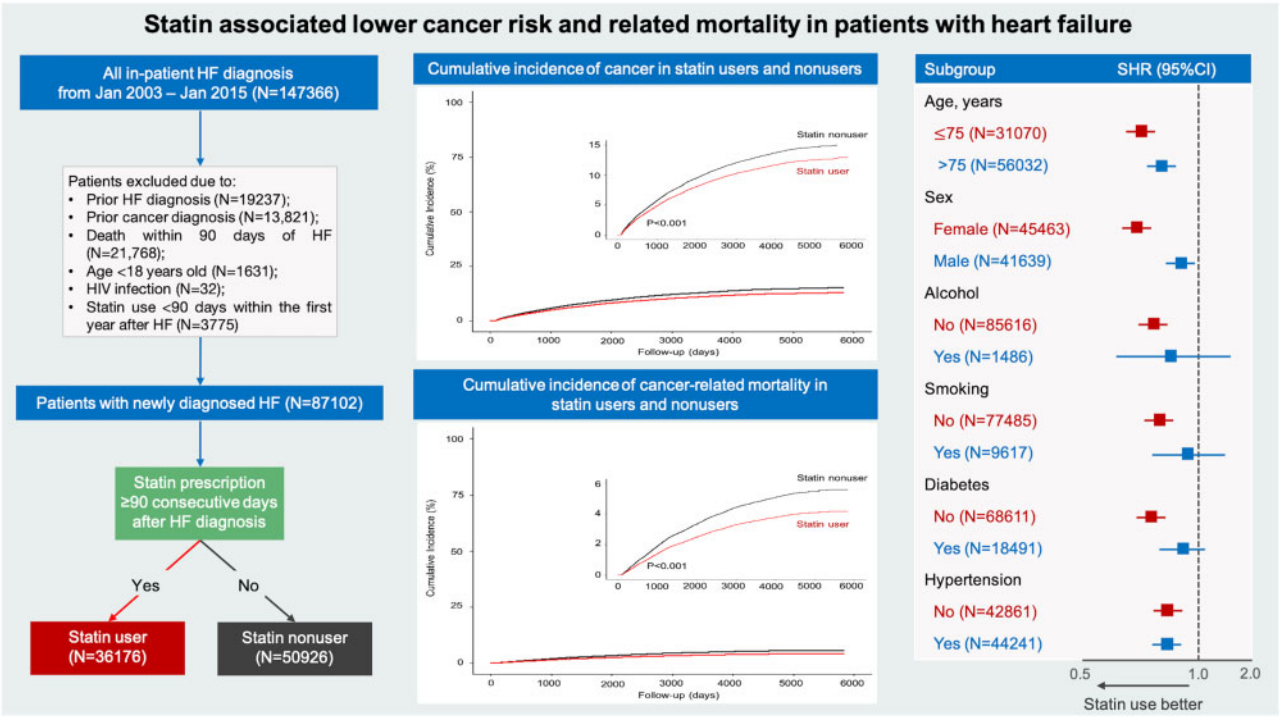
Graphical Abstract



Statin use is associated with a significantly lower risk of incident cancer and cancer-related mortality in patients with heart failure and results were consistent across clinical subgroups and in sensitivity analyses. The potential protective effect of statin on development of cancer merits evaluation in future randomized studies.

Keywords Heart failure • Cancer • Cardio-oncology • Statin • Prevention

Introduction

Heart failure (HF) and cancer are two major public health challenges worldwide.[1,2] The ageing demographics, along with increasing prevalence of antecedents, e.g. hypertension, diabetes, coronary artery disease, obesity, and atrial fibrillation,[3] are driving the epidemic of HF globally. The improvement of HF management has further extended the longevity and increased the clinical relevance of non-cardiac morbidity and mortality in patients with HF. Recent epidemiological studies have demonstrated that cancer is the leading cause of non-cardiac death in patients with HF.[4–6] Besides shared risk factors, such as diabetes mellitus, smoking, and dyslipidemia, it has been hypothesized that HF is an oncogenic condition, possibly related to links between neurohormonal activation to tumorigenesis, systemic pathological processes such as inflammation and oxidative stress, common genetic predisposition, and clonal hematopoiesis of cancer and HF.[7,8] Preventive strategies to reduce the burden of cancer in HF patients is hence urgently needed.

Both experimental[9] and clinical data[10–12] suggest that statin may be chemoprotective through diverse potential mechanisms including inhibition of mevalonate pathway [a critical pathway (with its metabolites) integral for tumour development and growth],[13] anti-inflammatory, antioxidant, and immune-modulatory properties. To date, there is a paucity of studies evaluating the association of statin use with cancer risk and cancer-related mortality in patients with HF. Accordingly, in this territory-wide cohort study, we aim to examine the relationship between the use of statin and the risk of cancer and cancer-related mortality among patients with HF.

