Statins attenuate but do not eliminate the reverse epidemiology of total serum cholesterol in patients with non-ischemic chronic heart failure

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Abbreviations: chronic heart failure (CHF), total serum cholesterol (TC), low-density lipoprotein cholesterol (LDL)

Abstract

Background: In patients with chronic heart failure (CHF) increasing levels of total serum cholesterol are associated with improved survival – while statin usage is not. The impact of statin treatment on the "reverse epidemiology" of cholesterol is unclear.

Methods: 2,992 consecutive patients with non-ischemic CHF due to left ventricular systolic dysfunction from the Norwegian CHF Registry and the CHF Registries of the Universities of Hull, UK, and Heidelberg, Germany, were studied. 1,736 patients were individually double-matched on both cholesterol levels and the individual propensity scores for statin treatment. All-cause mortality was analyzed as a function of baseline cholesterol and statin use in both the general and the matched sample.

Results: 1,209 patients (40.4%) received a statin. During a follow-up of 13,740 patient-years, 360 statin users (29.8%) and 573 (32.1%) statin non-users died. When grouped according to total cholesterol levels as low (≤3.6mmol/L), moderate (3.7-4.9mmol/L), high (4.8-6.2mmol/L), and very high (>6.2mmol/L), we found improved survival with very high as compared with low cholesterol levels. This association was present in statin users and non-users in both the general and matched sample ($p<0.05$ for each group comparison). The negative association of total cholesterol and mortality persisted when cholesterol was treated as a continuous variable (HR 0.83, 95%CI 0.77-0.90, $p<0.001$ for matched patients), but it was less pronounced in statin users than in non-users (F-test $p<0.001$).

Conclusions: Statins attenuate but do not eliminate the reverse epidemiological association between increasing total serum cholesterol and improved survival in patients with non-ischemic CHF.

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1. Introduction

Hypercholesterolemia is an established risk factor for the development of both cardiovascular disease and chronic heart failure (CHF) (1-3). In the general population, treatment of hypercholesterolemia with statins is effective in the primary and secondary prevention of major cardiovascular events, particularly when achieving very low levels of serum cholesterol (1, 2, 4). In patients with CHF, however, the prognostic significance of hypercholesterolemia seems to change: numerous observational studies have found that low values of total serum cholesterol (TC) and low-density lipoprotein cholesterol (LDL) are associated with worse rather than better survival in patients with CHF (5-15). This counterintuitive risk inversion has been referred to as "reverse epidemiology" (13). It has been observed in both patients with acute and with chronic CHF of ischemic and non-ischemic origin (5-13). Conversely, lipid-lowering therapy with statins seems to be of no benefit in patients with CHF (1, 2, 16, 17).

It is unclear to what extent treatment with statins contributes to the reverse epidemiology of serum lipids in CHF (8, 10, 12, 18). On the one hand, statins lower TC levels which might be beneficial, yet in patients with CHF, lower cholesterol levels may convey adverse prognosis. We therefore aimed to investigate the relative effects of statin treatment and TC levels on survival in a large international cohort of patients with non-ischemic CHF due to left ventricular systolic dysfunction.

2. Material and Methods

2.1. Databases

Patients' data were extracted from three different European CHF registries: the Norwegian Heart Failure Registry, the Heart Failure Registry of the Department of Academic Cardiology, University of Hull, United Kingdom, and the Heart Failure Registry of the University of Heidelberg, Germany. Recruitment was prospective and continuous for each database and center. All patients gave their written informed consent for data storage and evaluation. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees.

The Norwegian Heart Failure Registry was initiated in October 2000 and patients were enrolled from outpatients' clinics of 27 recruiting hospitals well-distributed in all regions of Norway ranging in size and scope from small community to large university hospitals. The participating centers recorded their data using a web-based database.

Patients who attended the community heart failure clinics of the University of Hull, UK, and the University of Heidelberg, Germany, for evaluation of CHF were offered inclusion into the local CHF registries. The registries were initiated in 1999 and 1996, respectively. Since both university hospitals serve as primary health care centers as well as tertiary referral centers, the registries reflect a broad representation of patients of their respective regions.

