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ORIGINAL RESEARCH

Racial Differences in the Effect of Granulocyte Macrophage Colony-Stimulating Factor on Improved Walking Distance in Peripheral Artery Disease: The PROPEL Randomized Clinical Trial

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***Background*—**The effects of race on response to medical therapy in people with peripheral artery disease (PAD) are unknown.

***Methods and Results*—**In the PROPEL (Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD) Trial, PAD participants were randomized to 1 of 4 groups for 6 months: supervised treadmill exercise+granulocyte-macrophage colony-stimulating factor (GM-CSF) (Group 1), exercise+placebo (Group 2), attention control+GM-CSF (Group 3), or attention control+placebo (Group 4). Change in 6-minute walk distance was measured at 12- and 26-week follow-up. In these exploratory analyses, groups receiving GM-CSF (Groups 1 and 3), placebo (Groups 2 and 4), exercise (Groups 1 and 2), and attention control (Groups 2 and 4) were combined, maximizing statistical power for studying the effects of race on response to interventions. Of 210 PAD participants, 141 (67%) were black and 64 (30%) were white. Among whites, GM-CSF improved 6-minute walk distance by +22.0 m (95% CI: −4.5, +48.5, *P*=0.103) at 12 weeks and +44.4 m (95% CI: +6.9, +82.0, *P*=0.020) at 26 weeks, compared with placebo. Among black participants, there was no effect of GM-CSF on 6-minute walk distance at 12-week (*P*=0.26) or 26-week (−5.0 m [−27.5, +17.5, *P*=0.66]) follow-up, compared with placebo. There was an interaction of race on the effect of GM-CSF on 6-minute walk change at 26-week follow-up (*P*=0.018). Exercise improved 6-minute walk distance in black (*P*=0.006) and white (*P*=0.034) participants without interaction.

***Conclusions*—**GM-CSF improved 6-minute walk distance in whites with PAD but had no effect in black participants. Further study is needed to confirm racial differences in GM-CSF efficacy in PAD.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01408901. **(*J Am Heart Assoc*. 2019;8: e011001. DOI: 10.1161/JAHA.118.011001.)**

Key Words: exercise training • peripheral artery disease • peripheral vasculature • stem cell

Black patients with lower extremity peripheral artery disease (PAD) present with more severe lower extremity atherosclerosis, have greater functional impairment, and have higher rates of mobility loss, compared with whites with PAD.[1–3] Black patients with PAD have higher rates of critical limb ischemia and amputation compared with nonblack people with PAD.[4–9] Despite these racial differences in disease severity and lower extremity outcomes, whether race affects responsiveness to medical therapy in people with PAD is unknown.

Colony-stimulating factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), mobilize progenitor cells from bone marrow and spleen into the peripheral circulation and may improve walking performance in people

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Accompanying Tables S1 through S5 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011001

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Clinical Perspective

What Is New?

- Among people with lower extremity peripheral artery disease (PAD) participating in a randomized clinical trial comparing granulocyte-macrophage colony-stimulating factor versus placebo, granulocyte-macrophage colony-stimulating factor improved 6-minute walk distance in white participants with PAD but not in black participants with PAD.
- In contrast to findings for granulocyte-macrophage colony-stimulating factor, supervised treadmill exercise improved 6-minute walk distance in both white and black participants with PAD.
- GM-CSF had a significantly greater beneficial effect in white participants with PAD compared to black participants with PAD.

What Are the Clinical Implications?

- Granulocyte-macrophage colony-stimulating factor may improve walking distance in white people with PAD but not in black people with PAD.

with PAD by promoting angiogenesis and improving endothelial function and cardiovascular health.[10–15] The PROPEL (Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD) randomized clinical trial studied whether GM-CSF with and without supervised treadmill exercise significantly improved 6-minute walk distance in people with PAD.[16] In post hoc exploratory analyses, the effects of race on the efficacy of GM-CSF and exercise in people with PAD were studied, to determine whether GM-CSF and exercise had differential effects on change in 6-minute walk distance in black participants with PAD compared with white participants with PAD.

Methods

The Institutional Review Board at Northwestern University and all recruitment sites approved the protocol. Participants provided written, informed consent. The data supporting the findings of this study are available from the corresponding author upon reasonable request, within constraints allowed by the institutional review board.

Participants were randomized between January 6, 2012 and December 22, 2016. The final follow-up visit was on August 15, 2017. The clinical trial used a 2×2 factorial design, and participants with PAD were randomized to 1 of 4 groups: supervised treadmill exercise+GM-CSF (Group 1), supervised treadmill exercise+placebo (Group 2), attention control+GM-CSF (Group 3), or attention control+placebo (Group 4). Methods and primary results have been reported.[15,16] In post hoc analyses, the effect of GM-CSF and exercise, respectively, on the primary outcome was evaluated by black versus white race. In these analyses, the 2 groups receiving GM-CSF (Groups 1 and 3), placebo (Groups 2 and 4), exercise (Groups 1 and 2), and attention control (Groups 3 and 4) were combined, to maximize sample sizes when evaluating the effect of GM-CSF and exercise on change in 6-minute walk distance among blacks and whites, respectively.

