

**The PCSK9-LDL Receptor Axis and Outcomes in Heart Failure:
a sub-analysis of BIOSAT-CHF**

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Short Title: PCSK9 and LDLR in heart failure

Word Count:

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ABSTRACT

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds low-density lipoprotein receptor (LDLR) preventing its recycling. PCSK9 is a risk predictor and a biotarget in atherosclerosis progression.

Objectives: We determined whether the PCSK9-LDLR axis could predict risk in patients with heart failure (HF).

Patients and Methods: The BIOSTAT-CHF is a multicenter, multinational, prospective, observational study that included patients with worsening HF signs and/or symptoms. The primary endpoints were all-cause mortality and the composite of mortality or unscheduled hospitalizations for HF. We implemented Cox proportional hazard regression to determine the simultaneously-adjusted effect of PCSK9 and LDLR on both outcomes, when added to the previously validated BIOSTAT risk scores.

Results: This study included 2174 patients (mean age 68 ± 12 years; 53.2% had a history of ischemic heart disease). Median (IQR) PCSK9 and LDLR levels were 1.81U/mL (1.45-2.18) and 2.98 U/mL (2.45-3.53), respectively. During follow-up, 569 deaths (26.2%) and 896 (41.2%) composite endpoints were ascertained. A multivariable analysis, which included BIOSTAT risk scores, LDLR, and statin treatment as covariates, revealed a positive linear association between PCSK9 levels and the risk of mortality (HR=1.24; 95%CI 1.04-1.49; p=0.020) and the composite endpoint (HR=1.21; 95%CI 1.05-1.40; p=0.010). A similar analysis for LDLR revealed a negative association with mortality (HR=0.86; 95%CI 0.76-0.98; p=0.025) and the composite endpoint (HR=0.92; 95%CI 0.83-1.01; p=0.087). Including PCSK9 and LDLR improved risk score performance.

Conclusions: The PCSK9-LDLR axis was associated with poor outcomes in patients with HF. Future studies must assess whether PCSK9 inhibition will result in better outcomes in HF.

Keywords: Proprotein convertase subtilisin/kexin type 9 (PCSK9), low-density lipoprotein receptor (LDLR), heart failure.

ABBREVIATIONS

HF - Heart failure

PCSK-9- Proprotein convertase subtilisin/kexin type 9

LDLR- low-density lipoprotein receptor

BIOSTAT-CHF- BIOlogy Study to TAilored Treatment in Chronic Heart Failure

LVEF- Left ventricular ejection fraction

ACE- Angiotensin-converting enzyme

PEA- Proximity Extension Assay technology

INTRODUCTION

Major advances in heart failure (HF) management have been achieved over the last three decades by targeting two main pathways activated in HF, namely the renin-angiotensin-aldosterone system and the sympathetic nervous system (1). These advances have provided the rationale for current evidence-based treatments, including angiotensin-converting enzyme (ACE)-inhibition, beta-blockade, mineralocorticoid receptor antagonism, and more recently, sacubitril-valsartan (2-5). Nevertheless, HF remains a syndrome with high morbidity and mortality, poor quality of life, and high health-care costs. Indeed, the most recent European data (ESC-HF pilot study) have demonstrated that patients with HF that were hospitalized or stable/ambulatory had 12-month all-cause mortality rates of 17% or 7%, respectively, and 12-month hospitalization rates of 44% or 32%, respectively (6).

Targeting alternative pathways that participate in the HF syndrome seem the next logical approach. One such pathway is atherosclerosis progression; however, the administration of statins in HF has led to debatable results. Indeed, the two major randomized trials that studied the effect of statin treatment in patients with chronic HF did not demonstrate sufficient evidence of benefit (7,8). However, at least in CORONA the secondary endpoint of heart failure hospitalization was significantly reduced by rosuvastatin (7). Also, some reports on real-life data have shown a positive association between statins and outcomes (9).

A new biotarget for treating atherosclerosis progression is proprotein convertase subtilisin/kexin type 9 (PCSK9)(10,11). Secreted into the plasma by the liver, PCSK9 binds the low-density lipoprotein (LDL) receptor (LDLR) at the surface of hepatocytes. This binding prevents LDLR recycling and enhances its degradation in endosomes and lysosomes, which results in reduced LDL-cholesterol clearance (12). The recent Glavov

(13) and Fourier (14) studies have demonstrated that PCSK9 inhibition with monoclonal antibodies could reduce the atherosclerosis disease burden and cardiovascular events.