Methods

This is a retrospective cohort study conducted with data from the Clinical Data Analysis Reporting System (CDARS), a territory-wide database developed by the Hong Kong Hospital Authority. As the statutory body and the singular provider of public healthcare services in Hong Kong, the Hospital Authority provides over 80% of inpatient services in Hong Kong, a territory with a population of 7.5 million.[14] CDARS prospectively collects patient information including, but not limited to, demographic data, diagnoses, drug prescriptions, procedures, laboratory tests, and episodes of hospital visits since 1993.[15] Prior studies have demonstrated a high percentage of coding accuracy in CDARS data.[15–18] Diagnostic data, specifically, were determined by using the International Classification of Diseases, Ninth Revision (ICD-9), also shown to have a high coding accuracy.[19,20]

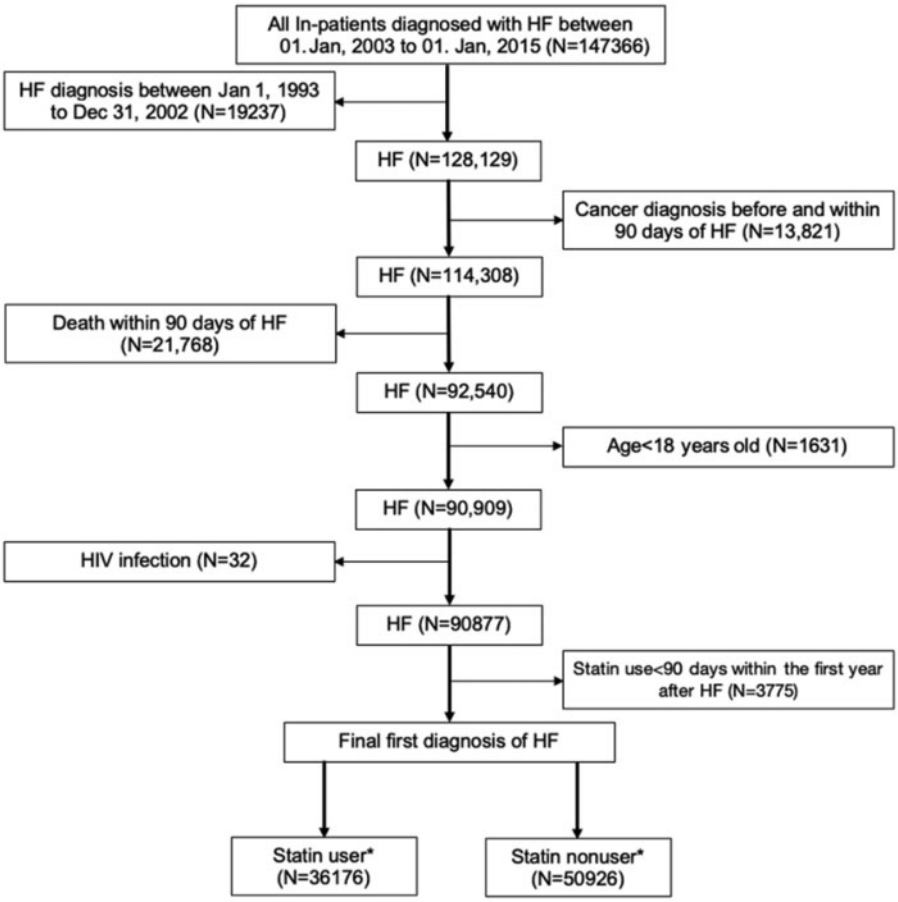


Figure 1 Flow chart of the study cohort. HF, heart failure; HIV, human immunodeficiency virus. *Statin user was defined by filled prescription for at least 90 consecutive days use of statin after the index date; statin nonuser was defined as never use of statin or <90 consecutive days of statin use after the index date.

Patient data (name and Hong Kong identification number) were de-identified in CDARS and unique reference numbers were generated. The study was approved by the institutional review board of the University of Hong Kong and the West Cluster of the Hong Kong Hospital Authority.

Outcome definition and study subjects

We searched for all patients aged 18 years old or above with HF (ICD-9: 402, 404, 425, 428) as a primary cause of hospitalization between 1 January 2003 and 1 January 2015. We subsequently identified all episodes of statin dispenses among the cohort, and the index date was defined as the date of first diagnosis of HF. We also excluded patients who were diagnosed with HF between 1 January 1993 to 31 December 2002 ($n = 19\,237$) to ensure the recruited patients had no prior history of HF. Furthermore, patients who had any history of cancer or cancer incidence within 90 days after the first diagnosis of HF, death within 90 days after the first diagnosis of HF, human immunodeficiency disease (HIV), and <90 days statin use within the first year of HF diagnosis were excluded (*Figure 1*). The primary outcome of the study was that of incident cancer subsequent to the diagnosis of HF, for which the association with statin use was determined. Patients were followed up until a diagnosis of cancer, death, or 31 December 2018, whichever came earlier.

Exposure definition

We used an intention-to-treat design in the study, where statin exposure was defined as ≥90 days consecutive use of statin beginning within the first year after the index date, as defined in previous publications.[17,21] In further analysis, we modelled statin use as a time-varying exposure to assess duration response. To evaluate duration, we summed the duration of all filled prescriptions (in days) and updated these data at each yearly interval of follow-up. Patients who received statin for a period of <90 consecutive days within the first year of HF diagnosis were excluded ($n = 3775$). The types of statins that were available in the public sector during the study period include simvastatin, atorvastatin, and rosuvastatin. Accordingly, we identified 36 176 statin users and 50 926 statin nonusers after the index date.