Participant Identification

Participants were identified from multiple Chicago-area medical centers, through newspaper or radio advertisements, and from postcard mailings to people age 55 years and older in the Chicago area. People with PAD who previously participated in research with the principal investigator (M.M.M.) and expressed interest in future research were contacted.

Inclusion Criteria

Inclusion criteria included an ankle-brachial index (ABI) ≤0.90.[17] Potential participants with an ABI >0.90 at baseline were eligible if there was hospital-affiliated vascular laboratory evidence of PAD. Participants with an ABI of >0.90 or ≤1.00 at the baseline study visit and those with a normal ABI and prior lower extremity revascularization were eligible if they had a 20% drop in ABI following a heel-rise test.[17,18]

Exclusion Criteria

Potential participants with a below- or above-knee amputation, wheelchair confinement, who used a walking aid other than a cane, who were unable or unwilling to attend exercise sessions 3 times per week, whose walking impairment was because of a reason other than PAD, or who had a foot ulcer, critical limb ischemia, or significant visual or hearing impairment were excluded. Potential participants who did not complete the study run-in were excluded. The run-in consisted of attending 1 weekly health education session and 1 treadmill exercise session within a 3-week period. Potential participants with major surgery or revascularization during the previous 3 months or planned during the next 6 months, participation in another clinical trial or cardiac rehabilitation within the past 3 months, Parkinson's disease, and those requiring oxygen with activity were excluded. Potential participants for whom exercise may be unsafe, including those with >Class II New York Heart Association heart failure or angina, an increase in angina pectoris during the prior 6 months, or an abnormal baseline stress test were excluded. Participants already exercising at a level similar to that in the intervention were excluded. Participants recently treated for cancer were excluded unless their cancer was early-stage and their cancer prognosis was excellent. Potential participants

with a Mini-Mental Status Examination score <23 were excluded.[19]

Race

Race was measured by asking participants how they classified their race, in an open-ended manner. Only participants who described their race as "black" or "white" were included in these analyses.

Randomization

Participants were randomized to 1 of 4 groups using a SAS computer program: GM-CSF+supervised exercise, GM-CSF+attention control, placebo+supervised exercise, or placebo+attention control. Randomization was stratified by diabetes mellitus.[20] Block randomization was used, with block sizes randomly selected from 8 and 12.

Interventions

GM-CSF and placebo

GM-CSF (250 μg/m^2 per day) or placebo was administered subcutaneously at the medical center 3 times weekly during the first 2 weeks after randomization, in a double-blinded fashion.

Supervised treadmill exercise and attention control

Supervised treadmill exercise was provided 3 times weekly, beginning at 15 minutes per session and increasing exercise by 5 minutes per session each week until up to 50 minutes of exercise per session was achieved. Participants randomized to the attention control group attended weekly 1-hour educational sessions on health topics of interest to PAD patients, including cancer screening, immunizations, nutritional supplements, and hypertension.

Outcomes

Outcome data were collected by individuals blinded to group assignment. The prespecified primary outcome was change in 6-minute walk distance between baseline and 12-week follow-up. Brachial artery flow-mediated dilation (FMD) was a secondary outcome. Endothelial progenitor cells were an exploratory outcome. To assess temporal changes, outcomes were also measured at 6- and at 26-week follow-up.

Six-Minute Walk Test

The 6-minute walk is a well-validated measure of walking endurance for people with PAD.[21–25] Following a standardized protocol,[21–25] participants walked up and down a 100-foot hallway for 6 minutes after instructions to cover as much distance as possible. The distance completed after 6 minutes was recorded. A small clinically meaningful change was defined as 20 m and a large meaningful change as 50 m.[25]

Brachial Artery FMD

FMD of the proximal brachial artery was performed using B-mode and Doppler ultrasound with a linear array vascular ultrasound transducer.[15,16,22] Doppler blood flow in the brachial artery was recorded at rest and immediately after hyperemia induction. Brachial artery diameters were recorded at rest and then 60 and 90 s after cuff deflation. FMD was defined as the ratio of the maximum brachial artery diameter after reactive hyperemia to the resting diameter, expressed as a percent. Images were interpreted by a single reader unaware of group assignment.[15,16,22]

Progenitor Cells

Progenitor cells were measured at baseline and 2-week follow-up. Peripheral blood from a peripheral venipuncture was washed in lysis buffer to lyse red blood cells. Remaining cell counts were obtained using the Countess Automated Cell Counter (Life Technologies, NY) as previously described.[15,26]

Additional Measures

Ankle-brachial index

A handheld Doppler probe (Nicolet Vascular Pocket Dop II, Golden, CO) was used to measure systolic blood pressures after the participant rested supine for 5 minutes. Pressures were measured in the following order: right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Pressures were repeated in reverse order. The ABI was calculated by dividing average pressures in each leg by the average of the 4 brachial pressures.[15–17,27,28] Heel-rise testing, when indicated for eligibility, consisted of 50 heel rises at a rate of 1 per s followed by repeat ABI measurement.[18]

Other measures

Medical history and demographics were obtained using patient report.[15,16] Body mass index (BMI) was calculated as weight (kg) divided by (height [meters])^2.