The potential of PCSK9 as a biotarget in HF is unknown. Herein, we aimed to decipher the value of the PCSK9-LDLR axis for predicting risk in patients with HF in the multicenter BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) cohort (15).

METHODS

BIOSTAT-CHF Cohort

The BIOSTAT-CHF was a multicenter, multinational, prospective, observational study that included 2516 patients with worsening signs and/or symptoms of HF from 69 centers in 11 European countries. The recruitment period was 24 months, from December 2010 to December 2012 (15). The median follow-up was 21 months [interquartile range (IQR) 15–27 months]. The Ethics Committees of participating institutions approved this study, and all patients provided written consent to participate in the study.

Eligible patients, exclusion criteria, and characteristics of the BIOSTAT-CHF cohort have been described elsewhere (15). In brief, the majority of patients were hospitalized for acute HF, and the remainder presented with worsening signs and/or symptoms of HF at outpatient clinics. Approximately half of the patients were classified as New York Heart Association class III.

All deaths and hospitalizations were recorded. The primary outcomes of interest were the time to all-cause mortality and the time to a composite of death or unscheduled hospitalization for HF.

PCSK9 and LDL Receptor Assays.

PCSK9 and LDLR were measured using the Proseek® Multiplex CVDIII panel (Olink Proteomics AB, Uppsala, Sweden) according to the manufacturer's instructions. The Proximity Extension Assay (PEA) technology used for the Proseek® Multiplex protocol has been well described (16). In brief, pairs of oligonucleotide-labeled antibody probes bind to their targeted protein, and if the two probes are brought in close proximity the oligonucleotides will hybridize in a pair-wise manner. The addition of a DNA polymerase leads to a proximity-dependent DNA polymerization event, generating a unique PCR target sequence. The resulting DNA sequence is subsequently detected and quantified using a microfluidic real-time PCR instrument (Biomark HD, Fluidigm). Data is then quality controlled and normalized using an internal extension control and an inter-plate control, to adjust for intra- and inter-run variation. The final assay read-out is presented in Normalized Protein eXpression (NPX) values, which is an arbitrary unit on Log2 scale where a high value corresponds to a higher protein expression. All assay validation data (detection limits, intra- and inter-assay precision data, etc) are available on manufacturer's website (www.olink.com).

Statistical analysis

Continuous variables are expressed as the mean $\pm$ standard deviation (SD) or the median (IQR) per variable distribution. Discrete variables are presented as percentages. Baseline characteristics among PCSK9 and LDLR quartiles were compared with ANOVA, Kruskal–Wallis, or chi-squared tests, as appropriate.

The bivariate correlation of the two exposures was assessed with Spearman's rank correlation coefficient. A multivariable linear regression analysis was performed to determine the association of LDLR with PCSK9 while adjusting for age, gender, ischemic heart disease, LDL-cholesterol, HDL-cholesterol, and eGFR.

The Cox proportional hazard regression was used to determine the simultaneously-adjusted effect of PCSK9 and LDLR on all-cause mortality and on the composite of mortality and HF hospitalization. Each of these models included as covariates the use of statins and tertiles of the previously derived BIOSTAT risk score (17). Briefly, the BIOSTAT risk score for each endpoint was calculated as the probability of achieving the endpoint at a 2-year follow-up. The BIOSTAT risk score for mortality included age, blood urea nitrogen, NT-proBNP, serum hemoglobin, and the use of a beta-blocker. The BIOSTAT risk score for the composite endpoint included age, previous HF-related hospitalization, the presence of edema, systolic blood pressure, and the estimated glomerular filtration rate (17). Results are expressed as hazard ratios (HR) with their respective 95% CI. The proportionality assumption – tested by means of the Schoenfeld residuals - was met for all models. In a sensitivity analysis, LDL cholesterol was added as an additional covariate to the previous prognostic models.

Measures of performance were assessed by means of Δ C-statistics, integrated discrimination improvement (IDI), and net reclassification improvement (NRI). In order to match the scope of the BIOSTAT risk score, these indices were calculated at a horizon of 2 years. Two variations of the analysis are presented: 1) PCSK9, LDLR, and the use of statins are compared over the BIOSTAT risk score alone, and 2) PCSK9 is contrasted against LDLR, use of statins, and the BIOSTAT risk score.

