SUPPLEMENTARY MATERIALS AND METHODS

Study population

Patients with a diagnosis of psoriasis without clinical cardiovascular disease were recruited as part of a randomized single-center open-label clinical trial (ClinicalTrials.gov: NCT03228017, entitled "subclinical cardiovascular disease in psoriatic disease," registration date 24 July 2017) to investigate the impact of aspirin and atorvastatin (2:1) on vascular endothelial health in psoriasis. Briefly, subjects with psoriasis were recruited from a single-center—New York University Langone Health dermatology, phototherapy, and psoriatic arthritis specialty clinics—between September 2017 and April 2019 (Garshick et al., 2019, 2020, 2021) with methodology previously reported (Garshick et al., 2019). Relevant inclusion criteria included ≥1% body surface area of psoriasis or psoriatic arthritis and ≥1 swollen/tender joint (consort diagram, Supplementary Figure S1), whereas exclusion criteria included those with a recent (<1 month before study enrollment) change or planned change in psoriasis therapy. The study protocol was approved by the New York University School of Medicine Institutional Review Board (i17-00692). All subjects provided written informed consent before participation, in line with the Declaration of Helsinki protocols, which were followed.

General study protocol

Fasting (>4 hours) participants with psoriasis underwent medical history, blood pressure, heart rate, anthropometrics, and peripheral blood collection, all done with established protocols (Kurtz et al., 2005; Pickering et al., 2005). As previously described (Jelic et al., 2010), a 20-gauge angiocatheter was then inserted into the brachial forearm, and three J-shaped endovascular guidewires (Teleflex, Reading, PA) were advanced into the brachial vein, removed, washed in endothelial dissociation buffer solution, and kept at 4 °C until further processing (Garshick et al., 2019).

Assignment, participant flow, and follow-up

After baseline assessment, participants with psoriasis were assigned using a random number (SAS Institute Inc, 2015) generator to 40 mg atorvastatin per day or to no treatment (Supplementary Figure S1). A repeat visit and full assessment occurred at week 2. The primary study endpoint and outcome measure were a change in the composite brachial vein endothelial cell inflammatory transcriptome, defined as the mean of the combined expression values from all assessed endothelial cell proinflammatory transcripts (mean expression of proinflammatory vascular endothelial transcript (composite transcript expression of *LTB, CCL3, CX3CL1, CCL2, CXCL1, ICAM1, IL-8, IL-1B, COX-2*) (Garshick et al., 2020).

Masking

All sample processing and post-sample analyses were performed blind to study assignment. No subjects experienced adverse outcomes over the 2-week time period, nor were any lost to follow-up.

Analysis, sample processing, and endothelial harvesting and isolation

Lipid profiles, high-sensitivity C-reactive protein, and complete blood count were performed at the New York University clinical laboratory (Abbott Architect System [Abbott Park, IL] and Sysmex XN-1000 PR Automated Hematology Analyzer [Kobe, Japan]). Serum proteins were measured through the commercially available Olink Proteomics platform, and values were expressed as a Normalized Protein eXpression (on a $\log_2$ scale) (Kim et al., 2018). Brachial vein endothelial cells were isolated using magnetic beads coated with CD146 antibody. Endothelial cells underwent mRNA extraction, cDNA conversion, and preamplification (Emin et al., 2016; Garshick et al., 2019). Transcripts of interest using TaqMan (Life Technologies, Carlsbad, CA) probes and primers were assessed by real-time quantitative polymerase chain reaction on an Applied Biosystems (Foster City, CA) 7500 Fast Real-Time PCR System. Any transcript with a cycle count >34 was considered to be 0 expressions. To ensure reproducibility across analyses, results were normalized to hARP for each sample and gene (Guttman-Yassky et al., 2008). Samples whose reference gene (either *hARP* or β-actin) expression was >2 SDs from the mean were deemed inadequate and were excluded.

Statistical analysis

For sample size determination, this project was intended as a pilot to explore the vascular endothelial transcriptomic changes after statin therapy compared with vascular endothelial transcript changes that occurred over time in untreated psoriatic disease. We estimated that 10 subjects (control) and 20 subjects (treatment) per group would provide a margin of error (95% confidence interval half width) of 0.13 (assuming an SD of 0.16) for the $\log_2$ fold change in vascular inflammation between treatment groups (Garshick et al., 2020; Kianifard and Islam, 2011) (nQuery, 2017, Statistical Solutions, Cork, Ireland).