Leg symptoms

Leg symptoms were characterized using the San Diego Claudication Questionnaire.[29,30] Intermittent claudication was defined as exertional calf pain that did not begin at rest, caused the participant to stop walking, and resolved within 10 minutes of rest. Participants without intermittent claudication were classified as either asymptomatic (ie, reported no exertional leg symptoms) or with exertional leg symptoms that did not meet criteria for intermittent claudication.[29,30]

Power Calculations

Results reported here are exploratory results for the PROPEL Trial[16] and therefore no power calculations were performed. For the overall trial, a target sample size of 240 participants was calculated to achieve the primary aim and recruitment ended when recruitment resources were exhausted.

Statistical Analysis

Baseline characteristics were compared between blacks and white participants using χ^2 testing for categorical variables and *t* testing for continuous variables. Among blacks and whites, characteristics of those randomized to GM-CSF and those randomized to placebo were compared using χ^2 tests

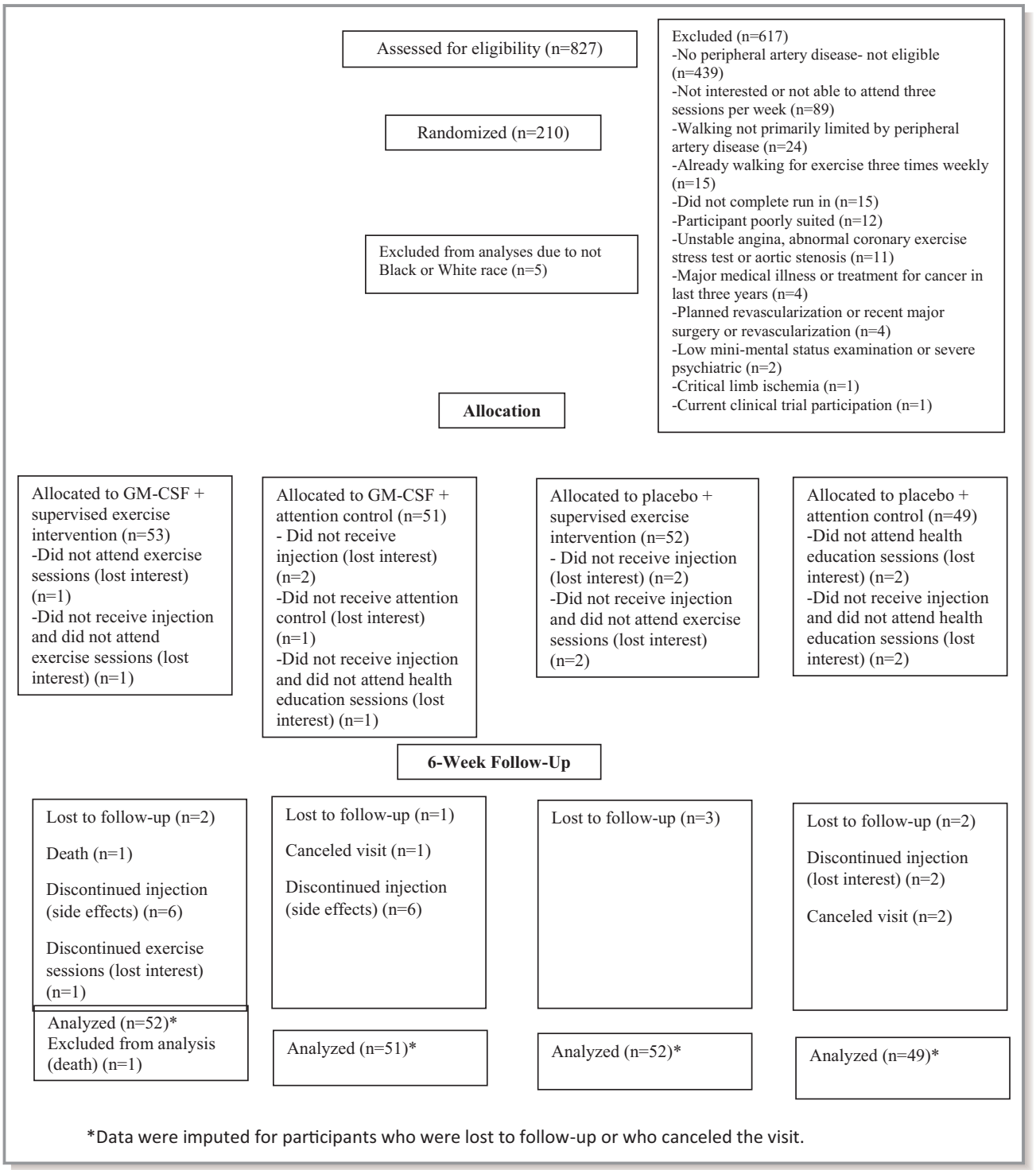

Figure 1. Consort diagram of randomization and follow-up rates by group.