We set a two-sided p-value of <0.05 as the threshold for statistical significance. Stata 14.2 (Stata Statistical Software, Release 14 [2015]; StataCorp LP, College Station, TX, USA), was used for the main analysis. Risk reclassification analyses were implemented in R (Version 3.40; R Foundation for Statistical Computing, Vienna, Austria) with the survIDINRI and SurvC1 modules.

RESULTS

A total of 2174 patients were included in this analysis (Online Figure 1). The mean age of the sample was 68 ± 12 years; 581 (49.7%) were female, 1156 (53.2%) had history of ischemic heart disease, and 1727 (88.7%) exhibited LVEF $\leq 40\%$. The median (IQR) values of PCSK9, LDLR, and NT-proBNP were 1.81U/mL (1.45-2.18), 2.98 U/mL (2.45-3.53), and 4148 pg/mL (2330-8136), respectively. The baseline values of PCSK9 and LDLR across quartiles are shown in Tables 1 and 2. Overall, patients in the higher PCSK9 quartiles displayed a higher prevalence of ischemic heart disease and prior coronary revascularization and higher values of creatinine, and potassium (Table 1). In contrast, the disease severity surrogates were inversely related to the LDLR quartiles. Indeed, those in the lower LDLR quartiles were older, more frequently males, and exhibited higher proportions of prior renal failure and atrial fibrillation. Similarly, the lower LDLR quartile displayed lower systolic blood pressure and hemoglobin, and higher values of urea and NT-proBNP (Table 2). Regarding medications, higher proportions of patients used statins in the upper quartiles of the two studied exposures. (Tables 1, 2).

Circulating PCSK9 predictors

Online Figure 2 shows the identified predictors of circulating PCSK9 levels. The model's adjusted R-squared was 0.422. A closer look at the positive correlation between PCSK9 and LDLR is depicted in Online Figure 3 ($r = 0.59$; $p < 0.001$).

Mortality endpoint

During a median follow-up of 1.78 years (IQR: 1.29-2.25), 569 deaths (26.2%) were registered. Multivariable analysis that included as covariates the BIOSSTAT risk score for mortality, LDLR, and statin treatment, revealed a positive linear association between PCSK9 and the risk of mortality ($p = 0.020$; Figure 1A). A similar analysis revealed a

negative linear association between LDLR and mortality ($p=0.025$; Figure 1B). The estimated HRs from regression modeling are shown in Table 3. Since PCSK9 and LDLR levels were highly correlated, we excluded one exposure at a time to assess -on the other one- if multicollinearity was artificially changing in the direction of the effect. Under this premise, a positive association for all-cause mortality was confirmed for PCSK9 and a negative one for LDLR (results not shown). Indeed, both variables' linear trajectories showed opposite directions, with increasing risk at higher PCSK9 levels and lower risk at higher LDLR levels (Figure 1).

In exploratory fashion, several interactions were tested, all with negative results: PCSK9 quartiles vs LDLR ($p = 0.388$); LDLR quartiles vs PCSK9 ($p = 0.143$); statins vs PCSK9 ($p = 0.432$); statins vs LDLR ($p = 0.860$); ischemic heart disease vs PCSK9 ($p = 0.271$); and ischemic heart disease vs LDLR ($p = 0.079$).

The added value in performance for PCSK9, LDLR, and statin treatment over the BIOSTAT risk score was confirmed by Δ C-statistic [0.0120 (0.002-0.022)], IDI ($p = 0.027$), and NRI ($p = 0.047$). Similarly, PCSK9 produced a better risk reclassification over LDLR, statin treatment, and the BIOSTAT risk score as evidenced by IDI ($p = 0.033$) and NRI ($p = 0.037$).

Composite endpoint

At a median follow-up of 1.53 years (IQR, 0.67-2.15), we ascertained 896 (41.2%) composite endpoints (composite of death or HF-related hospitalization). In a multivariable context, PCSK9 showed a linear and positive association with the risk of the combined endpoint ($p=0.011$; Figure 2A), independent of the effect of BIOSTAT risk score for the composite endpoint, LDLR, and statin treatment; LDLR, however, showed a negative but borderline association ($p=0.087$; Figure 2B). The estimated HRs from regression modeling are shown in Table 3. The direction of the effect for both

PCSK9 and LDLR were confirmed by excluding one of them at a time to rule-out changes due to multicollinearity.

