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Stromal Cell-Derived Factor 1 (SDF-1) as a Biomarker of Heart Failure and Mortality Risk

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Abstract

Objective—*CXCL12* encodes stromal cell-derived factor 1 alpha (SDF-1), which binds to the receptor encoded by *CXCR4.* Variation at the *CXCL12* locus is associated with coronary artery disease (CAD) and endothelial progenitor cell (EPC) numbers, while variation at the *CXCR4* locus is associated with leukocyte telomere length (LTL), which has been shown to be associated with CAD. We therefore examined the relations of plasma SDF-1 levels to cardiovascular disease (CVD)-related outcomes, risk factors, LTL, and EPCs.

Approach and Results—SDF-1 was measured in 3359 Framingham Heart Study participants. We used Cox regression to examine relations of SDF-1 to new-onset CVD, myocardial infarction (MI), heart failure (HF), and all-cause mortality; we used linear regression to evaluate associations of SDF-1 with risk factors, LTL, and CD34+ cell phenotypes. In multivariable models, higher SDF-1 levels were associated with older age, lower levels of HDL cholesterol, and cigarette smoking. Higher SDF-1 levels were associated with lower CD34+ cell frequency (p=0.02), but not with LTL. During follow-up (median 9.3 years), there were 263 new-onset CVD events, 160 MIs, 200 HF events, and 385 deaths. After adjusting for clinical risk factors, SDF-1 levels were associated with HF (p=0.04) and all-cause mortality (p=0.003), but not with CVD (p=0.39) or MI (p=0.10). The association of SDF-1 levels with MI was attenuated after adjustment for HDL cholesterol.

Conclusions—After adjusting for traditional CVD risk factors, SDF-1 is associated with HF and all-cause mortality risk. Further studies are needed to determine whether measurement of SDF-1 levels has clinical utility.

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Keywords

Cardiovascular disease; epidemiology; myocardial infarction; heart failure; mortality; stromal cell-derived factor 1; progenitor cells

Introduction

Genome-wide association studies (GWAS) of coronary artery disease (CAD) and myocardial infarction (MI) have identified 10q11.21 as a risk locus.[1–4] 10q11.21 harbors *CXCL12*, which encodes stromal cell-derived factor 1 alpha (SDF-1). In addition to the association of *CXCL12* with CAD and MI, we reported that its receptor, *CXCR4*, is associated in GWAS with leukocyte telomere length (LTL).[5] We and others have shown that LTL, in turn, is associated with CAD and MI.[5, 6] The dual GWAS links of the *CXCR4-CXCL12* axis with CAD/MI and with LTL makes SDF-1 an attractive protein biomarker for cardiovascular disease (CVD) and related phenotypes.

The *CXCR4-CXCL12* axis has been explored in experimental models and in population studies. SDF-1 governs the homing of endothelial progenitor cells (EPCs) from bone marrow to areas of vascular injury for angiogenesis and repair.[7] The Bruneck study reported that plasma SDF-1 levels are inversely related to circulating EPC numbers.[8] Additionally, in the same study, there was an association between *CXCL12* genetic variation, circulating SDF-1 levels, and circulating EPCs.[9] CD34+ cell count is an indicator of progenitor cell activity [10], is associated with CVD [11], and promotes neovascularization in the context of vascular disease.[12,13] Thus, alterations in *CXCL12* expression – and by inference, increased SDF-1 levels – may affect CD34+ abundance and recruitment in the context of CVD.

Collectively, these findings are consistent with the hypothesis that plasma SDF-1 levels and genetic variations at the *CXCL12* and *CXCR4* loci are linked to CVD risk and to CVD-related phenotypes through effects on progenitor cell recruitment and LTL dynamics. We thus sought to study the association of plasma SDF-1 levels with CVD-related outcomes and to investigate possible mechanistic connections. We hypothesized that higher plasma SDF-1 levels would be associated with increased risk for CVD-related outcomes, with a greater burden of CVD risk factors, and with shorter LTL and lower CD34+ cell numbers. To that end, we examined these relations in 3359 participants from the Framingham Heart Study (FHS).