2.2. Patient selection and follow-up

Patients were eligible for this study if they met **all** of the following criteria: a) attendance at the CHF outpatients' clinic of any of the participating hospitals, b) written informed consent for inclusion into the respective CHF registry, c) history of non-ischemic CHF due to left ventricular systolic dysfunction, and d) TC levels and medication recorded at the inclusion visit.

The diagnosis of CHF was established according to guidelines on the basis of typical symptoms and signs resulting from an objective abnormality of cardiac structure or function on echocardiography, cardiac magnetic resonance imaging, or left heart catheterization (19). Non-ischemic origin of CHF was verified by absence of a medical history of coronary heart disease or angina pectoris and absence of Q-waves from the electrocardiogram. When required, cardiac computer tomography, cardiac magnetic resonance imaging, or left heart catheterization was performed to exclude significant coronary heart disease. All included patients had a left ventricular ejection fraction <45%. Medication was at the discretion of the referring physician with respect to guideline recommended drugs.

Surviving patients were followed up for a minimum of six months. Determination of survival status and follow-up were performed by scheduled visits to the outpatients' clinic, by telephone calls either to the patients' homes or to their physicians, or by electronic hospital records. In addition, for the Norwegian Heart Failure Registry mortality data were obtained at regular intervals from the National

Statistics Bureau, Statistics Norway. All-cause mortality was the pre-defined endpoint for the purpose of the analysis.

2.3. Statistical analysis

Calculations were performed using IBM SPSS statistics 20 (IBM, Ehningen, Germany) and MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium). Graphs were displayed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA).

All tests are two-tailed and a P-value of less than 5% was regarded as being statistically significant. Variables are presented as mean±standard deviation, median (interquartile range), or number (percentages; %) as appropriate. Chi-squared test was used to compare frequencies. To test for significant differences between groups, the two-sample Wilcoxon test and Student's t test were used where appropriate. Differences in event-free survival were analyzed using Cox proportional hazard models and displayed using the Kaplan-Meier method for survival.

In order to analyze the relative effects of TC and statin treatment on survival, different strategies were applied:

First, survival was analyzed with respect to statin treatment in a univariable Cox regression analysis of the general sample. Then, patients were classified into 4 groups according to their TC at the inclusion visit defined as low (TC_1 ≤3.6mmol/L), moderate (TC_2 3.7-4.9mmol/L), high (TC_3 5.0-6.2mmol/L), and very high (TC_4 >6.2mmol/L) TC. The graduation into 4 groups was chosen as a trade-off between sufficiently large a group size and enough groups to demonstrate the potential relationship between TC level and survival. Survival was compared between TC groups in the general sample, in patients treated with statins and in patients without statin therapy. In addition, survival within each TC group was analyzed with respect to statin treatment.

Second, TC was treated as a continuous variable, and the impact of TC on mortality was analyzed using Cox regressions. Again, analyses were performed in the general sample, in statin users and non-statin users.

Third, to account for possible confounders, a propensity score for the conditional probability of receiving a statin was derived for each patient. The propensity score was calculated as the single composite variable from a non-parsimonious multivariate logit-linked binary logistic regression of all baseline characteristics. The propensity score may be used to balance covariates, and numerous studies have reported that it is an adequate tool to reduce bias in observational studies (20-22). Statin treatment was the dependent variable (23). The logit of the probability of receiving a statin according to the score formed the basis of our matching procedure. Patients were individually matched on both the propensity of receiving a statin AND their TC levels. The matching procedure was performed in two steps: firstly, caliper matching of the propensity score was applied with caliper size predefined as 0.2 of the standard deviation of the total sample (24). In a one-pass procedure starting with a given patient receiving a statin, the closest match of a patient without statin therapy was identified. Secondly, TC levels were compared. If TC levels varied ≤10%, the pair of patients was retained for analysis and removed from the total sample to allow for the next matching cycle to take place. If TC levels varied >10%, the pair was rejected. Then the first step of the matching process was repeated to identify the next closest match to the statin patients of the failed matched according to the propensity score. If a further patient without statin treatment was thus identified, the second step was repeated. In cases where we could find no match according to the propensity score AND TC level, the statin patient was removed from the total sample and the matching cycle started with the next statin patient.