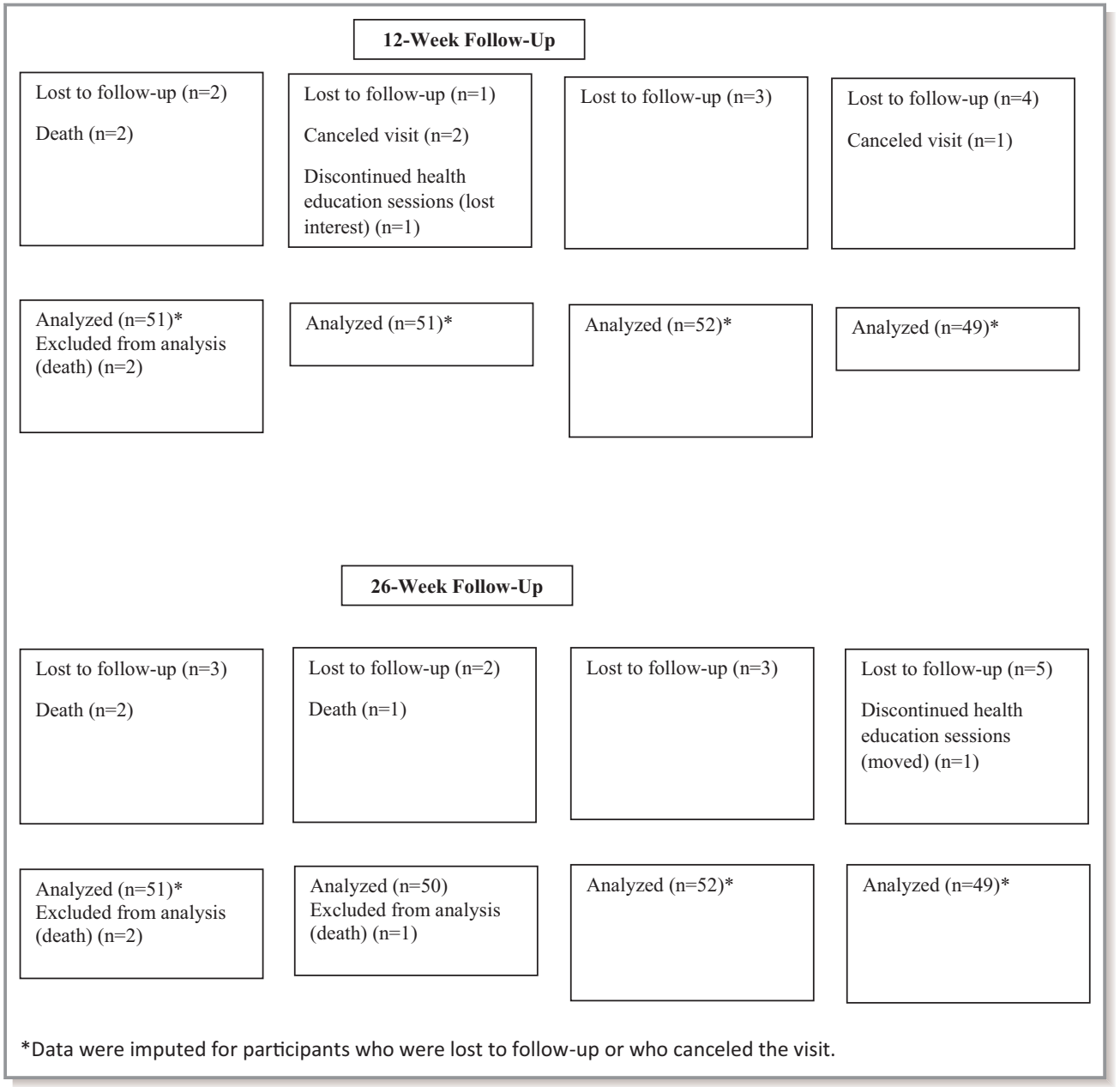

Figure 1. Continued.