Statin users

As different indications for statins could potentially define different subpopulations of patients with HF, the presence of an indication for statin use was classified into: *atherosclerotic disease* ($n = 21\,894$, 60.5%) defined based on ICD coding (coronary artery disease, ICD-9: 410–414/peripheral vascular disease, ICD-9: 440–444, 447/stroke, ICD-9: 430–438); *hypercholesterolaemia* ($n = 8326$, 23.0%) based on ICD coding

Table 1 Baseline characters before and after inverse propensity of treatment weighting

Characteristic[a]	All (n = 87 102)	Statin user[b] (n = 36 176)	Statin nonuser[b] (n = 50 926)	SMD before IPTW	SMD after IPTW
Age at index date (years)	76.5 ± 12.8	73.7 ± 12.0	78.5 ± 13.0	0.412	0.025
Male sex	41 639 (47.8)	18 650 (51.6)	22 989 (45.1)	0.121	0.013
Alcohol	1486 (1.7)	512 (1.4)	974 (1.9)	0.034	0.006
Smoke	9617 (11.0)	2576 (7.1)	7041 (13.8)	0.224	0.004
Diabetes	18 491 (21.2)	9375 (25.9)	9116 (17.9)	0.165	0.019
Obesity	845 (1.0)	511 (1.4)	334 (0.7)	0.076	0.001
Hypertension	44 241 (50.8)	20 123 (55.6)	24 118 (47.4)	0.147	0.011
Arrhythmia	26 883 (30.9)	10 030 (27.7)	16 853 (33.1)	0.110	0.013
Coronary artery disease	30 195 (34.7)	18 332 (50.7)	11 863 (23.3)	0.533	0.039
Peripheral vascular disease	16 475 (18.9)	7181 (19.9)	9294 (18.3)	0.009	0.007
Stroke	8553 (9.8)	3885 (10.7)	4668 (9.2)	0.030	0.006
Parkinson	1180 (1.4)	287 (0.8)	893 (1.8)	0.092	0.009
Dyslipidemia	10 975 (12.6)	8326 (23.0)	2649 (5.2)	0.481	0.064
Chronic renal failure	9226 (10.6)	4054 (11.2)	5172 (10.2)	0.006	0.003
Ankylosing spondylitis	8262 (9.5)	3084 (8.5)	5178 (10.2)	0.062	0.001
Rheumatoid arthritis	451 (0.5)	155 (0.4)	296 (0.6)	0.021	<0.001
Drug use					
Aspirin	29 970 (34.4)	15 677 (43.3)	14 293 (28.1)	0.284	0.023
ACE inhibitors	25 803 (26.9)	12 868 (35.6)	12 935 (25.4)	0.209	0.014
Angiotensin receptor blockers	4452 (5.1)	2803 (7.7)	1649 (3.2)	0.189	0.010
Beta-blockers	27 245 (31.3)	14 508 (40.1)	12 737 (25.0)	0.313	0.016
Calcium channel blockers	36 362 (41.7)	17 250 (47.7)	19 112 (37.5)	0.188	0.008
Statin	18 131 (20.8)	15 608 (43.1)	2523 (5.0)	0.902	0.083
Metformin	13 039 (15.0)	8021 (22.2)	5018 (9.9)	0.329	0.021

Values are given as median ± standard deviation, or n (%).
ACE, angiotensin-converting enzyme; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference.
[a]Clinical characteristics of the patients were defined according to validated diagnoses in the International Classification of Diseases coding system (Supplementary material online, *Table S1*).
[b]Statin user was defined by filled prescription for at least 90 consecutive days of statin after the index date; statin nonuser was defined as never use of statin or <90 consecutive days of statin use after the index date.

(dyslipidemia, ICD-9: 272, 272.1, 272.2, 272.3, 272.4) and LDL >2.6 mmol/L;[22] and *undefined* (n = 5956, 16.5%), where the exact indication was uncertain due to the lack of corresponding ICD coding or valid lipid baseline profile. We further evaluated the lipid control of statin users by calculating the time-weighted mean of LDL level (defined by time-weighted mean of LDL level from 3 months following initiation of statin until endpoint).[23] Among all statin users, 31 454 (86.9%) patients had post-statin LDL level available and were subsequently categorized according to the time-weighted mean of LDL <1.8 mmol/L (n = 9879, 31.4%), LDL 1.8–2.6 mmol/L (n = 15 319, 48.7%), and LDL >2.6 mmol/L (n = 6256, 19.9%).

Study covariates

We traced patient records to 3 years prior to the index date and collected data including age at index date, sex, comorbidities (diabetes, obesity, hypertension, dyslipidemia, arrhythmias, coronary heart disease, vascular diseases, stroke, cirrhosis, chronic renal failure, Parkinson disease, ankylosing spondylitis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus), and drug history (baseline use of aspirin, antihypertensives, anti-diabetics, beta-blockers, statin) as well as lifestyle factors (alcoholism and smoking).[22] Baseline drug use was defined as ≥90 days of consistent use before the index date. Details of ICD-9 codes used are in Supplementary material online, *Table S1*.

Statistical analysis

To address biases in the allocation of treatment due to lack of randomization, a propensity score approach was used. Covariates that were considered prognostically significant as well as those that influenced treatment selection were logistically regressed to the probability of receiving treatment.[24] An inverse propensity of treatment weighting (IPTW) was used, allowing a pseudo-population to be created through assigning individuals with weights that corresponded to the inverse of their probability of receiving treatment given observed covariates. The differences in the prevalence of covariates between statin users and nonusers were considered insignificant if the standardized mean difference was ≤0.10. Cox proportional-hazards modelling was used, and statin exposure was further entered as a time-dependent variable to determine the effect of statin use, including covariates used in calculating the propensity score in 'doubly robust estimation'.[25] A Fine and Gray model was used to adjust for competing risks, with the competing events being all-cause mortality and non-cancer-related death.[24] Associations were considered significant if the P-value was <0.05.

