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Statin Use is Associated with Lower Cancer Risk and Cancer Related Mortality in Patients with Heart failure: A territory-wide study

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Introduction

Heart failure (HF) and cancer are two major public health challenges worldwide. The ageing demographics, along with increasing prevalence of antecedents e.g. hypertension, diabetes, coronary artery disease, obesity and atrial fibrillation 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 epidemiologic studies have demonstrated that cancer is the leading cause of non-cardiac death in patients with HF. Besides shared risk factors, such as diabetes mellitus, smoking, 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. Preventive strategies to reduce the burden of cancer in HF patients is hence urgently needed.

Methodology

Propensity score (PS) approach was used to address biases in the allocation of treatment. Covariates that were considered prognostically significant as well as those influenced treatment selection were logistically regressed to the probability of receiving treatment. 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 (SMD) 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”. 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. Associations were considered significant if the p-value was below 0.05.

Figure 1. Flow Chart

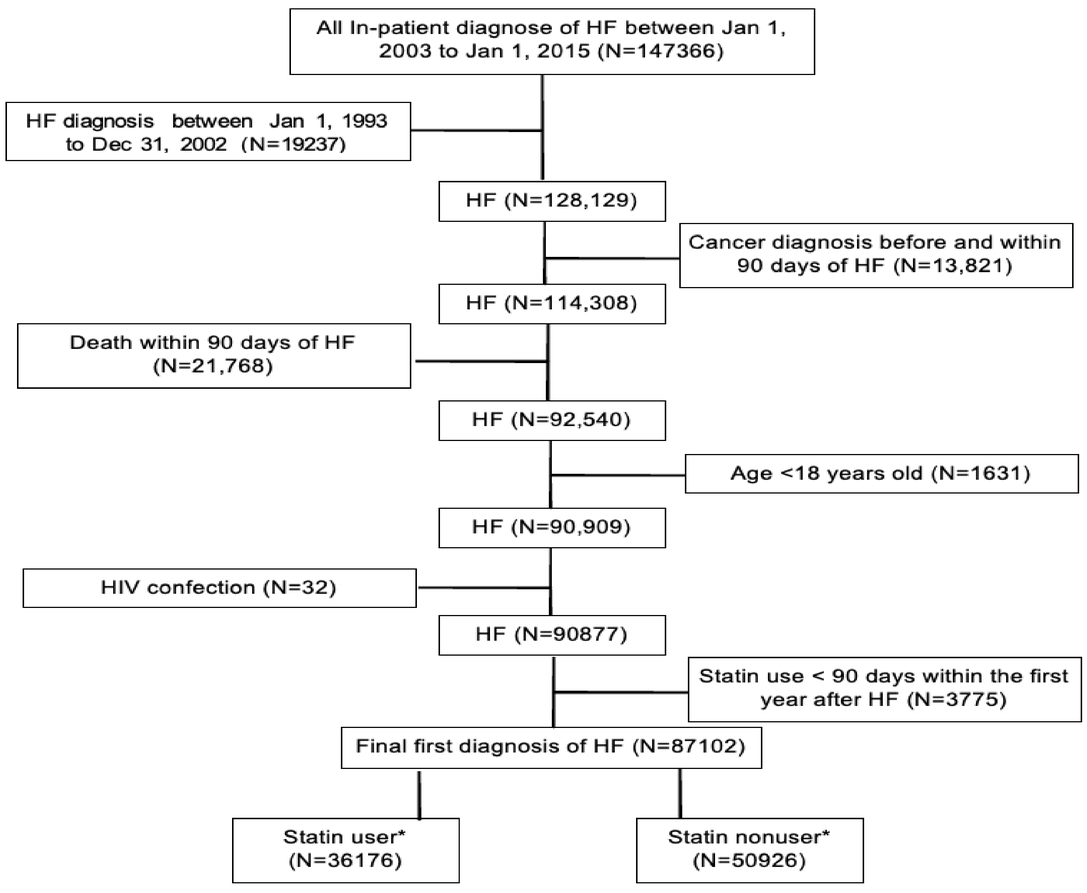

Figure 2

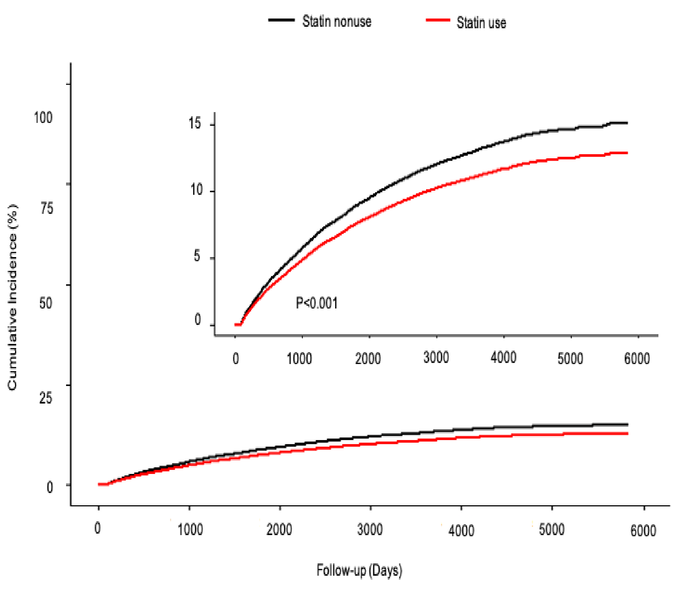

Figure 2. Cumulative incidence of cancer between statin user and non-user

Figure 3

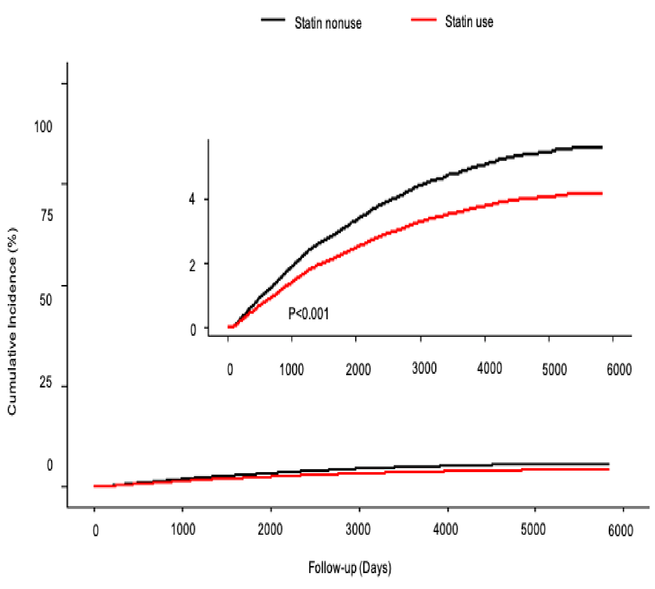

Figure 3. Cancer related mortality between statin user and non-user

Results