for categorical variables and *t* tests for continuous variables. Statistical analyses were performed according to intention to treat. A statistical test for interaction between GM-CSF and exercise was performed, to ensure that it was appropriate to examine the effect of exercise and GM-CSF, separately, in blacks and white participants. Changes in 6-minute walk distance between baseline and 12-week follow-up were compared between groups using a 2-sample *t* test. Analyses were repeated for changes in 6-minute walk distance at 6-week and at 26-week follow-up. For missing data, multiple imputation was used by using PROC MI, obtaining 20 imputed data sets. Imputation was performed by treatment group. Variables included in the imputation were age, ABI, BMI, sex, smoking status, baseline outcome measures, leg symptoms, and comorbidities. Imputed results were combined using PROC MI ANALYZE to account for randomness in multiple imputations. Statistical testing for interactions of race with each intervention (GM-CSF and exercise) for their effects on outcomes was performed to compare the treatment effect in black participants with the treatment effect in white participants. Analyses for interactions were repeated using analyses of covariance to adjust for differences in age, ABI, BMI,

leg symptoms, and smoking across the 4 groups defined by treatment and race, since these characteristics differed between black and white participants and were considered potential confounders. People who died were excluded from analyses at time points that occurred after their deaths. The analyses reported here were exploratory and statistical significance was defined as $P<0.05$. Analyses were performed using SAS software version 9.4 (Cary, NC).

Results

Of 827 potential participants who attended a baseline visit, 617 met 1 or more exclusion criteria and 210 were randomized (Figure 1). Of these, 141 participants (67.1%) were black and 64 (30.5%) were white. Five participants (2.4%) who identified themselves as neither black nor white were excluded.

Overall, 189/205 (92.2%) of participants had an ABI <0.90, 9 (4.4%) had an ABI of 0.90 to <1.0, and 7 (3.4%) had an ABI ≥1.0 at baseline. Among participants who were black, the corresponding number and proportion of participants in each category was 131 (92.9%), 6 (4.3%), and 4 (2.8%), respectively. Among participants who were white, the corresponding number and percent were 58 (90.6%), 3 (4.7%), and 3 (4.7%), respectively.

Among the 64 whites randomized, 61 (95.3%) completed 6-week follow-up, 61 (95.3%) completed 12-week follow-up, and 61 (95.3%) completed 26-week follow-up. Among the 141 black participants who were randomized, 132 (93.6%) completed 6-week follow-up, 129 (91.5%) completed 12-week follow-up, and 128 (90.8%) completed 26-week follow-up. The number of participants missing data for each outcome is shown by race in Table 1. There were no statistically significant interactions of GM-CSF and exercise (*P* value for statistical interaction at 6-week follow-up=0.65, *P* value for interaction at 12-week follow-up=0.64, *P* value for statistical interaction at 26-week follow-up=0.96).

Black participants were younger, had a lower BMI, and had a higher prevalence of current cigarette smoking and a lower prevalence of classic intermittent claudication symptoms, compared with white participants (Table 2). Table 3 compares black and white participants according to randomization to GM-CSF versus placebo and according to randomization to supervised exercise versus attention control.

Table 1. Missing Data for Each Outcome at Each Time Point by Race

	Black Participants		White Participants		
	GM-CSF (N=69)	Placebo (N=71)	GM-CSF (N=32)	Placebo (N=30)	Total (N=202)
Six-min walk*					
6-wk	4 (5.8%)	5 (7.0%)	2 (6.3%)	2 (6.7%)	13 (6.4%)
12-wk	5 (7.2%)	9 (12.7%)	0 (0%)	1 (3.3%)	15 (7.4%)
26-wk	5 (7.2%)	9 (12.7%)	0 (0%)	1 (3.3%)	15 (7.4%)
Brachial artery flow-mediated dilation					
Baseline	2 (2.9%)	2 (2.8%)	1 (3.1%)	2 (6.7%)	7 (3.5%)
6-wk	9 (13.0%)	6 (8.5%)	2 (6.3%)	4 (13.3%)	21 (10.4%)
12-wk	7 (10.1%)	11 (15.5%)	1 (3.1%)	3 (10.0%)	22 (10.9%)
26-wk	7 (10.1%)	9 (12.7%)	1 (3.1%)	5 (16.7%)	22 (10.9%)
	Exercise (N=67)	Attention Control (N=73)	Exercise (N=36)	Attention Control (N=26)	Total (N=202)
Six-min walk*					
6-wk	4 (6.0%)	5 (6.8%)	1 (2.8%)	3 (11.5%)	13 (6.4%)
12-wk	4 (6.0%)	10 (13.7%)	1 (2.8%)	0 (0%)	15 (7.4%)
26-wk	6 (9.0%)	8 (11.0%)	1 (2.8%)	0 (0%)	15 (7.4%)
Brachial artery flow-mediated dilation					
Baseline	3 (4.5%)	1 (1.4%)	1 (2.8%)	2 (7.7%)	7 (3.5%)
6-wk	7 (10.4%)	8 (11.0%)	2 (5.6%)	4 (15.4%)	21 (10.4%)
12-wk	7 (10.4%)	11 (15.1%)	2 (5.6%)	2 (7.7%)	22 (10.9%)
26-wk	7 (10.4%)	9 (12.3%)	4 (11.1%)	2 (7.7%)	22 (10.9%)

GM-CSF indicates granulocyte-macrophage colony-stimulating factor.
*There were no missing data for 6-minute walk distance at baseline.