Methods and Materials

Methods and Materials are available in the online-only Data Supplement.

Results

Baseline characteristics

The mean age of the study sample was 59 years and 53% were women. The mean SDF-1 level was 1894 pg/mL (range 742 pg/mL to 17,633 pg/mL). Two individuals with SDF-1

levels >5SD were excluded from analyses, leaving 3357 with SDF-1 data; 3216 participants had no missing covariates. Baseline clinical characteristics of the 3357 participants with measured SDF-1 levels are summarized in Table 1.

In unadjusted analyses, higher SDF-1 levels were associated with older age ($p<0.0001$), and waist circumference, higher prevalence of diabetes, hypertension treatment, and CVD ($p<0.0001$). Additionally, increasing quartiles of SDF-1 were associated with higher levels of low-density lipoprotein (LDL) cholesterol, triglycerides, systolic blood pressure, glucose, and BNP ($p<0.01$). In contrast, HDL cholesterol decreased across SDF-1 quartiles ($p<0.0001$). In multivariable analyses (Supplemental Table I), higher SDF-1 levels were associated with older age; lower SDF-1 levels were associated with lower BMI, HDL cholesterol, and systolic blood pressure.

SDF-1 and clinical outcomes

For analyses of new-onset atherosclerotic CVD, participants with prevalent atherosclerotic CVD (n = 168) and missing covariates (n=23) were excluded, and among the 3168 remaining participants, there were 263 incident atherosclerotic CVD events during follow-up (median [minimum, maximum] = 9.3 years [0.03, 15.7]). 160 of these 263 individuals developed MI. For analyses of HF, participants with prevalent HF (n=36) and missing covariates (n=27) were excluded, and the available sample size was 3296. There were 200 incident HF events during follow-up (9.3 years [0.005, 15.5]). For analyses of death from all causes, participants with missing covariates (n=26) were excluded and the available sample size was 3,333. There were 385 deaths during follow-up (9.3 years [0.3, 14.1]).

Table 2 displays the relations of SDF-1 levels (quartiles and continuous measures) to clinical outcomes. In age- and sex- adjusted analyses (Model 1), a one standard deviation increment in SDF-1 was associated with incident atherosclerotic CVD (hazards ratio [HR] 1.2, 95% confidence interval [CI] 1.1–1.4; $p=0.009$), MI (HR 1.3, 95% CI 1.1–1.6; $p=0.009$), HF (HR 1.4, 95% CI 1.1–1.6; $p=0.0012$), and death from all causes (HR 1.2, 95% CI 1.1–1.4; $p=0.0001$).

After additionally adjusting for clinical covariates (Model 2), SDF-1 remained associated with HF and death from all causes ($p<0.05$), but not with atherosclerotic CVD or MI. However, when HDL cholesterol was excluded from the multivariable model, SDF-1 was associated with MI (HR = 1.3, 95% CI 1.0–1.5; $p=0.02$). When additionally adjusting for BNP level (Model 3), SDF-1 remained associated with death from all causes. A Kaplan-Meier plot of survival as a function of baseline SDF-1 quartile is displayed in Figure 1.

In secondary analyses we explored the association of SDF-1 with cause-specific mortality (CVD deaths [n=110], cancer deaths [n=199], and deaths from other or unknown causes [n=176]; Supplemental Table II). In risk factor adjusted models, SDF-1 was associated with CVD death ($p=0.02$) and other or unknown causes of death ($p=0.003$), but not with cancer death ($p=0.22$).

SDF-1 levels and LTL

Of the 1185 individuals who had LTL data, the mean telomere length was 6.9 kilobase pairs (kbp) in men and 7.0 kbp in women. There was no statistically significant association between SDF-1 and LTL (Table 3).