All survival analyses were repeated in the matched sample. In addition, binary logistic regressions were performed to analyze the impact of TC on five-year mortality in matched statin users and non-users. For graphic display, the logits of the regression models were used to calculate the relative probability of five-year death of each matched patient (statin users and non-users) with respect to TC levels following: *probit = 1/(1+e^-logit)*. Curves were compared using the sum-of-squares F-test.

As a sensitivity analysis, the association of statin treatment, TC and mortality was analyzed in the general sample using stepwise multivariable Cox regression analyses. Variables that were significant in univariable analyses of the baseline characteristics were entered as covariates. Analyses were repeated in subgroups of statin users and non-users. In addition, as patients in the propensity score

matched cohort differed with respect to age and country, survival analyses were repeated in the matched sample after adjusting for age and country using multivariable Cox regression analyses. Again, analyses were repeated in subgroups of statin users and non-users.

3. Results

3.1. Patient characteristics and follow-up

We identified a total of 2,992 patients who met the inclusion criteria outlined above. Of these, 1,616 (54.0%), 893 (29.8%), and 483 (16.1%) patients were included from the Norwegian Heart Failure Registry, the Heart Failure Registry of the University of Heidelberg, and the Heart Failure Registry of the University of Hull, respectively. A total of 1,209 patients (40.4%) was treated with a statin. Mean TC in patients without statin treatment was 5.2±1.3mmol/L, while it was 4.8±1.3mmol/L in patients taking statins ($p<0.001$). Overall, patients on statins were older and more likely to suffer from co-morbidities such as arterial hypertension and diabetes mellitus than patients without statin treatment. Baseline characteristics of the complete patient sample with respect to statin treatment are shown in *table 1*.

Total follow-up was 13,740 patient-years with a mean follow-up duration of 51.1±35.3 months (4.26±2.94 years). During that time, a total of 933 patients (31.2%) died, 390 (29.8%) in the statin group and 573 (32.1%) in the non-statin group.

3.2. Prognostic significance of statin treatment and TC in the general sample

In univariable Cox regression analysis of the complete sample, treatment with statins was not associated with improved survival (HR 0.96, 95% CI 0.84-1.10, p=0.59 for use) (*figure 1*). When individual TC groups were analyzed separately, survival within each TC group was again not affected by statin treatment (HR 1.07, 95% CI 0.77-1.48, p=0.68; HR 0.84, 95% CI 0.67-1.04, p=0.11; HR 0.95, 95% CI 0.75-1.21, p=0.70; and HR 0.94, 95% CI 0.65-1.37, p=0.76 for use in TC_1, TC_2, TC_3, and TC_4, respectively).

Mortality was significantly lower in patients with moderate, high or very high TC levels as compared to patients with low TC levels. This was true for patients on statins as well as for patients without statin therapy. In patients without statin treatment, however, there was no difference in survival between patients with low and patients with moderate TC levels (*figures 2* and *3*).

When treating TC as a continuous variable, Cox regression analyses found a significant negative association between TC and all-cause mortality in the general sample, in statin users and statin non-users (HR 0.89, 95% CI 0.85-0.94, p<0.001; HR 0.87, 95% CI 0.80-0.94, p<0.001; and HR 0.90, 95% CI 0.84-0.96, p=0.001, respectively).

3.3. Prognostic significance of statin treatment and TC in the matched sample

The matching procedure identified 868 pairs of statin/non-statin patients with equal TC levels and equal probability of receiving a statin. The matching significantly reduced standardized differences below 10 % in the absolute values for the majority of observed covariates, demonstrating a substantial improvement in the covariate balance across the treatment groups. The baseline characteristics of the matched cohort are shown in *table 2*.