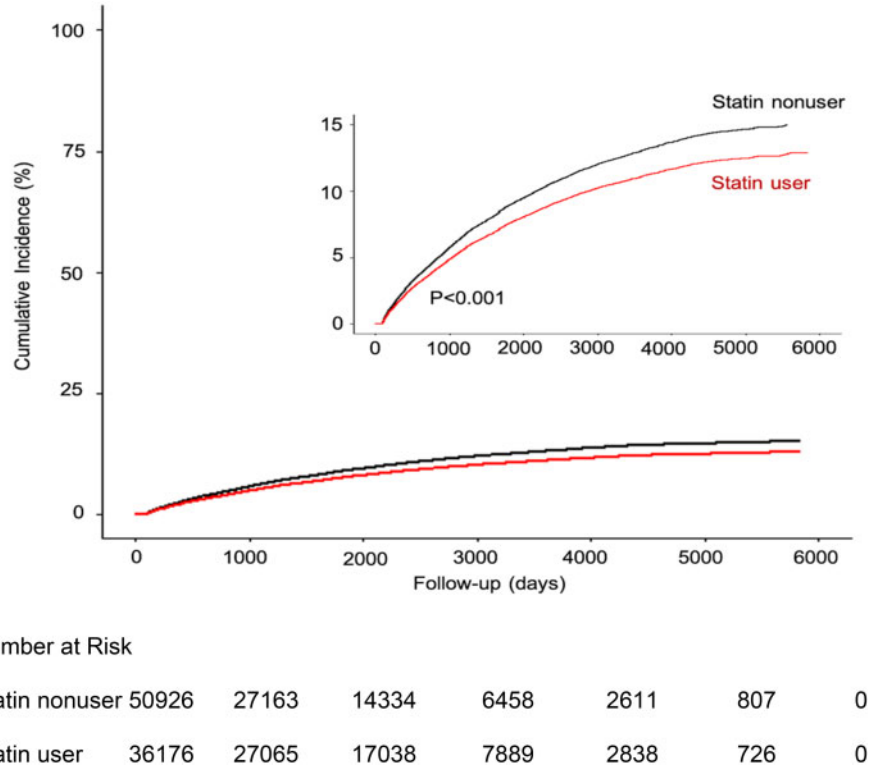


Figure 2 Cumulative incidence of cancer between statin user and nonuser. Statin user was defined by filled prescription for at least 90 consecutive days of statin use after the index date (the date on which a patient was diagnosed as incident heart failure). Statin nonuser was defined as never use of statin or <90 consecutive days of statin use after the index date. We calculated the *P*-value using Gray's test for equality of the cumulative functions between each exposure group after inverse probability of treatment weighting, accounting for competing risks of all-cause mortality. The inset shows the same data on an expanded *y*-axis.

Table 2 Effect of statin use on the risk of incident cancer and cancer-related death[a]

Event and treatment group	Number with event/total number	10-Year cumulative incidence %	SHR (95% CI)	
			Unadjusted	Adjusted[b]
Incident cancer				
Statin nonuser	6422/50 926	13.2%	1.00 (Ref.)	1.00 (Ref.)
Statin user	4630/36 176	11.2%	0.84 (0.78 to 0.87)	0.84 (0.80 to 0.89)
Absolute risk difference (95% CI)		-2.0% (-2.3% to -1.7%)		
Cancer-related death				
Statin nonuser	2474/50 926	5.2%	1.00 (Ref.)	1.00 (Ref.)
Statin user	1390/36 176	3.8%	0.64 (0.56 to 0.72)	0.74 (0.67 to 0.81)
Absolute risk difference (95% CI)		-1.4% (-1.6% to -1.2%)		

CI, confidential interval; SHR, subdistribution hazard ratio.

[a]Statin user was defined by filled prescription for at least 90 consecutive days of statin use after the index date. Ten-year cumulative incidence, absolute risk difference, and hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted cohort that accounted for competing risks; the model was conditioned on age at index date.

[b]A multivariable adjusted model further accounted for the following prognostic covariates: age at index date, sex, presence or absence of alcohol, smoking, comorbidities, including diabetes, obesity, hypertension, arrhythmia, coronary artery disease, peripheral vascular disease, stroke, Parkinson disease, dyslipidemia, chronic renal failure, cirrhosis, ankylosing spondylitis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and baseline use of aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, statin, and metformin.