In exploratory fashion, several interactions were tested, all with negative results: PCSK9 quartiles vs LDLR ($p = 0.200$); LDLR quartiles vs PCSK9 ($p = 0.929$); statins vs PCSK9 ($p = 0.485$); statins vs LDLR ($p = 0.403$); ischemic heart disease vs PCSK9 ($p = 0.170$); and ischemic heart disease vs LDLR ($p = 0.211$).

The added value in performance for PCSK9, LDLR, and statin treatment over the BIOSTAT risk score was confirmed by Δ C-statistic [0.014 (0.006-0.022)], IDI ($p < 0.001$), and NRI ($p = 0.010$). Similarly, PCSK9 produced a better risk reclassification over LDLR, statin treatment, and the BIOSTAT risk score both by IDI ($p = 0.047$), and NRI ($p = 0.047$).

Sensitivity analysis

In a sensitivity analysis, where plasma LDL cholesterol was added as an additional covariate, the results were consistent with the main findings, despite a drop in sample numbers ($n=1000$), due to missing LDL cholesterol values. Circulating PCSK9 and LDLR levels were independently associated with mortality risk and the composite endpoint (Online Table 1).

DISCUSSION

The present report is the first to show that the PCSK9-LDLR axis was associated with poor outcomes in patients with HF. Our sub-analysis of the BIOSTAT-CHF cohort indicated that soluble PCSK9 was positively associated with both all-cause mortality and the composite endpoint of mortality or HF-related rehospitalizations in patients with worsening HF. By contrast, as pathobiologically expected, circulating LDLR was

inversely associated with the same two endpoints. Interestingly, the predictive value of PCSK9 improved after adjusting for traditional prognosticators and soluble LDLR.

The predictive value of circulating PCSK9 concentrations was previously described in other clinical settings of cardiovascular pathology. An analysis of the Ottawa Heart Genomics Study and the Emory Cardiovascular Biobank reported that PCSK9 levels were elevated in patients with acute myocardial infarction relative to patients with stable coronary artery disease (19). In the European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis–Intravascular Ultrasound Study, PCSK9 levels were associated with an increased incidence of the composite endpoint of death and acute coronary syndrome, independent of serum LDL cholesterol levels or statin use (20). Similarly, in the present study, a comprehensive multivariable analysis with validated BIOSTAT risk scores showed that higher PCSK9 was associated with an increased incidence of the composite endpoint, and this relationship was independent of serum LDL cholesterol, statin use, or ischemic HF etiology. Thus, PCSK9 may be considered a risk predictor across the cardiovascular disease continuum, from asymptomatic dyslipidemia, through sub-clinical and clinical atherosclerosis, and in HF, based on our findings (Central Illustration).

Secreted PCSK9 follows two possible tracks: the first is to bind immediately to LDLRs in the liver, and the second is to enter the systemic circulation (12). Once bound, the PCSK9/LDLR complex is endocytosed, taken into the lysosomes, and undergoes degradation (21). The presence of PCSK9 enhances LDLR degradation; therefore this track reduces the LDLR abundance on the cell surface (22). In the plasma, circulating PCSK9 can bind to LDLRs on the membranes of various organ systems, such as the liver, intestines, kidneys, lungs, pancreas, and adipose tissues (23-27). In the present report, although the ability for risk prediction of PCSK9 and LDLR was

opposite when included in comprehensive multivariable models, their circulating concentrations showed a significant positive correlation. This finding may reflect the already recognized complexity of the PCSK9-LDLR axis (28). Indeed, Tavori et al report that in addition to the straightforward mechanism of action (PCSK9 terminating the lifecycle of LDLR), there are more complex interactions between PCSK9, LDLR and plasma lipoprotein levels, including: (a) the presence of both parallel and reciprocal regulation of surface LDLR and plasma PCSK9; (b) a correlation between PCSK9 and LDL cholesterol levels dependent not only on the fact that PCSK9 removes hepatic LDLR, but also due to the fact that up to 40% of plasma PCSK9 is physically associated with LDL; and (c) an association between plasma PCSK9 production and the assembly and secretion of triglyceride-rich lipoproteins (28).