The analyses in the matched sample confirmed those from the general sample. Again, treatment with statins was not associated with improved survival in either the complete matched sample (HR 0.90, 95% CI 0.75-1.07, p=0.24), or in the respective matched TC groups (HR 0.97, 95% CI 0.64-1.46, p=0.87; HR 0.78, 95% CI 0.59-1.03, p=0.07; HR 0.91, 95% CI 0.66-1.25, p=0.56; and HR 1.23, 95% CI 0.71-2.13, p=0.46 for use in TC_1, TC_2, TC_3, and TC_4, respectively).

As in the general sample, mortality was lower in matched patients with moderate, high, or very high TC levels as compared with matched patients with low TC levels (*figure 4*). Again, the association was seen in patients on statins as well as in patients without statin therapy, with the exception that in patients without statin therapy, survival did not differ between low and moderate TC levels (*figure 5-8*).

Treating TC as a continuous variable confirmed the negative relationship between TC and all-cause patients mortality in matched CHF patients (HR 0.83, 95%CI 0.77-0.90, p<0.001). The association

was less pronounced in matched patients with statin treatment as compared to non-users (HR 0.85, 95% 0.77-0.95, p=0.004; and HR 0.81, 95% CI 0.73-0.90, p=0.0001 for statin users and non-users, respectively).

Similarly, logistic regression analysis showed a significant inverse relationship between TC and five-year mortality in the common matched sample (OR 0.81, 95% CI 0.74-0.90, p<0.001), in matched statin users (OR 0.83, 95% CI 0.72-0.96, p=0.01), and non-users (OR 0.79, 95%CI 0.69-0.91, p=0.001). The slope of the respective probability plots was less pronounced in statin users than in statin non-users (p<0.001). The probability of five-year death with respect to TC levels and statin treatment for matched CHF patients is displayed in *figure 6*.

3.4. Sensitivity analyses

Multivariable analyses of both the general and the matched sample confirmed the results from the main analyses: In stepwise multivariable Cox regression analyses of the general sample including significant variables from univariable analyses, statin treatment was not associated with survival (p=0.12), while increasing levels of TC were associated with better survival (HR 0.89, 95% CI 0.81-0.97, p=0.009). This was true in statin users (HR 0.86, 95%CI 0.74-0.99, p=0.049) and non-users (HR 0.87, 95%CI 0.77-0.98, p=0.02).

Similarly, stepwise multivariable Cox regression analyses of the matched sample including age and country as covariates did not find a relationship between statin treatment and survival (HR 0.88, 95%CI 0.74-1.05, p=0.14). Increasing levels of TC were associated with better survival in all matched patients (HR 0.83, 95% CI 0.77-0.90, p<0.0001), matched statin users (HR 0.86, 95% CI 0.77-0.96, p=0.006) and matched non-users (HR 0.80, 95%CI 0.72-0.89, p<0.0001). Again, the relationship between TC and survival was less pronounced in statin users than in statin non-users.

4. Discussion

We investigated the relative effects of statin treatment and TC levels on survival in an international sample of ambulatory patients with chronic CHF not due to ischemic heart disease. We observed a "reverse epidemiological" association between increasing TC and better survival irrespective of statin therapy where low TC levels were associated with worse survival as compared with moderate, high, or very high TC concentrations. Although statin therapy did not affect survival, statins attenuated the strength of the inverse association between TC and outcome.

Statins have become the most important lipid lowering medications with proven efficacy in the treatment of hyperlipidemia (1, 2). In addition to lowering cholesterol, statins appear to have pleiotropic effects which might influence pathophysiology and could potentially confer benefits on patients with CHF (25-27). The beneficial effects of statins have been attributed to their anti-inflammatory properties, and their counter-regulatory actions on the renin–angiotensin–aldosterone and sympathetic systems as well as on the mechanisms of cardiac hypertrophy and fibrosis (26).

Treatment with statins in patients with CHF has been associated with reduced hospital admissions and mortality in several non-randomized studies (25, 28-31), post-hoc analyses (32, 33) and meta-analyses of randomized trials (34-36). The two largest randomized trials – the Controlled Rosuvastatin Multinational Study in Heart failure (CORONA) (16) and the Gruppo Italiano per lo Studio della Sopravvivenza Nell'Insufficienza Cardiaca Heart Failure study (GISSI-HF) (17) – however, failed to show a survival benefit of statins in patients with CHF. Current European guidelines therefore advise against statin therapy as a CHF treatment (1). The results of our study support this recommendation for patients with CHF due to non-ischemic etiologies, since survival was similar irrespective of statin treatment in both the general and the matched sample.