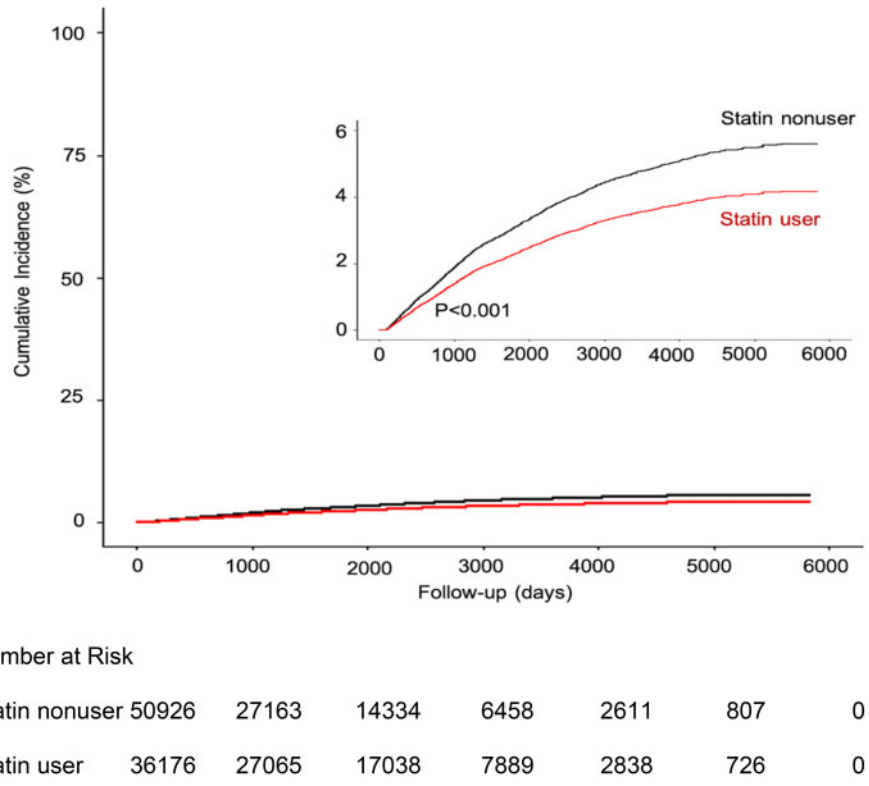


Figure 3 Cancer-related mortality between statin user and nonuser. Statin user was defined by filled prescription for at least 90 consecutive days of statin use after the index date (the date on which a patient was diagnosed as incident heart failure). Statin nonuser was defined as never use of statin or <90 consecutive days of statin use after the index date. We calculated the *P*-value using Gray's test for equality of the cumulative functions between each exposure group after inverse probability of treatment weighting, accounting for competing risks of non-cancer-related mortality. The inset shows the same data on an expanded *y*-axis.

We further performed conventional Cox regression without competing risks or without considering propensity score for comparison to previous cohort studies;[13,26,27] as well as subgroup analyses by age, sex, alcohol, smoke, comorbidities (diabetes and hypertension), and baseline drug use (aspirin, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, metformin) after accounting for competing risk. Several sensitivity analyses were conducted including: (i) models excluding persons with a history of alcohol abuse ($n = 1486$) or smoking ($n = 9617$); (ii) using an alternative 1:1 propensity score matched design; (iii) analyses excluding patients with any history of statin use ($n = 18\,131$); (iv) analyses excluding patients with a diagnosis of incident cancer or death within 3 years after the index date ($n = 46\,701$), to minimize reverse causation;[24] and (v) analyses of the relationship between statin use and incident gastrointestinal bleeding (excluding those with a prior history of gastrointestinal bleeding and simultaneous digestive cancer), as a falsification endpoint. All statistical analyses were performed using R v4.0.2.[28–31]

Results

Patient characteristics

We identified 87 102 patients who developed incident HF between 2003 and 2015, 56 045 (64%) were 75 years or older, 41 639 (48%) were men, more than half had hypertension ($n = 44\,241$, 51%) and nearly one-third had coronary artery disease ($n = 30\,195$, 35%). There were a total of 50 926 statin nonusers and 36 176 statin users (*Figure 1*). The baseline characteristics of the entire cohort are shown in *Table 1*. Upon adjustment by IPTW, patient characteristics were well balanced (*Table 1* and Supplementary material online, *Table S2*). During a median follow-up of 4.1 years [interquartile range (IQR): 1.6–6.8], with a total of 404 924 person-years, 11 052 (12.7%) patients were newly diagnosed with cancer. Cancer-related mortality occurred in 3864 (4.4%) patients (Supplementary material online, *Table S3*). The commonest type of cancer and cancer-related mortality was colorectal, stomach, lung, and liver/biliary system (Supplementary material online, *Table S4*).

Cancer

The median age at diagnosis of cancer was 79.7 years (IQR: 74.3–87.1 years) and the median time-to-diagnosis of cancer beginning from index date of HF was 3.8 years (IQR: 1.3–5.6 years). Propensity-matched statin users had a lower risk of developing cancer; the 5-year cumulative incidence of cancer was 7.9% among statin users and 10.4% among nonusers and the 10-year cumulative incidence of cancer was 11.2% among statin users and 13.2% among nonusers (*Figure 2*). Statin users had a 16% lower risk of cancer than nonusers

Table 3 Effect of duration of statin use on the risk of incident cancer and cancer-related death among statin users[a]

Event and duration of statin use	10-Year cumulative incidence	SHR (95% CI)	
	%	Unadjusted	Adjusted[b]
Incident cancer			
3 months to <2 years	11.8%	1.00 (Ref.)	1.00 (Ref.)
2 to <4 years	11.7%	0.98 (0.86 to 1.12)	0.99 (0.87 to 1.13)
4 to <6 years	7.6%	0.80 (0.68 to 0.95)	0.82 (0.70 to 0.97)
≥6 years	5.4%	0.74 (0.62 to 0.88)	0.78 (0.65 to 0.93)
Cancer-related death			
3 months to <2 years	4.5%	1.00 (Ref.)	1.00 (Ref.)
2 to <4 years	4.1%	0.93 (0.79 to 1.10)	0.94 (0.80 to 1.12)
4 to <6 years	2.4%	0.64 (0.51 to 0.81)	0.67 (0.53 to 0.85)
≥6 years	1.8%	0.57 (0.43 to 0.75)	0.61 (0.46 to 0.82)

CI, confidential interval; Ref., reference; SHR, subdistribution hazard ratio.
[a]Statin user was defined by filled prescription for at least 90 consecutive days of statin use after the index date. The cumulative duration of statin use was modelled as a time-varying exposure. Ten-year cumulative incidence and hazard estimates were obtained with the use of a proportional subdistribution hazards regression model fit to the inverse probability of treatment weighted cohort that accounted for competing risks; the model was conditioned on age at index date.
[b]A multivariable adjusted model further accounted for the following prognostic covariates: age at index date, sex, presence or absence of alcohol, smoking, comorbidities including diabetes, obesity, hypertension, arrhythmia, coronary artery disease, peripheral vascular disease, stroke, Parkinson disease, dyslipidemia, chronic renal failure, cirrhosis, ankylosing spondylitis, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and baseline use of aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, statin, and metformin.

after multivariable adjustment (SHR = 0.84; 95% CI, 0.80–0.89) (*Table 2*).