Despite numerous advances in HF treatments, which block both the sympathetic nervous system and the renin-angiotensin-aldosterone system, the morbidity and mortality of patients with HF remain unacceptably high (29). Our finding that PCSK9 could predict risk in HF may serve as a basis for designing prospective studies that aim to inhibit PCSK9, either with specific PCSK9 neutralizing monoclonal antibodies or with the administration of small, interfering RNAs (siRNAs) that specifically bind and inhibit translation of PCSK9 mRNAs (13,14,30).

In patients with acute coronary syndromes, the potential benefit of treatment with PCSK9 antibodies may be two-fold, because it could both reduce LDL cholesterol and stabilize plaques (10). Indeed, PCSK9 adversely affects coronary plaques through several pathways, including proinflammatory LDL oxidation and direct modification of plaque composition. Moreover, PCSK9 is associated with the inflammatory response, which is largely based on NF- κ B-mediated expression of proinflammatory genes, including cytokines, chemokines, and adhesion molecules (31,32). The PCSK9-induced

NF- κ B pathway can upregulate tissue factor expression, which enhances the thrombotic substrate in atherosclerotic plaques (33). In the context of HF, it is reasonable to speculate that plaque stabilization, combined with reductions in the prothrombotic and proinflammatory states, accomplished by inhibiting PCSK9, might represent a new avenue of treatment for preventing disease progression, when the current optimal medical treatment is insufficient. It is unclear whether this strategy will be useful across all HF etiologies, or only for those of ischemic origin; this issue should be investigated in future, well-designed, prospective clinical trials.

Two randomized clinical trials that explored reducing cholesterol levels with rosuvastatin in patients with HF did not demonstrate a clear benefit (7,8). Rosuvastatin is a hydrophilic statin, which relies on active transport into hepatocytes to exert its effect and has poor penetration into extrahepatic tissues; thus, it has less risk of adverse effects but also very low uptake by cardiac muscle. No randomized studies have been performed with lipophilic statins (simvastatin, atorvastatin), which tend to achieve higher levels of exposure in nonhepatic tissues, have very high cardiac muscle uptake, and in real-life scenarios have shown some benefit (9,34). Current guidelines do not recommend the use of statins in patients with HF (1). Whether interfering with cholesterol-related mechanistic pathway may be beneficial in selected patients with HF is not a totally settled issue.

Limitations: The current study had some limitations. First, the data presented here are valid for patients with worsening HF, mainly due to reduced LVEF. It remains to be determined whether soluble PCSK9 is also a good predictor for patients with stable chronic HF. Currently available data in the context of coronary artery disease showed in mice that plasma PCSK9 concentration was mostly elevated in the early hours after an acute coronary syndrome (35). The second limitation was that the assay used to measure

PCSK9 and LDLR was designed for research only, and its use cannot be recommended in clinical practice. Nevertheless, both exposures were measured with state-of-the-art proteomics technology, currently available and well validated (16). The last limitation was that genetic mutations that might determine PCSK9 levels were not measured in patients enrolled in the BIOSTAT-CHF trial. PCSK9 gain-of-function mutations have been associated with increased severity in coronary atherosclerosis (36).

CONCLUSION

The PCSK9-LDLR axis has been investigated expeditiously, from discovery to targeted therapy, in dyslipidemia and coronary atherosclerosis. Here, we provided the first evidence of PCSK9 participation in HF. Indeed, HF risk was positively associated with circulating PCSK9 and negatively associated with LDLR in patients with worsening HF. Future studies are needed to better understand the PCSK9-LDLR axis in HF, and to assess whether PCSK9 inhibition or silencing might lead to better outcomes in HF.

PERSPECTIVES

Competency in Medical Knowledge: Proprotein convertase subtilisin/kexin type 9 (PCSK9), which binds the low-density lipoprotein receptor (LDLR) and prevents its recycling, is a risk predictor and biotarget in atherosclerosis progression. Here, we demonstrated that HF risk was positively associated with circulating PCSK9 and negatively associated with LDLR levels.

Translational Outlook: Our data provided a basis for future research to investigate whether HF outcomes might be improved by inhibiting PCSK9, either with specific PCSK9-neutralizing monoclonal antibodies or with small interfering RNAs (siRNAs).

Funding: This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29). AB-G was supported by grants from the Ministerio de Educación y Ciencia (SAF2014-59892), Fundació La MARATÓ de TV3 (201502, 201516), CIBER Cardiovascular (CB16/11/00403), and AdvanceCat 2014-2020.