SDF-1 and CD34+ cell phenotypes

We examined natural log-transformed CD34+ cell numbers (n=1579) in relation to SDF-1 levels. CD34+ frequency was associated with higher SDF-1 levels in both age- and sex-adjusted and multivariable adjusted models (p=0.02 for one standard deviation increment in SDF-1, Table 4). The association of SDF-1 with CD34+ cells remained statistically significant after adjustment for clinical covariates (p=0.02)

Discussion

Based on GWAS results linking the *CXCL12*-*CXCR4* axis to CAD [2–4] and LTL [5], we explored the relations of plasma SDF-1, the protein coded by *CXCL12*, to CVD outcomes and CVD risk factors. Additionally, we examined LTL and CD34+ cell frequency as intermediate phenotypes.[9] Our findings are three-fold. First, SDF-1 levels were associated with several CVD risk factors. Second, higher SDF-1 levels were associated with HF (continuous model adjusted for clinical HF risk factors, p= 0.03) and all-cause mortality (continuous model adjusted for risk factors, p=0.003), but not with atherosclerotic CVD. Finally, SDF-1 levels were associated with CD34+ cell frequency (continuous model adjusted for CVD risk factors, p=0.02), but not with LTL.

Extensive phenotypic data from the FHS allowed us to investigate the relations of SDF-1 to several CVD risk factors in a large sample size of 3359 individuals. In multivariable adjusted models, we found that SDF-1 levels were associated with age, smoking status, and HDL cholesterol (Supplemental Table I). Prior studies have reported similar associations between plasma SDF-1 and clinical CVD risk factors.[14, 15]

To further explore the association of SDF-1 with CVD, we analyzed the association of SDF-1 with MI and found that SDF-1 was associated with MI when HDL cholesterol was not included as a covariate in the multivariable model, (p=0.02), however, that association was attenuated when HDL cholesterol was included as a covariate (Supplemental Table II). Thus, we conclude that the (inverse) association of SDF-1 with HDL cholesterol is partly responsible for the attenuation of the association of SDF-1 with MI. Analyses of cause-specific mortality revealed that SDF-1 levels were associated to deaths due to CVD (p=0.02) and deaths from other or unknown causes (p=0.003), but not with cancer deaths (Supplemental Table II).

Single nucleotide polymorphisms (SNPs) rs501120 and rs1746048 at the *CXCL12* locus that were previously reported to be associated with MI/CAD [2, 4, 16] were found to be associated with increased SDF-1 levels in our Framingham participants (p-value ≤0.0005 in age- and sex-adjusted models; Supplemental Table III). These findings are consistent with the PennCath Study that found a similar effect size and directionality between rs1746048 and CAD/MI,[17] and the Bruneck Study that found an association between rs1746048 and

carotid intimal-medial thickness.[18] While the literature and our preliminary data suggest that the rs1746048-C allele is associated with higher SDF-1 levels, inferences linking the SDF-1 risk allele to atherogenesis should be made with caution.

We found that SDF-1 levels were associated with risk of HF and death. Higher SDF-1 levels were associated with a 20% increase in risk of new-onset HF (HR per one standard deviation increment in ln(SDF-1)=1.2, 95% CI [1.0–1.5]; p=0.03]) after adjusting for HF clinical risk factors; this association was attenuated after adjusting for plasma BNP levels. We also found an association of SDF-1 levels with all-cause mortality (HR per one SD increment = 1.2, 95% CI [1.1–1.3], p=0.003 after adjusting for clinical covariates). The association between SDF-1 and all-cause mortality in the general population is novel.