To enable comparisons to prior reports, we also computed the multivariable SHR before propensity matching (0.82; 95% CI, 0.78–0.86). Without consideration of competing risks, a conventional multivariable Cox regression yielded a hazard ratio (HR) of 0.83 (95% CI, 0.80–0.87) for cancer risk (Supplementary material online, *Table S5*).

Cancer-related mortality

The 10-year cancer-related mortality was 3.8% (1390 episodes) among statin users and 5.2% (2474 episodes) among nonusers (*Figure 3*). The use of statin was significantly associated with a lower adjusted risk of cancer-related death than nonusers (SHR = 0.74; 95% CI, 0.67–0.81) (*Table 2*). Of interest, the 10-year all-cause mortality was 60.5% (21 886 episodes) among statin users and 78.8% (40 130 episodes) among nonusers. The use of statin was significantly associated with a lower adjusted risk of all-cause mortality than nonusers (HR = 0.62; 95% CI 0.61–0.64).

Statin users

Among statin users, the crude 10-year cumulative incidence of cancer among those with atherosclerotic disease (11.34%) and hypercholesterolaemia (11.27%, as indications for statin initiation) did not differ (absolute risk difference: 0.07%, $P > 0.05$). Similarly, the corresponding incidence among lipid control (time-weighted mean LDL measured at least 3 months following statin initiation) groups defined by LDL <1.8, 1.8–2.6, and >2.6 mmol/L was 10.3%, 10.5%, and 10.8% ($P > 0.05$), respectively. After multivariable adjustment and accounting for competing risk, cancer incidence in statin users was not related to the indication for statin (atherosclerotic disease vs. hypercholesterolaemia, SHR = 1.01, 95% CI 0.81–1.26) or time-weighted LDL control (LDL 1.8–2.6 vs. LDL > 2.6 mmol/L, SHR = 1.01, 95% CI 0.91–1.14; LDL <1.8 vs. LDL > 2.6 mmol/L, SHR = 0.99, 95% CI 0.87–1.12).

Duration of statin use

The inverse relationship between statin use and the risk of cancer appeared to be duration dependent. We modelled the duration of statin use as a time-varying exposure to avoid immortal time bias.[24,25] As shown in *Table 3* where the population was restricted to statin users, compared to short-term use (from 3 months up to 2 years), the risk of cancer was significantly lower with the use of statin from 4 years up to 6 years (adjusted SHR 0.82; 95% CI, 0.70–0.97), and further lowered with long-term statin use of >6 years (adjusted SHR 0.78; 95% CI, 0.65–0.93). Similar results of duration response can be found in the association between statin use and cancer-related death. The risk of cancer-related death was significantly lower in statin use from 4 to 6 years and >6 years (adjusted SHR = 0.67; 95% CI, 0. 53–0.85 and adjusted SHR = 0.61; 95% CI, 0.46–0.82, respectively) compared with short-term use of statin, while no such association was observed in statin use from 2 to 4 years. As a sensitivity analysis, no significant difference in cancer incidence and cancer-related death was observed when comparing 90 days to 6 months, 6 months to 1 year, and 1–2 years' use of statin (Supplementary material online, *Table S6*). Consequently, short-term use (defined as 3 months up to 2 years) was used as a referent.

Subgroup analyses

As shown in *Figure 4*, the association of statin use with lower risk of incident cancer was consistent across subgroups of age, sex, alcohol use, smoking status, presence of diabetes or hypertension, and concomitant use of aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or metformin. We further assessed different types of cancer and found that statin use (compared to non-