Of all eligible subjects, the mean age was 76.5±12.8 years, 47.8% was male. Over a median follow-up of 4.1 years (interquartile range [IQR]: 1.6 to 6.8), 11052 (12.7%) were diagnosed with cancer.(Figure 1) Statin use (vs. none) was associated with a 16% lower risk of cancer incidence (multivariable adjusted sub-distribution hazard ratio [SHR]=0.84; 95% Confidence Interval [CI], 0.80 to 0.89). (Table 1, Figure 2) 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 were 0.99 (95% CI, 0.87 to 1.13) for 2 to < 4 years of use, 0.82 (95% CI, 0.70 to 0.97) for 4 to < 6 years of use, and 0.78 (95% CI, 0.65 to 0.93) for ≥6 years of use. (Table 2) 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 to 0.81). Statin use (vs. none) was associated with a 26% lower risk of cancer incidence (SHR =0.74; 95%CI, 0.67 to 0.81).(Table 1, Figure 3)

Table 1

Table 1. Effect of statin use on the risk of incident cancer and cancer-related death*

Event and Treatment group	No. with Event/ Total No.	10-Yr Cumulative Incidence %	SHR (95% CI) Unadjusted	SHR (95% CI) Adjusted¥
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%)		

Table 2

Table 2. Effect of duration of statin use on the risk of incident cancer and cancer-related death among statin user*

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

Discussion

In this territory-wide cohort study of more than 87000 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 years, >6 years) of statin using being associated with a lower risk of cancer and cancer-related mortality compared to short-term use (<2 year). Results were consistent across clinical subgroups and in sensitivity analyses.

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 1970-1979 to 58.7% between 2000-2009. 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. Accumulating evidence has suggested that HF *per se* may predispose to cancer development, for example, through hyper-activation of the renin-angiotensin-aldosterone system, which also promotes tumor growth.