Conflicts of interest: AB-G received board membership fees and travel expenses from Novartis, Roche Diagnostics, and Critical Diagnostics. JN Received board membership fees and travel expenses from Novartis, Roche Diagnostics, Abbott, Rovi and Vifor. AAV received consultancy fees and/or research grants from: Alere, Amgen, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, GSK, Merck/MSD, Novartis, Servier, Stealth Peptides, Singulex, Sphingotec, Trevena, Vifor, and ZS Pharma. SAA received grants from Vifor and Abbott Vascular and consultancy fees from Vifor, Bayer, Boehringer Ingelheim, Brahms, Cardiorientis, Janssen, Novartis, Relypsa, Servier, Stealth Peptides, and ZS Pharma. KD has received honoraria and/or research support from Medtronic, Boston Scientific St. Jude, Biotronik and Sorin (device companies), and from Merck, Novartis, Amgen, Boehringer Ingelheim, Astra Zeneca, Pfizer, Bayer, GSK, Roche, Sanofi, Abbott, Otsuka, Leo, Servier, and Bristol Meyers Squibb (pharmaceutical companies). GF has received fees and/or research grants from Novartis, Bayer, Cardiorientis, Vifor, Servier, Alere, and Abbott. PvdH received a research grant from Abbott. CL received consultancy fees and/or research grants from Amgen, Astra Zeneca, MSD, Novartis, and Servier. DVV received board membership fees or travel expenses from Novartis, Johnson & Johnson, and Vifor. MM has received consulting honoraria from Amgen, Bayer, Novartis, and Servier, and speaker's fees from Abbott Vascular, Bayer, and ResMed. All other authors declare no conflict of interest.

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FIGURE LEGENDS

Figure 1: Multivariable analyses for all-cause mortality. (A) HR-gradient, with the median PCSK9 value (1.81 U/mL) as reference. Analysis adjusted for LDLR, statins, and the BIOSTAT risk score for mortality. (B) HR-gradient, with the median LDLR value (2.98 U/mL) as reference. Analysis adjusted for PCSK9, statins, and the BIOSTAT risk score for mortality. HR, hazard ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein- receptor. U/mL, is a Normalized Protein eXpression (NPX) arbitrary unit (see Methods for details).

Figure 2: Multivariable analyses for the composite endpoint (mortality or HF-related hospitalization). (A) HR-gradient, with the median PCSK9 value (1.81 U/mL) as reference. Analysis adjusted for LDLR, statins, and the BIOSTAT risk score for the composite endpoint. (B) HR-gradient, with the median LDLR value (2.98 U/mL) as reference. Analysis adjusted for PCSK9, statins, and the BIOSTAT risk score for the composite endpoint. HR, hazard ratio; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein-receptor. U/mL, is a Normalized Protein eXpression (NPX) arbitrary unit (see Methods for details).

Central Illustration: PCSK9 across the cardiovascular continuum. In heart failure we proved evidence of elevated PCSK9 levels, which were associated with poor outcomes. There is no evidence of PCSK9 inhibition in HF.

Online Figure 1: Flow-chart of the patients included in the analysis.

Online Figure 2: PCSK9 predictors. PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein-receptor; LDL-c, LDL cholesterol; HDL-c, high density lipoproteins cholesterol; eGFR, estimated glomerular filtration rate. Adjusted R-squared = 0.4218

Online Figure 3: Positive correlation between circulating PCSK9 and LDLR concentrations. PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein-receptor. U/mL, is a Normalized Protein eXpression (NPX) arbitrary unit (see Methods for details).

Table 1: Demographic, clinical, laboratory and treatment characteristics relative to PCSK9 quartiles