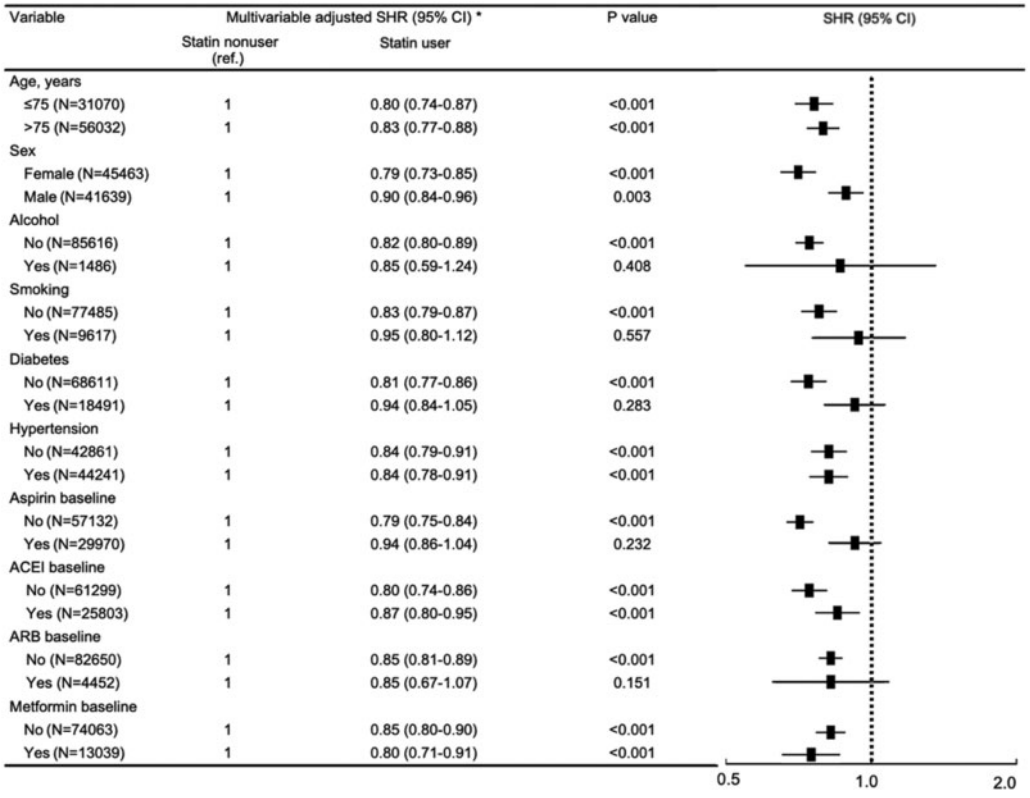


Figure 4 Multivariable stratified analysis of the association between statin use and risk of cancer. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; SHR, subdistribution hazard ratio. *Statin use was defined by filled prescription for at least 90 consecutive days of statin use after the index date (the date on which a patient was diagnosed as incident heart failure). We calculated the *P*-value using Gray's test for equality of the cumulative functions between each exposure group after inverse probability of treatment weighting, accounting for competing risks of all-cause mortality.

use) was associated with a lower incidence of cancers involving the colorectum, lung, liver, lymph, breast, haematological system, pancreas, and kidney; with no association for cancers involving the stomach, skin, prostate, brain, bladder, female reproductive system, head, or oesophagus (all following IPTW adjustment and accounting for competing risks). However, these results should be interpreted with caution because of small sample size in some subgroups (Supplementary material online, *Table S7*).

Sensitivity analysis

Sensitivity analyses revealed consistent results after excluding patients with a history of alcohol abuse (SHR for incident cancer, 0.82; 95% CI, 0.80–0.89) or patients with a history of smoking (SHR for incident cancer, 0.83; 95% CI, 0.79–0.87). Without propensity matching, a multivariable SHR was 0.82 (95% CI, 0.78–0.86). Without consideration of competing risks, a conventional multivariable Cox regression yielded a HR of 0.83 (95% CI, 0.80–0.87) for cancer risk (Supplementary material online, *Table S5*). We further created a 1:1 matched cohort using the propensity score directly without IPTW. Upon trimming 5% of the propensity score, each statin user was matched in a fixed 1:1 ratio with a statin nonuser using a 'genetic' algorithm with a caliper of 0.0001. Using this approach, we successfully matched 30 845 statin users to 35 735 nonusers to create a propensity score matched cohort of 66 580 patients; the multivariable adjusted SHR was 0.81 (95% CI, 0.77–0.84) after accounting for competing risk (Supplementary material online, *Table S8*). Furthermore, we excluded 18 131 patients with a history of baseline statin use to include only new users of statin after the index date followed by a 1:1 propensity score matching to create a matched cohort ($n = 28\ 894$). After accounting for competing risk, multivariable adjusted SHRs of the association between statin new user and risk of incident cancer and cancer-related mortality were 0.80 (95% CI, 0.75–0.86) and 0.70 (95%CI, 0.62–0.78) compared with nonuser, respectively (Supplementary material online, *Table S9*). After excluding patients with incident cancer diagnosed within the first 3 years after the index date, the multivariable adjusted SHR was 0.88 (95% CI, 0.81–0.96) among statin users compared with nonusers after accounting for competing risk (Supplementary material online, *Table S10*). We finally used gastrointestinal bleeding as a negative control, of which we excluded 20 644 patients with a prior history of gastrointestinal bleeding diagnosis before the index date of HF and 435 patients with simultaneous digestive cancer, for further analysis (Supplementary material online, *Table S11*). Among the remaining 66 023 patients, 7937 diagnoses of gastrointestinal bleeding were recorded between

index date and patient mortality. The risk of gastrointestinal bleeding was nonetheless similar between statin users and non-users with SHR of 1.01 (95% CI, 0.96–1.06) after multivariable adjustment.

Discussion

In this territory-wide cohort study of >87 000 patients with HF, we demonstrated that statin use was independently associated with a 16% decrease in risk of developing cancer and a 26% decrease in risk of cancer-related mortality. There was some evidence of a dose–response relationship, with longer durations (4–6 and >6 years) of statin use being associated with a lower risk of cancer and cancer-related mortality compared to short-term use (<2 years). Results were consistent across clinical subgroups and in sensitivity analyses (*Graphical Abstract*).