Among participants randomized to GM-CSF, black participants received 351 out of 420 possible injections (83.6%), while white participants received 187 out of 204 possible injections (91.7%) (*P*=0.37). Among participants randomized to placebo, black participants received 393 out of 426 possible injections (92.3%) and white participants received 174 out of 180 possible placebo injections (96.7%) (*P*=0.83). Among participants randomized to exercise, black participants attended 3111 out of a possible 4510 exercise sessions (69.0%) and white participants attended 1891 out of a possible 2543 exercise sessions (74.4%) (*P*=0.14). Among participants randomized to attention control, black participants attended 1175 out of a possible 1550 sessions (75.8%) and white participants attended 455 out of a possible 599 sessions (76.0%) (*P*=0.51).

Progenitor Cell Increases in Response to GM-CSF

Circulating progenitor cells significantly increased among white and among black participants, respectively, at 2-week follow-up (Table S1). There were no significant differences in the magnitude of progenitor cell increases in blacks versus whites who received GM-CSF at 2-week follow-up (Table S1).

Effects of GM-CSF Versus Placebo on 6-Minute Walk

Among white participants, GM-CSF increased the 6-minute walk by +12.9 m (95% CI: −10.8, +36.5, *P*=0.29) at 6-week follow-up, +22.0 m (95% CI: −4.5, +48.5, *P*=0.103) at 12-week follow-up, and +44.4 m (95% CI: +6.9, +82.0, *P*=0.020) at 26-week follow-up, compared with placebo (Table 4 and Figure 2A). Among black participants, GM-CSF did not increase the 6-minute walk (Table 4 and Figure 2A). There was a statistically significant interaction for race on the effect of GM-CSF on change in 6-minute walk distance at 26-week follow-up (*P*=0.018) and a nearly statistically significant effect at 12-week follow-up (*P*=0.076). Results did not substantially change when analyses were repeated, adjusting for baseline differences in age, ABI, BMI, leg symptoms, and smoking between blacks and whites (interaction term at 12-week follow-up: *P*=0.078, interaction term at 26-week follow-up: *P*=0.028). When results were repeated among the 189 participants with ABI <0.90, results were similar; however, at 12-week follow-up, GM-CSF had a statistically significant effect on improvement in 6-minute walk among white participants (+29.0 m, 95% CI: +1.2, +56.8, *P*=0.041). The statistical significance of the interaction term for race on the effect of GM-CSF on change in 6-minute walk was *P*=0.012 at 12-week follow-up and *P*=0.008 at 26-week follow-up among participants with ABI <0.90.

Table 2. Characteristics of Black Versus White Participants in the PROPEL Trial

Characteristic	Black (N=141)	White (N=64)	*P* Value
Age, y	65.8 (7.8)	69.4 (9.6)	0.004
Men	N=82 (58.2%)	N=43 (67.2%)	0.22
ABI	0.68 (0.18)	0.73 (0.21)	0.070
BMI, kg/m^2	29.8 (6.3)	32.2 (6.7)	0.017
Current cigarette smoking	N=57 (40.4%)	N=13 (20.3%)	0.005
Former cigarette smoking	N=75 (53.2%)	N=38 (59.4%)	0.41
Hypertension	N=118 (83.7%)	N=53 (82.8%)	0.88
Diabetes mellitus	N=48 (34.0%)	N=29 (45.3%)	0.12
Angina	N=31 (22.0%)	N=11 (17.2%)	0.43
Heart failure	N=19 (13.5%)	N=8 (12.5%)	0.85
Myocardial infarction	N=29 (20.6%)	N=16 (25.0%)	0.48
Baseline 6-min walk, m	332.6 (98.3)	349.9 (102.3)	0.25
Intermittent claudication	N=37 (26.2%)	N=26 (40.6%)	0.039
Baseline progenitor cell concentration (%)			
CD34$^+$CD45lo	0.026 (0.016)	0.028 (0.014)	0.38
CD34$^+$CD45loCD133$^+$	0.016 (0.010)	0.017 (0.010)	0.44
CD34$^+$CD45loCD31$^+$	0.023 (0.015)	0.025 (0.014)	0.32
CD34$^+$CD45loCD31$^+$ CD133$^+$	0.017 (0.013)	0.018 (0.010)	0.59

ABI indicates ankle-brachial index; BMI, body mass index; PROPEL, Progenitor Cell Release Plus Exercise to Improve Functional Performance in PAD.