Data are reported as mean ± SEM or SD where appropriate. Non-normally distributed data are reported as the median and interquartile range (first quartile, third quartile). Statistical significance was determined with Spearman's test for correlations and between study groups using parametric and nonparametric tests as appropriate. Log transformation with paired sample *t*-test or Wilcoxon test for changes between baseline and follow-up data points were also performed as appropriate. Statistical significance was determined using a two-tailed $\alpha < 0.05$, with all analyses performed in Stata, version 14 (StataCorp LP, College Station, TX).

SUPPLEMENTARY REFERENCES

Emin M, Wang G, Castagna F, Rodriguez-Lopez J, Wahab R, Wang J, et al. Increased internalization of complement inhibitor CD59 may contribute to endothelial inflammation in obstructive sleep apnea. Sci Transl Med 2016;8. 320ra321.

Garshick MS, Barrett TJ, Wechter T, Azarchi S, Scher JU, Neimann A, et al. Inflammasome signaling and impaired vascular halth in psoriasis. Arterioscler Thromb Vasc Biol 2019;39: 787—98.

Garshick MS, Tawil M, Barrett TJ, Salud-Gnilo CM, Eppler M, Lee A, et al. Activated platelets induce endothelial cell inflammatory response in psoriasis via COX-1. Arterioscler Thromb Vasc Biol 2020;40:1340—51.

Garshick MS, Baumer Y, Dey AK, Grattan R, Ng Q, Teague HL, et al. Characterization of PCSK9 in the blood and skin of psoriasis. J Invest Dermatol 2021;141:308—15.

Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Zaba LC, Cardinale I, Nograles KE, et al. Low expression of the IL-23/Th17 pathway in atopic dermatitis compared to psoriasis. J Immunol 2008;181:7420—7.

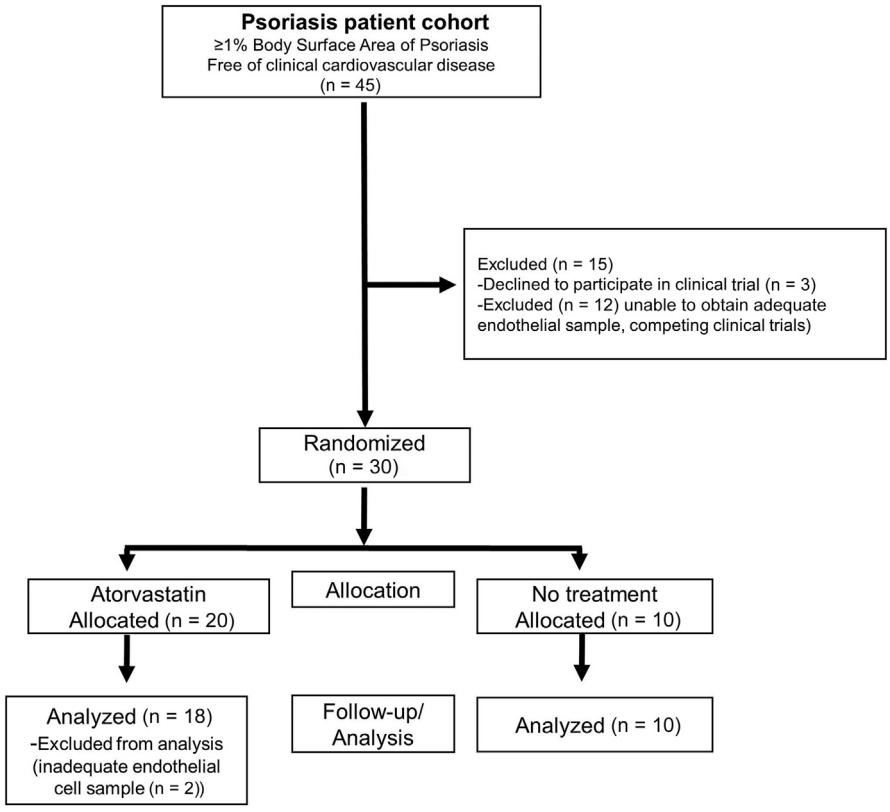
Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, et al. Vascular inflammation in obesity and sleep apnea. Circulation 2010;121:1014–21.

Kianifard F, Islam MZ. A guide to the design and analysis of small clinical studies. Pharm Stat 2011;10:363–8.