A recent prospective study by Mehta et al reported an association of SDF-1 with incident MI, and death in a kidney disease cohort. Our results for MI and HF complement their findings. Of note, as was the case in our analyses, Metha et al found an association between SDF-1 and MI in a model that did not adjust for HDL.[15] Additionally, an investigation from the Diabetes Heart Study found an association of rs1746048 at the *CXCL12* locus with all-cause mortality in people with type 2 diabetes mellitus.[19]

We found that plasma SDF-1 was associated with reduced frequency of CD34+ cell phenotypes, an association that persisted after adjusting for CVD risk factors. This inverse relationship contrasts with mouse models that suggest a direct association between SDF-1 and CD34+, a circulating cell marker associated with progenitor cell activity. Previous studies have found that SDF-1 binds to the CXCR4 receptor found on CD34+ cells and directs CD34+ cell release from the bone marrow.[20] The release of CD34+ cells aids in neovascularization and angiogenesis, processes that may mediate tissue healing in the context of CVD.[13] Our findings are consistent with population-based studies that have shown that CD34+ frequency is inversely related to CVD-risk factors (age and smoking status) and a higher Framingham Risk Score.[21]

Several lines of evidence implicate an association of SDF-1 with HDL cholesterol, and we therefore hypothesize that HDL cholesterol modulates the *CXCL12-CXCR4* axis. HDL cholesterol was significantly ($p<0.0001$) associated with SDF-1 levels in our multivariable model. Additionally, HDL cholesterol was the major covariate that attenuated the association of SDF-1 with MI. Of note, a GWAS of HDL cholesterol identified a suggestive signal for rs768676 ($p=4.3\times10-6$) located near *CXCL12*.[22] Although these merging lines of evidence are highly speculative, the relationship of SDF-1 to HDL cholesterol warrants further exploration.

Our study has several limitations. We measured SDF-1 levels at one time point. Evidence suggests that there is acute modulation of SDF-1 levels in humans.[23] The number of incident atherosclerotic CVD and HF events in our analyses was modest, thereby limiting our power. Our study was restricted to a predominantly white, middle-aged sample; thus, our ability to generalize our findings to other groups is limited. Last, the association of SDF-1 with mortality and HF warrants replication in other studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
EPC	Endothelial progenitor cell
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HF	Heart failure
LTL	Leukocyte telomere length
MI	Myocardial infarction
SDF-1	Stromal cell-derived factor 1 alpha

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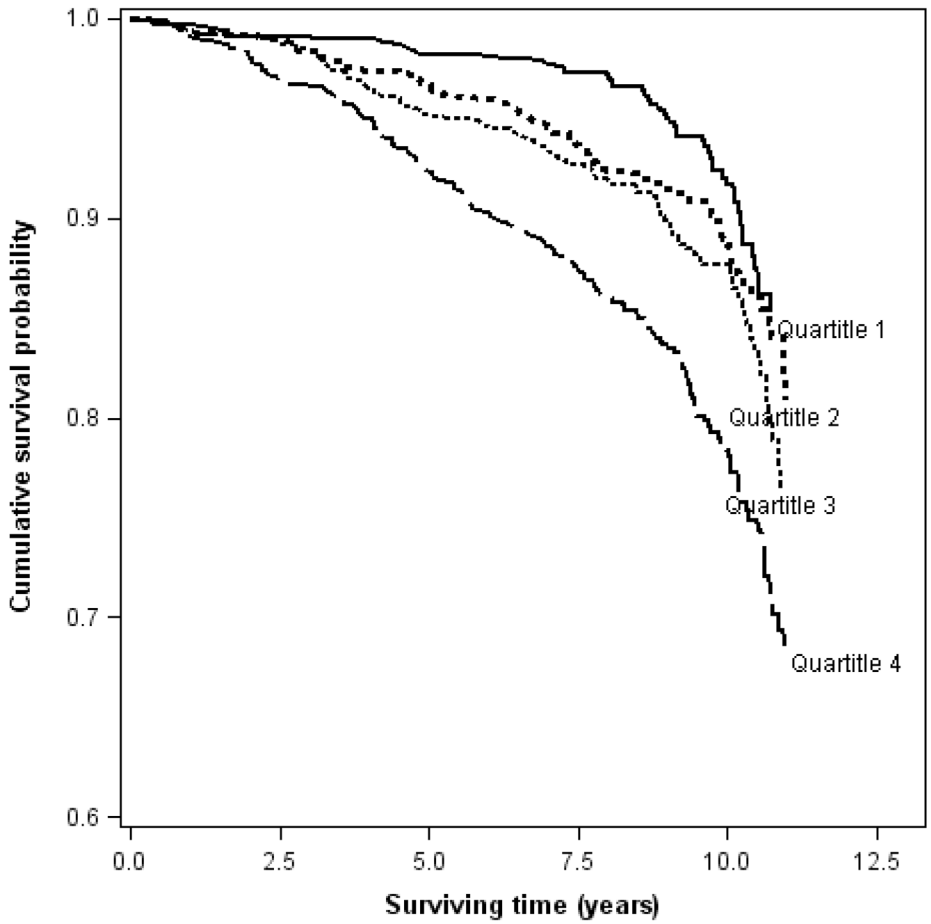
platelets is increased in patients with acute coronary syndrome and correlates with the number of CD34+ progenitor cells. Eur Heart J. 2009; 30:584–593. [PubMed: 19109356]