Our study also confirms the reverse epidemiological association between TC and survival in patients with chronic CHF. The phenomenon has been reported from numerous observational studies and post-hoc analyses (5-15), and it has also been described for other cardiovascular risk factors such as obesity and hypertension (11, 13). The mechanisms underlying the risk inversion of classical risk factors in chronic CHF are presently unclear. In recent years, a number of plausible hypotheses has been

proposed (13, 37-40) including the malnutrition–inflammation complex syndrome (13, 40) or theories focusing on endotoxin lipoproteins (37), ubiquinone (38), and selenoproteins (39).

Data regarding the influence of statin therapy on the reverse epidemiology are scarce. Silva et al. suggested that the low TC levels were not causally related to worse survival but simply represented an advanced stage of CHF. In a retrospective cohort study of 464 ambulatory CHF patients, they found that only patients with intrinsically low TC concentrations (<3.9mmol/L) were at increased risk of death, while outcomes were best in CHF patients with pharmacologically induced low TC (12) – thus effectively arguing against the presence of reverse epidemiology in patients on statin therapy. Similarly, an Israeli study of 297 patients with advanced CHF reported that the negative association between LDL cholesterol level and mortality was only present in patients taking statins (18). In contrast, Kahn et al. reported that treatment with statins did not impact the reverse epidemiology of LDL in a study of 2,428 patients with acute CHF. (8).

In agreement with Kahn et al., we observed that low TC levels were associated with increased mortality as compared with high and very high TC levels irrespective of statin treatment. However, statins seem to attenuate the extent of risk inversion, since the negative relationship between TC and mortality was more pronounced in non-statin users. Whether this risk modulation is mediated by pleiotropic effects of statins remains speculative. Prospective trials are warranted to clarify the nature of risk inversion in CHF, the role of statins and possible treatment targets.

5. Limitations

A potential limitation to the present study is its observational design, implying the possibility of selection bias and unadjusted confounding. In addition, since matching was performed after treatment allocation, the relation between statin therapy, TC and all-cause mortality is associative, not causal. However, our data result from large comprehensive outpatient databases with continuous inclusion and close surveillance. Our study adds significant evidence to current knowledge by providing a large international patient cohort with a long follow-up and a robust statistical analysis. Notably, the

presence of a reverse epidemiology of TC irrespective of statin treatment was established in univariable and multivariable regression analyses of both the general and the matched sample. Our data reflect the effects of TC levels and statin therapy in real-world patients in contrast to randomized trials. Our findings are clinically relevant to the population at interest given the known differences between study cohorts and "real world" patients.

We chose to restrict our analysis to patients with non-ischemic CHF since patients with ischemic CHF are usually treated with statins for coronary heart disease. Not only would this have hampered adequate matching to patients without statin therapy but the intrinsic prognostic benefit in coronary artery disease is unquestioned. A recently published observational study of 21,864 patients reported improved outcomes in statin users with CHF due to ischemic heart disease (31). Our results will therefore not be transferable to patients with CHF of ischemic origin. In addition, the classification as non-ischemic CHF may have been inexact in some patients since left heart catheterization was not performed in all patients. However, other studies observed a reverse epidemiology of TC in both ischemic and non-ischemic CHF (5, 7, 8, 10-12).

The present study was limited by not having information on LDL levels. However, the "reverse epidemiology" has been reported for LDL as well as TC (5-15), and statins similarly affect both LDL and TC levels (41, 42). Therefore, it is likely that our results may be transferred to LDL measurements.

This study was further limited by not having information on the type of statin that was used in patients. As pharmacokinetics of lipophilic statins may differ from that of hydrophilic statins, a differential effect of certain statins cannot be ruled out (43, 44). Moreover, we cannot comment on medication adherence. Statin therapy may have been stopped during the course of follow-up. However, inclusion into the analyses of our study was performed after stabilization of both clinical status and medication in an ambulatory setting. This may reduce the necessity for further modulation of statin treatment.