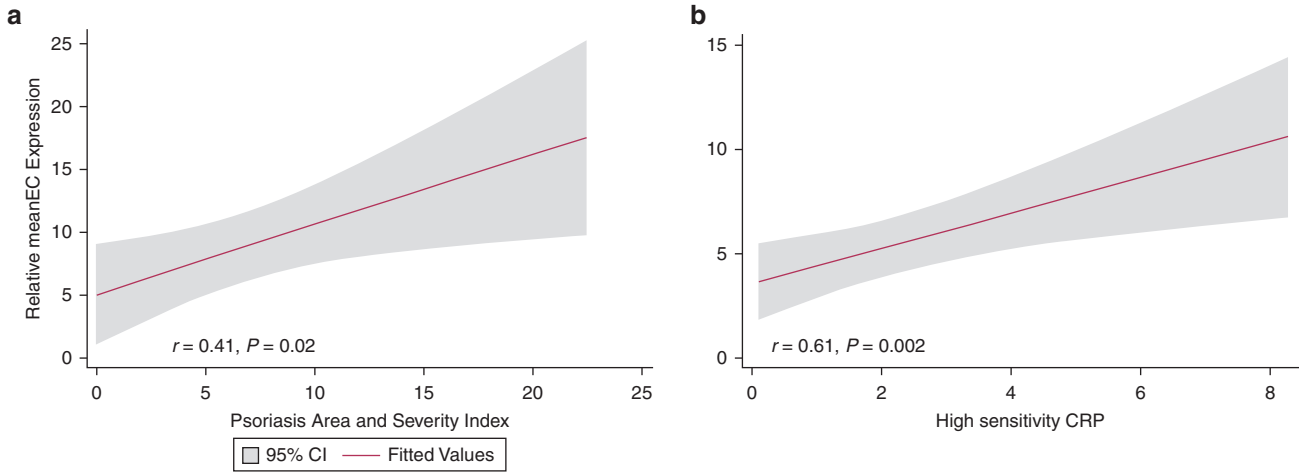
Kim J, Tomalin L, Lee J, Fitz LJ, Berstein G, Correa-da Rosa J, et al. Reduction of inflammatory and cardiovascular proteins in the blood of patients with psoriasis: differential responses between tofacitinib and etanercept after 4 weeks of treatment. J Invest Dermatol 2018;138:273–81.

Kurtz TW, Griffin KA, Bidani AK, Davisson RL, Hall JE; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: part 2: blood pressure measurement in experimental animals: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Arterioscler Thromb Vasc Biol 2005;25:e22–33.

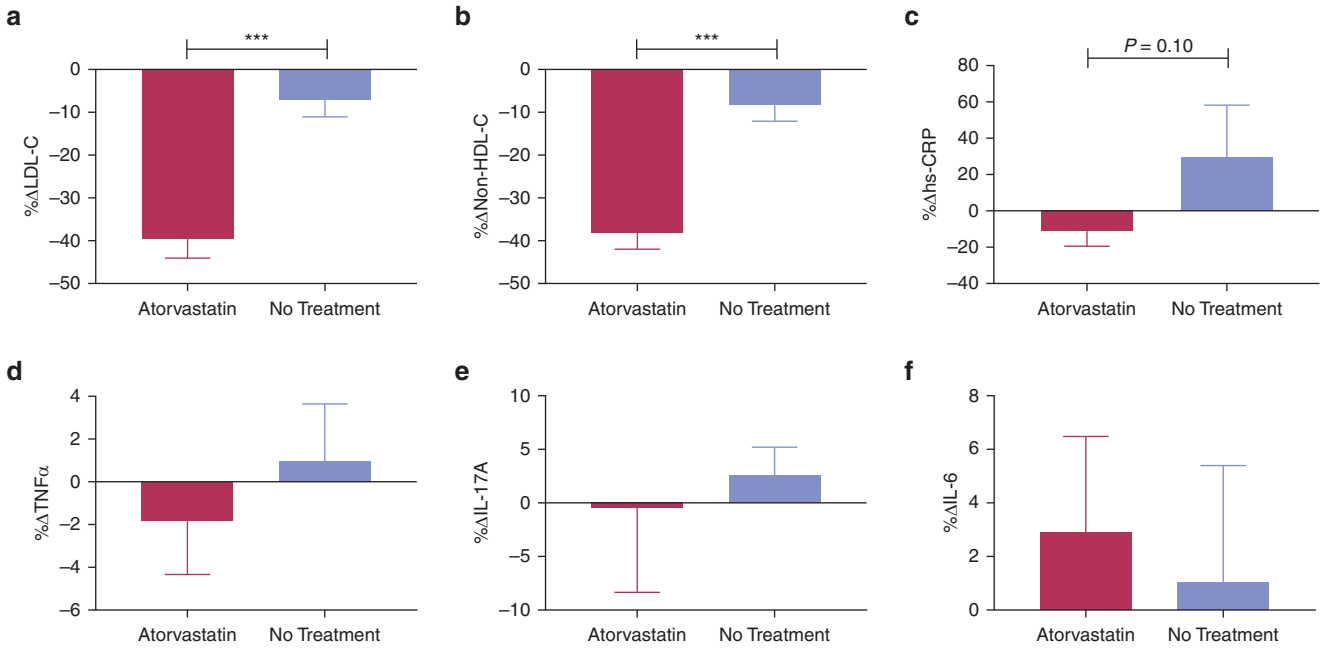
Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for blood pressure measurement in humans and experimental animals. Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Circulation 2005;111:697–716.