Significance

We report an association of higher plasma SDF-1 levels with risk of HF and mortality. We found no association of SDF-1 levels with risk of atherosclerotic CVD after adjusting for CVD risk factors. SDF-1 was associated with several CVD risk factors, most notably HDL cholesterol. We explored several intermediate phenotypes and found that higher SDF-1 levels were associated with reduced CD34+ cell frequency. We speculate that HDL cholesterol may mediate the association between SDF-1 and MI. Molecular studies may be helpful to evaluate the role of HDL cholesterol in these associations. Additional population-based studies are needed to validate the associations of SDF-1 with HF and mortality.



	Individuals Alive		
Quartile	0 years	5 years	10 years
1	806	713	239
2	882	786	270
3	809	707	240
4	836	707	232

Figure 1.

10-year survival according to quartile of plasma SDF-1. Kaplan-Meier survival plots are unadjusted for covariates. A log-rank test of survival across quartiles of SDF-1 is highly significant ($p<0.001$).

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Table 1

Unadjusted baseline characteristics according to quartiles of SDF-1 levels

		SDF-1 Quartiles					
		Quartile 1 (n=810)	**Quartile 2 (n=889)**	**Quartile 3 (n=815)**	**Quartile 4 (n=843)**	**p-value per quartile increment in ln(SDF-1)†**	**p-value per 1 SD increment in ln(SDF-1)**
Mean SDF-1 [range] (pg/mL)*		1330 [742–1518]	1676 [1539–1818]	1973 [1839–2135]	2588 [2156–5980]		
Age (years)	mean (SD)	56 (9)	58 (9)	60 (10)	63 (10)	<0.0001	< 0.0001
Women	n (%)	457 (56)	436 (49)	441 (54)	441 (52)	0.36	0.075
BMI (kg/m2)	mean(SD)	28 (5)	28 (5)	28 (5)	28 (5)	0.28	0.71
Waist circumference (cm)	mean (SD)	38 (5)	38 (5)	39 (5)	38 (5)	0.97	0.37
Total cholesterol (mg/dl)	mean (SD)	205 (38)	205 (36)	206 (38)	207 (49)	0.31	0.70
HDL cholesterol (mg/dl)	mean (SD)	54 (16)	52 (16.3)	50 (16)	48 (16)	<0.0001	< 0.0001
LDL cholesterol (mg/dl)	mean (SD)	124 (35)	127 (32)	127 (34)	129 (39)	0.012	0.008
Triglycerides (mg/dl)	mean (SD)	135 (93)	135 (88)	144 (111)	152 (210)	0.0035	0.008
Systolic blood pressure (mmHg)	mean (SD)	127 (19)	127 (18)	130 (19)	130 (19)	0.0001	< 0.0001
Diastolic blood pressure (mmHg)	mean (SD)	76 (9)	75 (9)	76 (10)	74 (10)	0.0001	< 0.0001
Glucose (mg/dl)	mean (SD)	103 (26)	103 (25)	103 (25)	107 (31)	0.006	0.0002
BNP	mean (SD)	11 (18)	14 (17)	16 (20)	26 (36)	<0.0001	< 0.0001
Smoking status (current)	n (%)	111 (14)	141 (16)	122 (15)	134 (16)	0.32	0.63
CVD	n (%)	22 (3)	35 (4)	42 (5)	69 (8)	<0.0001	< 0.0001
Diabetes (yes)	n (%)	69 (9)	72 (8)	74 (9)	116 (14)	0.0003	< 0.0001
Hypertension treatment (yes)	n (%)	301 (37)	334 (38)	377 (46)	379(45)	<0.0001	< 0.0001
Statin treatment	n (%)	81 (0.1)	89 (0.1)	82 (0.1)	84 (0.1)	0.17	0.10