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Figure legends

Figure 1

Title: Kaplan–Meier curves for 10-year survival for chronic heart failure outpatients with respect to statin treatment

Legend: Small numbers indicate the numbers at risk at the respective follow-up.

Figure 2:

Title: Forrest plot for Cox regression analyses for all-cause mortality in the general cohort, in patients with statin treatment and in patients without statin treatment with respect to total serum cholesterol levels.

Legend: TC_1, total serum cholesterol ≤3.6mmol/L; TC_2, total serum cholesterol 3.7-4.9mmol/L; TC_3, total serum cholesterol 5.0-6.2mmol/L; TC_4, total serum cholesterol >6.2mmol/L; HR, hazard ratio; CI, confidence interval.

Figure 3 a) and b)

Title: Kaplan–Meier curves for 10-year survival for chronic heart failure outpatients a) with statin treatment, and b) without statin treatment with respect to total serum cholesterol levels.

Legend: TC_1, total serum cholesterol ≤3.6mmol/L; TC_2, total serum cholesterol 3.7-4.9mmol/L; TC_3, total serum cholesterol 5.0-6.2mmol/L; TC_4, total serum cholesterol >6.2mmol/L.Small numbers indicate the numbers at risk at the respective follow-up.

Figure 4:

Title: Cox regression analyses for all-cause mortality in the matched cohort, in matched patients with statin treatment and in matched patients without statin treatment with respect to total serum cholesterol levels.

Legend: TC_1, total serum cholesterol ≤3.6mmol/L; TC_2, total serum cholesterol 3.7-4.9mmol/L; TC_3, total serum cholesterol 5.0-6.2mmol/L; TC_4, total serum cholesterol >6.2mmol/L; HR, hazard ratio; CI, confidence interval.

Figure 5 a) and b)

Title: Kaplan–Meier curves for 10-year survival for matched chronic heart failure outpatients a) with statin treatment and b) without statin treatment with respect to total serum cholesterol levels.

Legend: TC_1, total serum cholesterol ≤3.6mmol/L; TC_2, total serum cholesterol 3.7-4.9mmol/L; TC_3, total serum cholesterol 5.0-6.2mmol/L; TC_4, total serum cholesterol >6.2mmol/L. Small numbers indicate the numbers at risk at the respective follow-up.

Figure 6

Title: Probability of five-year death in matched chronic heart failure patients with respect to total serum cholesterol levels and statin treatment

Table 1: Baseline characteristics for the complete cohort and separate with respect to statin treatment

Characteristic	All patients (n=2,992)	No statin (n=1,783)	*P*-value	Statin (n=1,209)
Age, *years*	63.8±15.0	62.2±16.2	*<0.001*	65.5±12.9
Male, *n (%)*	2,025 (67.7)	1,176 (66.0)	*0.014*	849 (70.2)
Aetiology, *n (%)*			0.25	
DCM	1,569 (52.4)	953 (53.4)		616 (51.0)
Hypertensive	383 (12.8)	233 (13.1)		150 (12.4)
Valvular	260 (8.7)	156 (8.7)		104 (8.6)
Other	780 (26.1)	441 (24.7)		339 (28.0)
NYHA, *n (%)*			*0.003*	
I	659 (22.2)	418 (23.7)		241 (20.2)
II	1,505 (50.8)	914 (51.8)		591 (49.4)
III	777 (26.2)	422 (23.9)		355 (29.7)
IV	21 (0.7)	12 (0.7)		9 (0.8)
SBP, *mmHg*	124±22	124±23	0.42	125±22
HR, *1/min*	70±14	71±15	*0.015*	70±13
BMI, *kg/m²*	27.3±5.4	27.1±5.5	*0.015*	27.6±5.3
LVEF, *%*	34±14	35±14	0.19	34±14
Co-morbidity				
aHT, *n (%)*	1,303 (43.5)	738 (41.4)	*0.004*	565 (46.7)
COPD, *n (%)*	489 (16.3)	285 (16.0)	0.52	204 (16.9)
Diabetes, *n (%)*	449 (15.0)	215 (12.1)	*<0.001*	234 (19.4)
Smoker, *n (%)*	432 (14.4)	249 (14.0)	0.45	183 (15.1)
Country, *n (%)*			*<0.001*	
Norway	1,616 (54.0)	878 (49.2)		738 (61.0)
Germany	893 (29.8)	562 (31.5)		331 (27.4)

