Atorvastatin reduces serum cholesterol and triglycerides with limited improvement in vascular function in adults with sickle cell anemia

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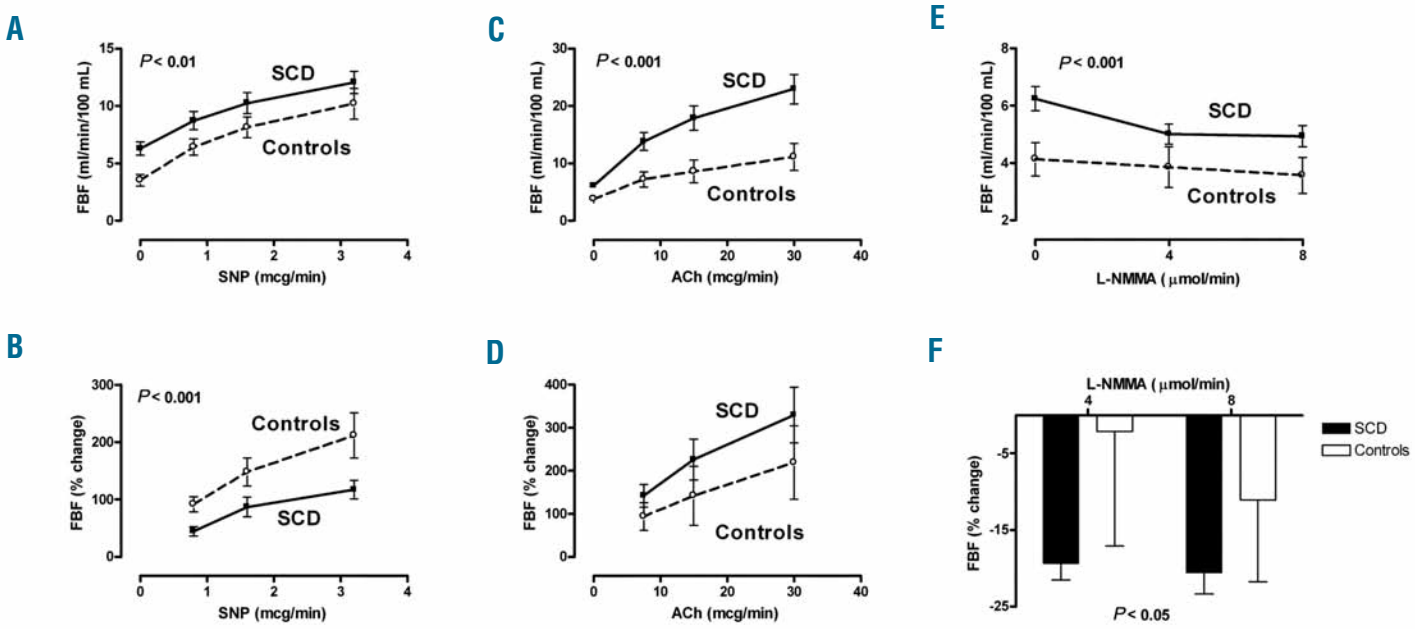
Online Supplementary Table S1. Characteristics of sickle cell anemia (SCA) and control subjects.

		SCA (n=25)		Control (n=10)		
Variable	Units	Mean	SD	Mean	SD	*P*
Age	years	36.7	9.6	35.9	8.5	0.82
Females	fraction	0.56		0.40		0.47
Hydroxyurea treatment	fraction	0.68		n/a		n/a
Hydroxyurea dose	mg	1395	773	n/a		n/a
Tricuspid regurgitant velocity	m/s	2.5	0.3	nd		nd
NT-proBNP	pg/mL	98	116	29	33	0.09
C-reactive protein	mg/L	0.83	0.89	0.37	0.38	0.14
Creatinine	mmol/L	58	24	78	13	0.02
Urea	mmol/L	2.5	1.6	3.2	0.9	0.18
Alkaline phosphatase	IU/L	90	44	2	0	0.04
Alanine aminotransferase	IU/L	24	9	23	4	0.55
Aspartate aminotransferase	IU/L	43	18	1	0	<0.001
Lactate dehydrogenase	IU/L	357	137	147	24	<0.001
Total bilirubin	mmol/L	60	38	11	3	<0.001
Direct bilirubin	mmol/L	8.2	5.8	2.4	0.9	<0.001
Leukocytes	10^9/L	9.5	3.9	4.9	1.4	0.008
Hemoglobin	g/L	84	16	132	16	<0.001
Mean corpuscular hemoglobin	fL	99	15	87	8	<0.001
Platelets	10^9/L	308	162	251	69	<0.001
Reticulocytes	10^9/L	233	117	54	15	<0.001
Fetal hemoglobin	fraction	0.106	0.069	0.003	0.005	<0.001
Sickle hemoglobin	fraction	0.803	0.078	0.000	0.000	<0.001
Hemoglobin A	fraction	0.036	0.056	0.967	0.006	<0.001