Advancement of treatment has greatly improved the clinical outcome of patients with HF, with a two-fold improvement of 5-year survival rates from 29.1% between 1970 and 1979 to 59.7% between 2000 and 2009.[3] A decline in cardiovascular mortality was however offset by a considerable increase in non-cardiovascular mortality, with cancer-related death being the most prevalent cause.[26] While one may attribute that the increased cancer-related mortality in patients with HF could be due to shared comorbidities among the two conditions, accumulating evidence has suggested that HF *per se* may predispose to cancer development, for example through hyperactivation of the renin-angiotensin-aldosterone system, which also promotes tumour growth.[27] In a large cohort involving 9307 patients with HF, the risk of cancer was found to be 24% greater compared to patients without HF.[5] In patients with myocardial infarction, those who developed HF had a 71% higher risk of developing cancer compared with those without HF.[6] The increased risk of cancer in patients with HF was further confirmed by a case–control study that demonstrated a higher incidence of cancer, irrespective of diabetes control measured by glycated haemoglobin.[32] Thus, beyond shared risk factors, HF itself may be an oncogenic condition, possibly related to links between neurohormonal activation to tumorigenesis, systemic pathological processes such as inflammation and oxidative stress, common genetic predisposition and clonal haematopoiesis of cancer and HF.[7,8] These findings underscore the strong association of HF with cancer, and call for potential strategies to reduce the risk of cancer and cancer-related mortality in patients with HF. Our result corroborates prior literature suggesting an inverse association between statin use and cancer development and extends these observations for the first time to a large Asian population-based cohort. In an observational study that utilized pharmacy records of dispensing history in eight Dutch cities, regular use of statin was associated with a 20% risk reduction of cancer.[28] In a nationwide study, statin users had a 15% risk reduction cancer-related mortality, regardless of the administrative dose.[10] These non-randomized studies without consideration for some indications of statin, however, may be susceptible to biases in allocation of treatment, and also are limited in their consideration of confounders including co-morbidities and concurrent drug uses. The vigorous adjustment of these confounders in our study provides compelling evidence of the chemoprotective role of statin in patients with HF.

Mechanisms of statin's chemoprotective effects in patients with HF is uncertain but can be postulated by multiple pleiotropic properties of statin, in addition to the cholesterol-lowering effect. First, the presence of escalated inflammation and oxidative stress is a common milieu in HF and cancer. For instance, proinflammatory cytokines correlate with incident HF in the general population[29] and are associated with adverse outcome in HF.[30] Chronic inflammation correspondingly contributes to cancer initiation and progression which result in poorer outcome.[31] The prominent anti-inflammatory properties of statin may thus lessen the development of cancer in patients with HF with an increased inflammatory load. Further, HF modulation of p53 dependent pathways, not only induce cardiac apoptosis[33] but has also promoted carcinogenesis. The inhibition of the mevalonate pathway by statin, up-regulated by p53, reverts the malignancy potential and reduce the invasiveness of in situ cancers.[34] Finally, the potential to halt the cell-cycle progression in cancer cells, as a result of the anti-proliferative effect of statin, may further justify the observed capacity to reduce the incidence of cancer, as well as cancer-related mortality in our patients with HF.[35] Our results provide further support for the pleiotropic effects of statin, independent of LDL-cholesterol, in that neither the underlying indication for statin (atherosclerotic disease vs. hypercholesterolaemia) nor the extent of lipid control (measured by time-weighted mean LDL) was associated with incident cancer among statin users. It is noteworthy that despite the presence of an established indication for statin therapy, a substantial proportion of patients with coronary artery disease (23.3%), stroke (9%), and dyslipidaemia (5.2%) did not receive statins. Although the exact reason is uncertain, we postulate that a higher rate of statin intolerance among Asians may have contributed to the observed suboptimal adherence. Indeed, Asian ethnicity is included among the list of risk factors for statin-associated muscle symptoms by the European Atherosclerosis Society Consensus Panel Statement,[36] and prior studies in Asian patients with atherosclerotic cardiovascular disease have shown discontinuation rates of up to 33% within 12 months of initiating either a statin or ezetimibe.[37]

There are several limitations in the present study. Risk factors such as a family history of cancer were not available. Nonetheless, variables such as family history are unlikely to impact drug prescription, thus conferring minimal confounder effects in drug–cancer association studies.[38] Furthermore, the left ventricular ejection fraction of our patients was not recorded in the reporting system and thus the differential chemoprotective effect in HF patients with preserved and reduced ejection fraction of statin cannot be evaluated. Studies have consistently shown that HF was associated with cancer incidence, irrespective of left ventricular ejection fraction,[4,5,32] indicating that our finding can conceivably be generalizable to a wide range of HF patients. Finally, it is possible that residual confounders remain despite utilizing propensity score analytics,

Strengths of the present study include the use of a territory-wide, well-validated electronic healthcare database (CDARS) with records of all diagnoses, hospitalizations, and details of drug dispenses, allowing the collection of the relevant information required to preclude common biases in conventional observational studies such as selection and recall biases. The validity of the current result is further improved by the adjustment of potential chemoprotective agents, such as metformin[19] and aspirin,[24] that is commonly prescribed concomitantly with statin. Furthermore, statin users are likely to have

more comorbidities than nonusers, which minimize the concern of healthy user bias. The application of IPTW to an unselected population with HF with detailed clinical and medication history provides compelling evidence regarding the potential benefits of statin in the reduction of cancer risk and cancer-related mortality. In addition, we found that statin's chemoprotective effect is present in a duration-response manner by using a time-varying model, indicative of a potential causal relationship. The reduction of cancer incidence and cancer-related mortality with at least 4 years of statin use is consistent with the result from other observational studies.[24,39,40] The current study, therefore, provides robust evidence on the relationship between statin and risk of cancer in patients with HF through a thorough consideration of potential sources of confounding and biases.

Conclusion

In this large population-based cohort of patients with HF, we demonstrated that incident cancer was not uncommon; notably, statin use was associated with a reduced risk of cancer and cancer-related mortality. These findings have major clinical implications to reduce the associated burden in HF. The potential protective effect of statin on the development of cancer merits evaluation in future randomized studies.

Supplementary material

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

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Permission information

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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Data availability

Data are available upon reasonable request to Dr Yiu Kai-Hang.

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