UK	483 (16.1)	343 (19.2)		140 (11.6)
NTproBNP, *pmol/L*	135 (31-555)	157 (31-724)	*0.003*	112 (29-354)
Creatinine, *µmol/L*	91 (77-113)	90 (75-113)	*0.024*	92 (78-113)
eGFR, *mL/min/1.73m²*	70 (53-88)	71 (54-90)	*0.001*	69 (52-85)
Sodium, *mmol/L*	139±9	139±11	*0.013*	139±5
Potassium, *mmol/L*	4.4±0.5	4.3±0.5	*0.004*	4.4±0.5
BUN, *µmol/L*	405 (321-500)	399 (315-506)	0.35	411 (327-494)
TC, *mmol/L*	5.0±1.3	5.2±1.3	*<0.001*	4.8±1.3
TC, *n (%)*			*<0.001*	
≤3.6 mg/dL	436 (14.6)	216 (12.1)		220 (18.2)
3.7-4.9 mg/dL	1,058 (35.4)	570 (32.0)		488 (40.4)
5.0-6.2 mg/dL	1,029 (34.4)	682 (38.3)		347 (28.7)
>6.2 mg/dL	469 (15.7)	315 (17.7)		154 (12.7)
Treatment				
Aspirin, *n (%)*	744 (24.9)	359 (20.1)	*<0.001*	385 (31.8)
ACEI, *n (%)*	2,111 (70.6)	1,238 (69.4)	0.10	873 (72.2)
ACEI dose equivalent, *%*	100 (50-100)	100 (50-100)	0.07	100 (50-100)
ARB, *n (%)*	600 (20.1)	344 (19.3)	0.22	256 (21.2)
ACEI and/or ARB, *n (%)*	2,614 (87.4)	1,529 (85.8)	*0.001*	1,080 (89.3)
ACEI/ARB dose equivalent, *%*	75 (50-100)	62.5 (50-100)	0.06	75 (50-100)
Beta blocker, *n (%)*	2,429 (81.2)	1,390 (78.0)	*<0.001*	1,039 (85.9)
Beta blocker dose equivalent, *%*	53 (26-100)	53 (26-100)	0.054	53 (26-100)

Aldosterone antagonist, *n (%)*	945 (31.6)	558 (31.3)	0.22	387 (32.1)
Loop diuretic, *n (%)*	2,100 (70.2)	1,226 (68.8)	*0.038*	874 (72.3)
Loop diuretic dose, *mg furosemide*	40 (40-80)	40 (40-80)	0.51	40 (40-80)

DCM, dilated cardiomyopathy; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; HR, heart rate; BMI, body mass index; LVEF, left ventricular ejection fraction; aHT, arterial hypertension; COPD, chronic obstructive pulmonary disease; UK, United Kingdom; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; BUN, blood urea nitrogen; TC, total serum cholesterol; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Italic nnumbers indicate significant p-values ($p<0.05$).

Table 2: Baseline characteristics for matched patients and separate with respect to statin treatment