Variables	PCSK9				P value
	1 st Quartile N= 544	2 nd Quartile N=543	3 rd Quartile N=544	4 th Quartile N=543	
Age, years, mean (sd)	69 (12)	69 (13)	67 (12)	68 (12)	0.08
Sex, male, n (%)	413 (75.9)	401 (73.8)	391 (71.9)	388 (71.5)	0.32
Ischemic heart disease, n (%)	273 (50.7)	273 (51.3)	277 (52.7)	333 (61.8)	0.001
Dilated cardiomyopathy, n (%)	167 (30.7)	186 (34.3)	157 (28.9)	156 (28.7)	0.17
Hypertension, n (%)	347 (63.8)	322 (59.3)	323 (59.4)	355 (65.4)	0.09
Diabetes mellitus, n (%)	173 (31.8)	172 (31.7)	171 (31.4)	185 (34.1)	0.77
Renal failure, n (%)	162 (29.8)	153 (28.2)	131 (24.1)	169 (31.1)	0.06
Atrial fibrillation, n (%)	243 (44.7)	266 (49.0)	254 (46.7)	228 (42.0)	0.12
Heart rate (bpm), mean (SD)	81 (19)	80 (20)	79 (20)	80 (19)	0.67
LVEF %, mean (SD)*	32 (11)	30 (10)	31 (10)	31 (11)	0.28
Laboratory					
Hemoglobin (g/dL), mean (SD)	13.0 (1.9)	13.1 (1.8)	13.2 (1.9)	13.4 (2.0)	0.07
Serum creatinine, mg/dl, mean (SD)	1.28 (0.52)	1.27 (0.53)	1.27 (0.67)	1.38 (0.74)	0.008
NT-proBNP (ng/L), median (IQR)	3975 (2288; 7751)	4654 (2364; 8475)	3784 (2242; 8105)	3949 (2360; 8000)	0.61
LDLc (mmol/L), mean (SD) [†]	2.54 (0.99)	2.50 (0.98)	2.65 (1.11)	2.67 (1.14)	0.21

Treatment					
Diuretics, n (%)	543 (99.8)	543 (100.0)	544 (100.0)	542 (99.8)	0.57
MRA, n (%)	270 (49.6)	290 (53.4)	300 (55.1)	282 (51.9)	0.31
Betablocker, n (%)	454 (83.5)	451 (83.1)	443 (81.4)	459 (84.5)	0.59
ACEI/ARB, n (%)	390 (71.7)	387 (71.3)	383 (70.4)	399 (73.5)	0.72
Statins, n (%)	257 (47.3)	251 (46.1)	301 (55.3)	340 (62.2)	<0.001

PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein receptor; LDLc, LDL cholesterol; NTpro-BNP, N-terminus pro B-type natriuretic peptide; MRA, mineralo-receptor antagonists; ACEI, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor 2 inhibitors; SD, standard deviation; IQR, interquartile range; bpm, beats per minute. U/mL, is a Normalized Protein eXpression (NPX) arbitrary unit (see Methods for details). * data available in 1946 patients; †data available in 1000 patients.

Table 2: Demographic, clinical, laboratory and treatment characteristics relative to LDLR quartiles

Variables	LDLR				P value
	1st Quartile N= 544	2nd Quartile N=543	3rd Quartile N=544	4th Quartile N=543	
Age, years, mean (sd)	70 (12)	69 (12)	68 (12)	66 (12)	< 0.001
Sex, male, n (%)	425 (78.1)	409 (75.3)	397 (73.0)	362 (66.7)	< 0.001
Ischemic heart disease, n (%)	280 (52.3)	295 (55.5)	288 (54.0)	293 (54.8)	0.76
Dilated cardiomyopathy, n (%)	154 (28.3)	161 (29.7)	163 (30.0)	188 (34.6)	0.12
Hypertension, n (%)	349 (64.2)	314 (57.8)	327 (60.1)	357 (65.7)	0.03
Diabetes mellitus, n (%)	167 (30.7)	162 (29.8)	177 (32.5)	195 (35.9)	0.15
Renal failure, n (%)	180 (33.1)	153 (28.2)	136 (25.0)	146 (26.9)	0.02
Atrial fibrillation, n (%)	285 (52.4)	259 (47.7)	250 (46.0)	197 (36.3)	< 0.001
Heart rate (bpm), mean (SD)	80 (19)	80 (20)	81 (21)	80 (19)	0.94
LVEF %, mean (SD)*	31 (11)	30 (11)	31 (11)	31 (10)	0.50
Laboratory					
Hemoglobin (g/dL), mean (SD)	12.8 (1.9)	13.2 (1.9)	13.2 (1.9)	13.5 (1.9)	< 0.001
Serum creatinine, mg/dl, mean (SD)	1.32 (0.59)	1.28 (0.71)	1.31 (0.60)	1.29 (0.58)	0.66
NT-proBNP (ng/L), median (IQR)	4339 (2420; 8068)	5302 (2767; 9449)	3632 (2358; 7340)	3499 (1775; 7337)	< 0.001
Treatment					