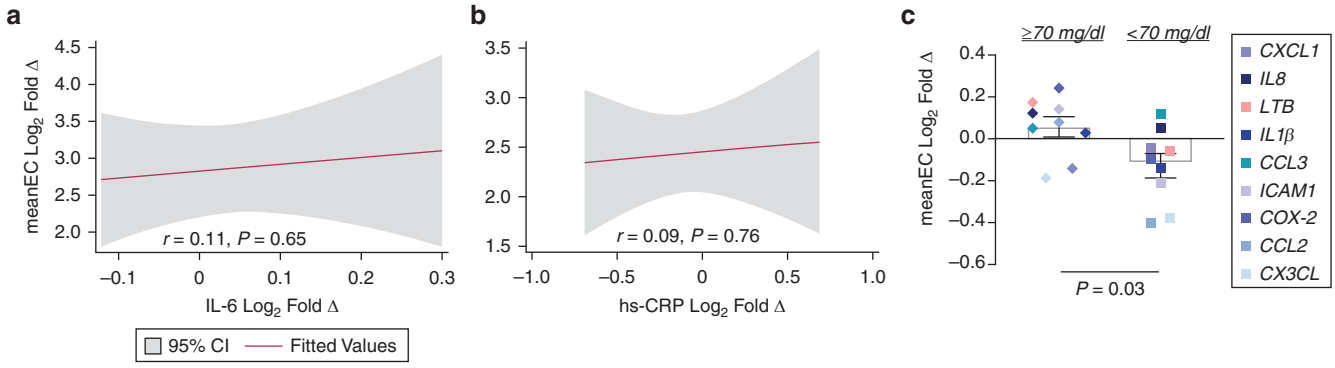
Supplementary Figure S1. Consort flowchart of patients enrolled in a randomized clinical trial of atorvastatin therapy compared with those in no treatment to improve vascular health in psoriasis.



Supplementary Figure S2. Regression plot assessing the correlation between psoriasis severity and vascular endothelial inflammation. meanEC indicates the composite transcript expression of *LTB, CCL3, CX3CL1, CCL2, CXCL1, ICAM1, IL-8, IL-1B, COX-2*. CI, confidence interval; meanEC, mean expression of proinflammatory vascular endothelial transcript.



Supplementary Figure S3. Change in lipid and inflammatory paramters in statin and control psoriasis subjects. Change in lipid (**a, b**) parameters, (**c**) hs-CRP, (**d**) TNF-α, (**e**) IL-17A, and (**f**) IL-6 values after 2 weeks of atorvastatin or no treatment. ***$P < 0.0001$. HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.



Supplementary Figure S4. A 2-week lipid-lowering therapy with atorvastatin reduces vascular endothelial inflammation, which is dependent on the degree of LDL-C reduction. Correlation in the composite log_2 fold change in brachial vein endothelial inflammatory transcript expression in atorvastatin-treated patients and (**a**) IL-6 or (**b**) hs-CRP. (**c**) Composite log_2 fold change in brachial vein endothelial inflammatory transcript expression in atorvastatin-treated patients who achieved an LDL-C < 70 mg/dl (n = 13[1]) or did not (n = 5). [1]Two atorvastatin-treated patients with psoriasis did not have adequate follow-up brachial vein endothelial collection. MeanEC indicates the composite transcript expression of *LTB, CCL3, CX3CL1, CCL2, CXCL1, ICAM1, IL-8, IL-1B,* and *COX-2*. ***$P <$ 0.001. CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; meanEC, mean expression of proinflammatory vascular endothelial transcript.