Characteristic	Matched patients (n=1,736)	No statin (n=868)	*P*-value	Statin (n=868)
Age, *years*	64.6±14.2	63.8±15.2	*0.02*	65.4±13.0
Male, *n (%)*	1,188 (68.4)	581 (66.9)	0.18	607 (69.9)
Aetiology, *n (%)*			0.89	
DCM	906 (52.2)	449 (51.7)		457 (52.6)
Hypertensive	210 (12.1)	104 (12.0)		106 (12.2)
Valvular	153 (8.8)	81 (9.3)		72 (8.3)
Other	467 (26.9)	234 (27.0)		233 (26.8)
NYHA, *n (%)*			0.05	
I	333 (19.2)	147 (16.9)		186 (21.4)
II	914 (52.6)	483 (55.6)		431 (49.7)
III	480 (27.6)	233 (26.8)		247 (31.6)
IV	9 (0.5)	5 (0.6)		4 (0.5)
SBP, *mmHg*	123±22	123±22	0.67	123±21
HR, *1/min*	70±14	70±14	0.87	70±13
BMI, *kg/m²*	27.2±5.3	27.2±5.5	0.91	27.2±5.0
LVEF, *%*	33±13	34±13	0.83	34±13
Co-morbidity				
aHT, *n (%)*	799 (46.0)	392 (45.2)	0.47	407 (46.9)
COPD, *n (%)*	277 (16.0)	139 (16.0)	0.95	138 (16.0)
Diabetes, *n (%)*	273 (15.7)	134 (15.4)	0.74	139 (16.0)
Smoker, *n (%)*	258 (14.9)	129 (14.9)	1.00	129 (14.9)
Country, *n (%)*			*0.03*	
Norway	1,061 (61.1)	516 (59.4)		545 (62.8)
Germany	455 (26.2)	224 (25.8)		231 (26.6)

UK	483 (12.7)	128 (14.7)		92 (10.6)
NTproBNP, *pmol/L*	128 (35-475)	152 (43-607)	0.004	110 (29-335)
Creatinine, *µmol/L*	91 (78-114)	92 (78-117)	0.29	91 (77-111)
eGFR, *mL/min/1.73m²*	69 (52-86)	69 (51-86)	0.48	70 (54-86)
Sodium, *mmol/L*	139±3	139±3	1.00	139±3
Potassium, *mmol/L*	4.4±0.5	4.4±0.5	0.59	4.4±0.4
BUN, *µmol/L*	406 (327-500)	405 (327-506)	0.94	411 (333-494)
TC, *mmol/L*	4.9±1.2	4.9±1.2	0.97	4.9±1.2
TC, *n (%)*			0.99	
≤3.6 mmol/L	274 (15.8)	139 (16.0)		135 (15.6)
3.7-4.9 mmol/L	684 (39.4)	339 (39.1)		345 (39.7)
4.9-6.2 mmol/L	549 (31.6)	276 (31.8)		273 (31.5)
>6.2 mmol/L	229 (13.2)	114 (13.1)		115 (13.2)
Treatment				
Aspirin, *n (%)*	502 (28.9)	246 (28.3)	0.60	256 (29.5)
ACEI, *n (%)*	1,315 (75.7)	661 (76.2)	0.70	654 (75.3)
ACEI dose equivalent, *%*	100 (50-100)	100 (50-100)	0.84	100 (50-100)
ARB, *n (%)*	351 (20.2)	173 (19.9)	0.77	178 (20.5)
ACEI and/or ARB, *n (%)*	1,602 (92.3)	809 (93.2)	0.31	798 (91.9)
ACEI/ARB dose equivalent, *%*	100 (50-100)	100 (50-100)	0.74	100 (50-100)
Beta blocker, *n (%)*	1,524 (87.8)	767 (88.4)	0.46	757 (87.2)
Beta blocker dose equivalent, *%*	53 (26-100)	53 (26-100)	0.28	53 (38-100)

Aldosterone antagonist, *n (%)*	586 (33.8)	297 (34.2)	0.66	289 (33.3)
Loop diuretic, *n (%)*	1,265 (72.9)	635 (73.2)	0.79	630 (72.6)
Loop diuretic dose, *mg furosemide*	40 (40-80)	40 (40-80)	0.68	40 (40-80)

DCM, dilated cardiomyopathy; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; HR, heart rate; BMI, body mass index; LVEF, left ventricular ejection fraction; aHT, arterial hypertension; COPD, chronic obstructive pulmonary disease; UK, United Kingdom; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; BUN, blood urea nitrogen; TC, total serum cholesterol; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Italic numbers indicate significant p-values ($p<0.05$).