Effects of Supervised Treadmill Exercise Versus Attention Control on 6-Minute Walk

Among white participants, supervised treadmill exercise increased the 6-minute walk distance by +19.5 m (95% CI: −4.4, +43.5, *P*=0.11) at 6-week follow-up, by +26.2 m (95% CI: −0.3, +52.7, *P*=0.053) at 12-week follow-up, and by +44.5 m (+6.5, +82.5, *P*=0.022) at 26-week follow-up, compared with control (Table 5 and Figure 2B). Among black participants, supervised treadmill exercise increased 6-minute walk distance by +13.4 m (95% CI: −4.4, +31.2, *P*=0.14) at 6-week follow-up, by +37.8 m (95% CI=+14.7, +61.0, *P*=0.001) at 12-week follow-up, and by +31.9 m (95% CI: +9.7, +54.1, *P*=0.005) at 26-week follow-up, compared with control (Table 5 and Figure 2B). There were no statistically significant interactions of race on the effect of supervised exercise on change in 6-minute walk performance. Results did not substantially change when analyses were repeated, adjusting for racial differences in age, ABI, BMI, leg symptoms, and smoking. Findings were

Table 3. Characteristics of Participants by Race and Randomization Assignment

Characteristic	Black Participants		White Participants	
	GM-CSF (N=70)	Placebo (N=71)	GM-CSF (N=34)	Placebo (N=30)
Age, y	66.3 (7.8)	65.3 (7.9)	69.0 (9.7)	70.0 (9.5)
ABI, mean (SD)	0.70 (0.19)	0.66 (0.16)	0.71 (0.18)	0.75 (0.24)
Women, N (%)	27 (38.6)	32 (45.1)	11 (32.4)	10 (33.3)
BMI, kg/m^2	29.8 (6.8)	29.9 (5.8)	31.0 (6.5)	33.5 (6.8)
Diabetes mellitus, N (%)	24 (34.3)	24 (33.8)	15 (44.1)	14 (46.7)
Angina history, N (%)	20 (28.6)	11 (15.5)	7 (20.6)	4 (13.3)
Myocardial infarction, N (%)	18 (25.7)	11 (15.5)	12 (35.3)	4 (13.3)
Heart failure, N (%)	10 (14.3)	9 (12.7)	5 (14.7)	3 (10.0)
Pulmonary disease	7 (10.0)	11 (15.5)	7 (20.6)	1 (3.3)
Intermittent claudication	16 (22.9)	21 (29.6)	14 (41.2)	12 (40.0)
Atypical exertional leg symptoms	50 (71.4)	49 (69.0)	18 (52.9)	16 (53.3)
Six-min walk, m	336.0 (100.3)	329.2 (96.9)	338.4 (115.7)	362.9 (84.8)
Randomized to supervised treadmill exercise	35 (50.0)	33 (46.5)	18 (52.9)	19 (63.3)
Characteristic	Black Participants		White Participants	
	Exercise (N=68)	Attention Control (N=73)	Exercise (N=37)	Attention Control (N=27)
Age, mean (SD) (y)	65.5 (7.6)	66.0 (8.0)	69.7 (10.8)	69.1 (7.6)
ABI, mean (SD)	0.68 (0.19)	0.68 (0.17)	0.73 (0.21)	0.73 (0.21)
Women, N (%)	30 (44.1)	29 (39.7)	13 (35.1)	8 (29.6)
BMI, kg/m^2	30.1 (6.2)	29.6 (6.4)	32.2 (6.2)	32.2 (7.4)
Diabetes mellitus, N (%)	25 (36.8)	23 (31.5)	13 (35.1)	16 (59.3)
Angina history, N (%)	14 (20.6)	17 (23.3)	8 (21.6)	3 (11.1)
Myocardial infarction, N (%)	12 (17.7)	17 (23.3)	9 (24.3)	7 (25.9)
Heart failure, N (%)	7 (10.3)	12 (16.4)	3 (8.1)	5 (18.5)
Pulmonary disease, N (%)	7 (10.3)	11 (15.1)	5 (13.5)	3 (11.1)
Intermittent claudication, N (%)	22 (32.4)	15 (20.6)	15 (40.5)	11 (40.7)
Atypical exertional leg symptoms, N (%)	44 (64.7)	54 (74.0)	18 (48.6)	16 (59.3)
Six-min walk, m	330.1 (105.0)	334.8 (92.4)	353.5 (97.3)	344.9 (110.6)
Randomized to supervised treadmill exercise, N (%)	35 (51.5)	35 (47.9)	18 (48.6)	16 (59.3)

ABI indicates ankle-brachial index; BMI, body mass index; GM-CSF, granulocyte-macrophage colony-stimulating factor.

not substantially changed when black and white participants were categorized according to presence versus absence of diabetes mellitus (Tables S2 and S3).

Figure S1 shows the effects of each of the 4 study groups (GM-CSF+exercise, GM-CSF+control, placebo+exercise, and placebo+control) on change in 6-minute walk distance at each follow-up time point by participant race.