Diuretics, n (%)	543 (99.8)	543 (100.0)	544 (100.0)	542 (99.8)	0.57
MRA, n (%)	297 (54.6)	299 (55.1)	277 (50.9)	269 (49.5)	0.18
Betablocker, n (%)	440 (80.9)	462 (85.1)	448 (82.4)	457 (84.2)	0.25
ACEI/ARB, n (%)	396 (72.8)	383 (70.5)	382 (70.2)	398 (73.3)	0.58
Statins, n (%)	268 (49.9)	279 (51.3)	278 (51.1)	324 (59.7)	0.003

LDLR, low density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; LDLc, LDL cholesterol; NTpro-BNP, N-terminus pro B-type natriuretic peptide; MRA, mineralo-receptor antagonists; ACEI, angiotensin converting-enzyme inhibitors; ARB, angiotensin receptor 2 inhibitors; SD, standard deviation; IQR, interquartile range; LVEF, left ventricular ejection fraction; bpm, beats per minute. U/mL, is a Normalized Protein eXpression (NPX) arbitrary unit (see Methods for details). *data available in 1946 patients; ¶data available in 1000 patients

Table 3. Regression modeling for all-cause mortality and the composite endpoint of mortality and/or HF-related hospitalization

Endpoint	HR	95% CI	P-value
All-cause mortality			
PCSK9	1.24	1.04 - 1.49	0.020
LDLR	0.86	0.76 - 0.98	0.025
Statins	1.03	0.87 - 1.22	0.725
Risk score [†]			<0.001*
Tertile 1	1.00		
Tertile 2	2.35	1.76 - 3.13	0.000
Tertile 3	6.41	4.92 - 8.36	0.000
Mortality/HF-related hospitalization			
PCSK9	1.21	1.05 - 1.40	0.011
LDLR	0.92	0.83 - 1.01	0.087
Statins	1.25	1.09 - 1.42	0.001
Risk score [‡]			<0.001*
Tertile 1	1.00		
Tertile 2	2.87	2.32 - 3.56	0.000
Tertile 3	6.13	5.00 - 7.52	0.000

PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein- receptor; HR, hazard ratio; CI, confidence interval. [†]BIOSTAT Score for mortality includes: age, blood urea nitrogen, NT-pro-BNP, serum hemoglobin, and use of beta-blocker; [‡]BIOSTAT Score for mortality/HF-related rehospitalization includes: age, previous HF-related hospitalization, presence of edema, systolic blood pressure, and estimated glomerular filtration rate. *Omnibus P value.

Online Table 1: Regression modeling for all-cause mortality and the composite endpoint of mortality and HF-related hospitalization for the sensitivity analysis, including LDL cholesterol.

Endpoint	HR	95% CI	P-value
All-cause mortality			
PCSK9	1.38	1.05 - 1.82	0.020
LDLR	0.76	0.62 - 0.93	0.007
Statins	0.91	0.71 - 1.16	0.434
LDL cholesterol	0.97	0.84 - 1.12	0.657
Risk score [†]			<0.001*
Tertile 1	1.00		
Tertile 2	2.29	1.51 - 3.47	0.000
Tertile 3	6.16	4.13 - 9.19	0.000
Mortality/HF-related hospitalization			
PCSK9	1.36	1.08 - 1.70	0.007
LDLR	0.86	0.74 - 1.02	0.077
Statins	0.99	0.81 - 1.22	0.932
LDL cholesterol	0.91	0.81 - 1.02	0.093
Risk score [†]			<0.001*
Tertile 1	1.00		
Tertile 2	2.93	2.12 - 4.06	0.000
Tertile 3	5.80	4.20 - 8.01	0.000

PCSK9, proprotein convertase subtilisin/kexin type 9; LDLR, low density lipoprotein-

receptor; LDLc, LDL cholesterol; HR, hazard ratio; CI, confidence interval. [†]BIOSTAT Score for mortality includes: age, blood urea nitrogen, NT-pro-BNP, serum hemoglobin, and use of beta-blocker; [‡]BIOSTAT Score for mortality/HF-related rehospitalization includes: age, previous HF-related hospitalization, presence of edema, systolic blood pressure, and estimated glomerular filtration rate. *Omnibus P value.