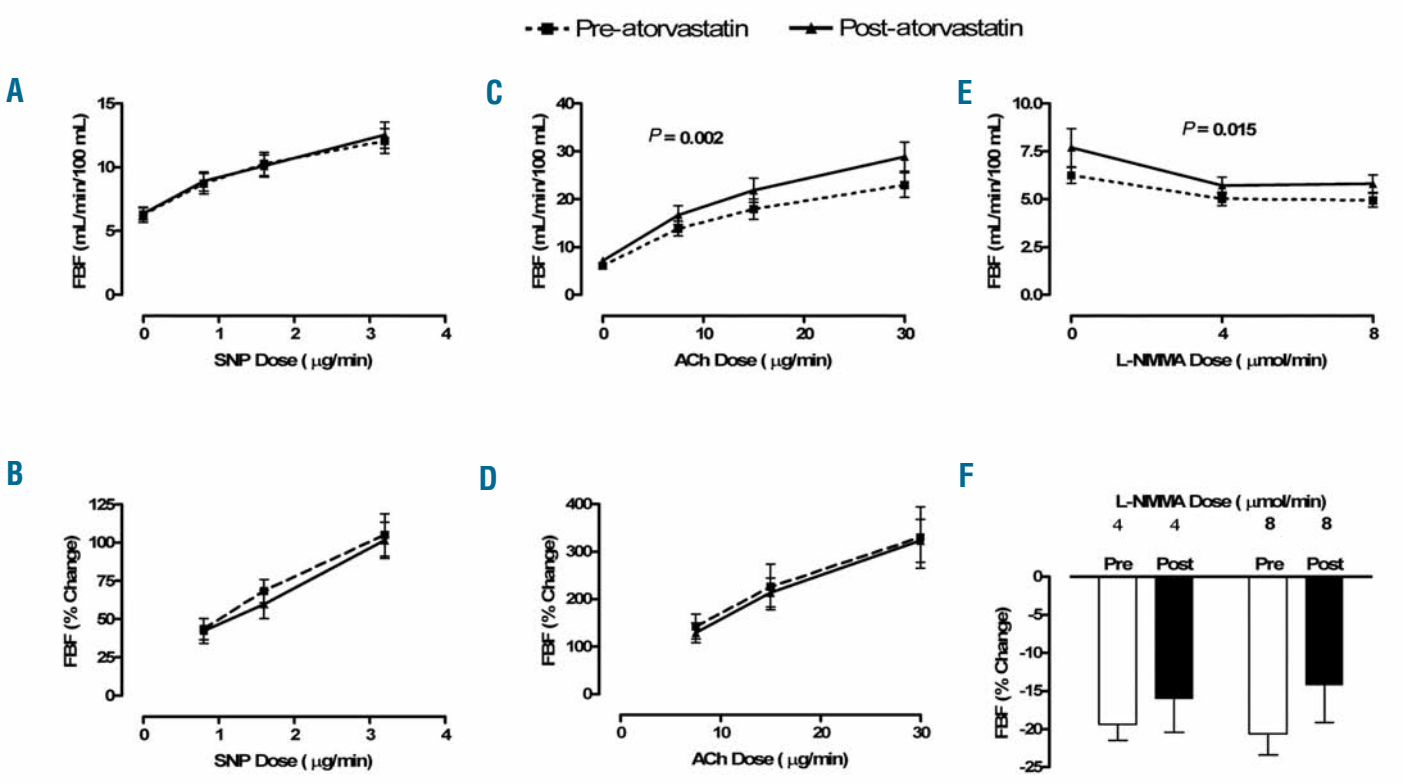
SCA: sickle cell anemia; NT-proBNP: amino terminal pro-brain natriuretic hormone; SD: standard deviation; n/a: not applicable; nd: not done. Statistical significance calculated by unpaired t-test or Fisher's exact test as appropriate.

Online Supplementary Table S2. Selected laboratory markers before and following atorvastatin therapy. Values indicate median and interquartile ratios, with significance tested by Kruskal-Wallis test.