*Ln(SDF-1) range: Q1 [6.61–7.33]; Q2 [7.33–7.52]; Q3[7.52–7.67]; Q4 [7.67–8.69]

†Values are unadjusted (single variable analysis)

‡1 standard deviation of ln(SDF-1): 0.26

Table 2

Risk for new-onset atherosclerotic cardiovascular disease, myocardial infarction, heart failure, or all-cause mortality according to levels of SDF-1

	Ln (SDF-1) quartiles					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Per quartile increment in ln(SDF-1)	Per 1 SD increment in ln(SDF-1)
	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI] (p-value)	HR [95% CI] (p-value[§])
Cardiovascular disease (CVD), n=263						
Model 1	Referent	1.0 [0.69–1.6]	1.2 [0.77–1.8]	1.3 [0.89–2.1]	1.1 [1.0–1.3] (0.10)	1.2 [1.1–1.4] (0.009)
Model 2[*]	Referent	1.0 [0.68–1.6]	1.1 [0.74–1.7]	1.1 [0.68–1.7]	1.0 [0.90–1.2] (0.70)	1.1 [0.9–1.2] (0.39)
Model 3	Referent	1.0 [0.68–1.6]	1.1 [0.73–1.7]	1.1 [0.64–1.6]	1.0 [0.90–1.20] (0.90)	1.1 [0.9–1.3] (0.31)
Myocardial Infarction (MI), n=160						
Model 1	Referent	1.1 [0.61–1.9]	1.1 [0.63–1.9]	1.7 [1.0–2.9]	1.2 [1.0–1.4] (0.03)	1.3 [1.1–1.6] (0.009)
Model 2[*]	Referent	1.0 [0.57–1.7]	1.0 [0.59–1.8]	1.4 [0.80–2.5]	1.1 [0.9–1.4] (0.20)	1.1 [0.9–1.2] (0.10)
Model 3	Referent	1.0 [0.57–1.7]	1.0 [0.59–1.8]	1.4 [0.78–2.4]	1.1 [0.9–1.3] (0.40)	1.1 [0.9–1.3] (0.31)
Heart failure (HF), n=200						
Model 1	Referent	1.1 [0.64–1.9]	1.4[0.84–2.4]	1.9[1.1–3.1]	1.2 [1.0–1.50] (0.006)	1.4 [1.1–1.6] (0.0012)
Model 2[†]	Referent	1.1 [0.65–1.9]	1.4[0.83–2.4]	1.6 [0.92–2.6]	1.2 [1.0–1.40] (0.06)	1.2 [1.0–1.5] (0.04)
Model 3	Referent	1.0 [0.62–1.7]	1.2[0.72–2.1]	1.1 [0.66–1.9]	1.0 [0.90–1.20] (0.60)	1.1 [0.9–1.3] (0.27)
Death from all causes, n=385						
Model 1	Referent	1.3 [0.96–1.8]	1.4 [1.0–2.0]	1.6 [1.1–2.2]	1.1 [1.0–1.2] (0.007)	1.2 [1.1–1.4] (0.0001)
Model 2[‡]	Referent	1.3 [0.91–1.7]	1.4 [1.0–1.9]	1.4 [1.0–1.9]	1.1 [1.0–1.2] (0.04)	1.2 [1.1–1.3] (0.003)
Model 3	Referent	1.2 [0.91–1.7]	1.4 [1.0–1.9]	1.3 [0.9–1.8]	1.1 [1.0–1.2] (0.10)	1.2 [1.0–1.3] (0.02)

Model 1: Adjusted for age and sex

[*] Model 2: Adjusted for age, sex, systolic blood pressure, hypertension treatment, total cholesterol, HDL, diabetes, smoking status, statin use. After excluding HDL from Model 2, the HR [95% CI] per 1 SD increment in ln(SDF-1) did not change for CVD, and the p-value was insignificant (p=0.11). For MI, exclusion of HDL from Model 2 had a HR= 1.2 [1.0–1.5] and p-value = 0.020.

[†] Model 2: Adjusted for age, sex, systolic blood pressure, hypertension treatment, HDL, BMI, diabetes, smoking status, atrial fibrillation, coronary heart disease, valvular heart disease

[‡] Model 2: Adjusted for age, sex, systolic blood pressure, hypertension treatment, total cholesterol, HDL, diabetes, smoking status, angina, atherosclerotic CVD, and HF

Model 3: Adjusted for respective Model 2 outcome+ BNP

[§] 1 standard deviation of ln(SDF-1): 0.26

[||] P-value for the association of ln(SDF-1) as a continuous variable with clinical outcomes

Table 3

Leukocyte telomere length according to SDF-1 quartiles

Ln (SDF-1) quartiles	Quartile 1* (n=270)	Quartile 2* (n=325)	Quartile 3* (n=295)	Quartile 4* (n=295)	p-value per quartile increment in ln(SDF-1)	p-value† per 1 SD‡ increment in ln(SDF-1)
Leukocyte telomere length, LTL (kbps)						
Model 1	7.0 (0.03)	7.0 (0.03)	7.0 (0.03)	6.9 (0.03)	0.20	0.18
Model 2	7.0 (0.03)	7.0 (0.03)	7.0 (0.03)	7.0 (0.03)	0.40	0.37

*Values reflect least square means (standard error)

†P-value for the association of ln(SDF-1) as a continuous variable with LTL

‡1 standard deviation of ln(SDF-1): 0.26

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, BMI, total cholesterol/HDL cholesterol ratio, smoking status, diabetes, systolic blood pressure, hypertension treatment

Table 4

CD34+ frequency according to SDF-1 quartiles

Ln(SDF-1) quartiles	Quartile 1* (n=424)	Quartile 2* (n=438)	Quartile 3* (n=383)	Quartile 4* (n=358)	p-value per quartile increment in ln(SDF-1)	p-value† per 1 SD‡ increment in ln(SDF-1)
CD 34+ (% of CD34+ cells in peripheral blood excluding red blood cells, platelets and cell debris) [95% CI]						
Model 1	0.081 (0.077–0.085)	0.076 (0.073–0.080)	0.075 (0.070–0.079)	0.073 (0.069–0.077)	0.01	0.02
Model 2	0.080 (0.076–0.084)	0.076 (0.073–0.080)	0.074 (0.071–0.078)	0.073 (0.069–0.077)	0.01	0.02

*Values reflect least square means (standard error)

†P-value for the association of ln(SDF-1) as a continuous variable with CD34+

‡1 standard deviation of ln(SDF-1): 0.26

Model 1: Adjusted for age and sex

Model 2: Adjusted for age, sex, BMI, total cholesterol/HDL cholesterol ratio, smoking status, diabetes, systolic blood pressure, hypertension treatment