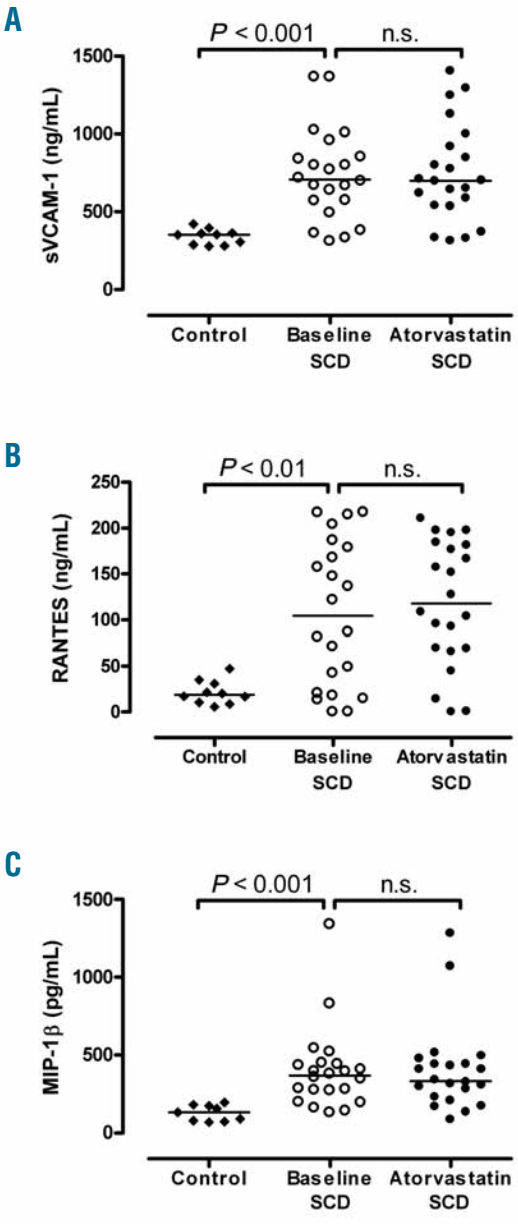
Marker	Baseline	Atorvastatin 10 mg	Atorvastatin 20 mg	*P*
Tricuspid regurgitant velocity (m/sec)	2.4 (2.3, 2.7)	2.5 (2.3, 2.7)	2.5 (2.3, 2.7)	0.8
Urinary microalbumin (mg/L)	18 (7, 122)	13 (4, 72)	9 (3, 45)	0.6
NT-proBNP (pg/mL)	60 (15, 95)	76 (28, 129)	64 (38, 110)	0.8
C-reactive protein (mg/L)	6 (4, 9)	5 (2, 8)	5 (2, 9)	0.7



Online Supplementary Figure S1. Altered vascular responsiveness in subjects with sickle cell disease. Prior to initiation of atorvastatin therapy, vasodilatory responses to brachial artery infusions of sodium nitroprusside (SNP), acetylcholine (ACh) and L-NG-monomethylarginine (L-NMMA) were measured by venous occlusion strain gauge plethysmography. Results are presented both in terms of absolute blood flow (A, C, E) and percentage change from baseline (B, D, F). Sickle cell subjects (n=25) showed lower relative responsiveness than African-American controls of comparable age (n=10) to the NO donor SNP (B), although on average hyperresponsiveness to ACh (C, D). The control group included 3 subjects with atypically low responsiveness to L-NMMA (F). Data points represent mean values and error bars indicate the standard error of the mean. Significance was tested by two-way analysis of the variance of the mean with repeated measures (A-E), or paired t-test (F).



Online Supplementary Figure S2. Effect of atorvastatin on vascular function in sickle cell anemia. Vasodilatory responses to brachial artery infusions of sodium nitroprusside (SNP), acetylcholine (ACh) and L-NG-monomethylarginine (L-NMMA) were measured by venous occlusion strain gauge plethysmography before and after four weeks of atorvastatin administration. Results are presented both in terms of absolute blood flow (A, C, E) and percentage change from baseline (B, D, F). Compared to the pre-study baseline forearm blood flow values, vascular responsiveness to SNP was unchanged by atorvastatin (A, B), but absolute blood flow response to ACh increased by a modest but significant degree, an effect that persisted during L-NMMA infusion (C). Data points represent mean values and error bars indicate the standard error of the mean. Significance was tested by two-way analysis of the variance of the mean with repeated measures (A-E), or paired t-test (F).



Online Supplementary Figure S3. Markers of endothelial and monocyte activation in SCD and controls. Plasma levels were significantly higher in SCD subjects (n=22) than healthy African-American control subjects (n=9) at baseline for (A) soluble vascular cell adhesion molecule-1 (sVCAM-1, $P<0.001$, unpaired t-test); (B) monocyte chemokines RANTES ($P=0.002$, unpaired t-test); and (C) macrophage inflammatory protein 1β (MIP-1β, $P<0.001$, Mann-Whitney test). Following the 4-week course of atorvastatin in the SCD subjects, no significant changes were observed in these three variables ($P>0.05$, Wilcoxon's matched-pairs signed rank test or unpaired t-test).