Brachial Artery FMD

Among white participants, GM-CSF significantly improved brachial artery FMD at 6-week follow-up, compared with placebo (+1.96%, 95% CI: +0.51, +3.42, P=0.008), but there were no effects of GM-CSF on brachial artery FMD at 12- or 26-week follow-up (Table S2). Among black participants, there was no effect of GM-CSF on brachial artery FMD at any time point (Table S4). Exercise did not increase brachial artery FMD at any time point among blacks or whites (Table S5).

Serious Adverse Events

Twenty-two of 70 (31.4%) black participants who received GM-CSF had 1 or more serious adverse events, compared with 13 of 71 (18.3%) black participants who received placebo

Table 4. Effects of GM-CSF on Changes in 6-Minute Walk Distance Over Time Among Black and White Participants (Data Shown Are in Meters)

	Black		White	
	GM-CSF (N=69)	Placebo (N=71)	GM-CSF (N=32)	Placebo (N=30)
Baseline	333 (98)	329 (97)	346 (115)	363 (85)
6-wk follow-up	344 (94)	338 (93)	360 (110)	364 (84)
12-wk follow-up	334 (99)	344 (96)	367 (105)	362 (96)
26-wk follow-up	346 (102)	347 (90)	371 (115)	344 (113)
Within-group change at 6-wk follow-up	+11.1 (−1.3, +23.6)	+8.9 (−3.7, +21.4)	+14.1 (−2.3, +30.6)	+1.2 (−15.7, +18.2)
Between-group change at 6-wk follow-up (mean difference in change, 95% CI)	+2.3 (−15.3, +19.8) *P*=0.80		+12.9 (−10.8, +36.5) *P*=0.29	
Within-group change at 12-wk follow-up	+0.8 (−15.9, +17.6)	+14.4 (−2.2, +31.1)	+20.9 (+2.9, +38.9)	−1.1 (−20.0, +17.9)
Between-group change at 12-wk follow-up	−13.6 (−37.4, +10.3) *P*=0.26		+22.0 (−4.5, +48.5) *P*=0.103	
Within-group change at 26-wk follow-up	+12.4 (−3.3, +28.2)	+17.4 (+1.2, +33.6)	+25.4 (−0.3, +51.1)	−19.1 (−45.8, +7.6)
Between-group change at 26-wk follow-up	−5.0 (−27.5, +17.5) *P*=0.66		+44.4 (+6.9, +82.0) *P*=0.020	

GM-CSF indicates granulocyte-macrophage colony-stimulating factor.

Table 5. Effects of Exercise on Changes in 6-Minute Walk Distance Over Time Among Black and White Participants (Data Shown Are in Meters)

	Black		White	
	Exercise (N=67)	Attention Control (N=73)	Exercise (N=36)	Attention Control (N=26)
Baseline	327 (103)	335 (92)	356 (97)	351 (108)
6-wk follow-up	344 (98)	338 (90)	372 (90)	348 (107)
12-wk follow-up	355 (97)	324 (96)	378 (89)	346 (112)
26-wk follow-up	359 (96)	335 (96)	379 (101)	329 (126)
Within-group change: 6-wk follow-up	+17.0 (+4.2, +29.8)	+3.6 (−8.7, +15.8)	+16.1 (+0.9, +31.2)	−3.5 (−21.9, +14.9)
Between-group change: 6-wk follow-up	+13.4 (−4.4, +31.2) *P*=0.14		+19.5 (−4.4, +43.5) *P*=0.11	
Within-group change: 12-wk follow-up	+27.5 (+11.1, +43.8)	−10.4 (−26.4, +5.7)	+21.3 (+4.1, +38.4)	−4.9 (−24.7, +14.9)
Between-group change: 12-wk	+37.8 (+14.7, +61.0) *P*=0.001		+26.2 (−0.3, +52.7) *P*=0.053	
Change between baseline and 26-wk follow-up	+31.6 (+16.2, +47.0)	−0.3 (−16.2, +15.5)	+22.5 (−1.9, +46.9)	−22.0 (−50.5, +6.6)
Between group change: 26-wk	+31.9 (+9.7, +54.1) *P*=0.005		+44.5 (+6.5, +82.5) *P*=0.022	

(*P*=0.071). Eight of 34 (23.5%) white participants who received GM-CSF group had 1 or more serious adverse events, compared with 8 of 30 (26.7%) white participants who received placebo (*P*=0.77). Seventeen of 68 (25.0%) black participants in the exercise group reported at least 1 serious adverse event, compared with 18 of 73 (24.7%) black participants in the health education group (N=0.96). Ten of 37 (27.0%) white participants reported at least 1 serious adverse event in the exercise group, compared with 6 of 27 (22.2%) in the health education group (N=0.66). Three deaths occurred during the study: 1 among black participants and 2 among white participants. No deaths were considered to be related to study interventions.

Discussion

In exploratory analyses of the PROPEL Trial, GM-CSF had a significantly greater effect on improving 6-minute walk

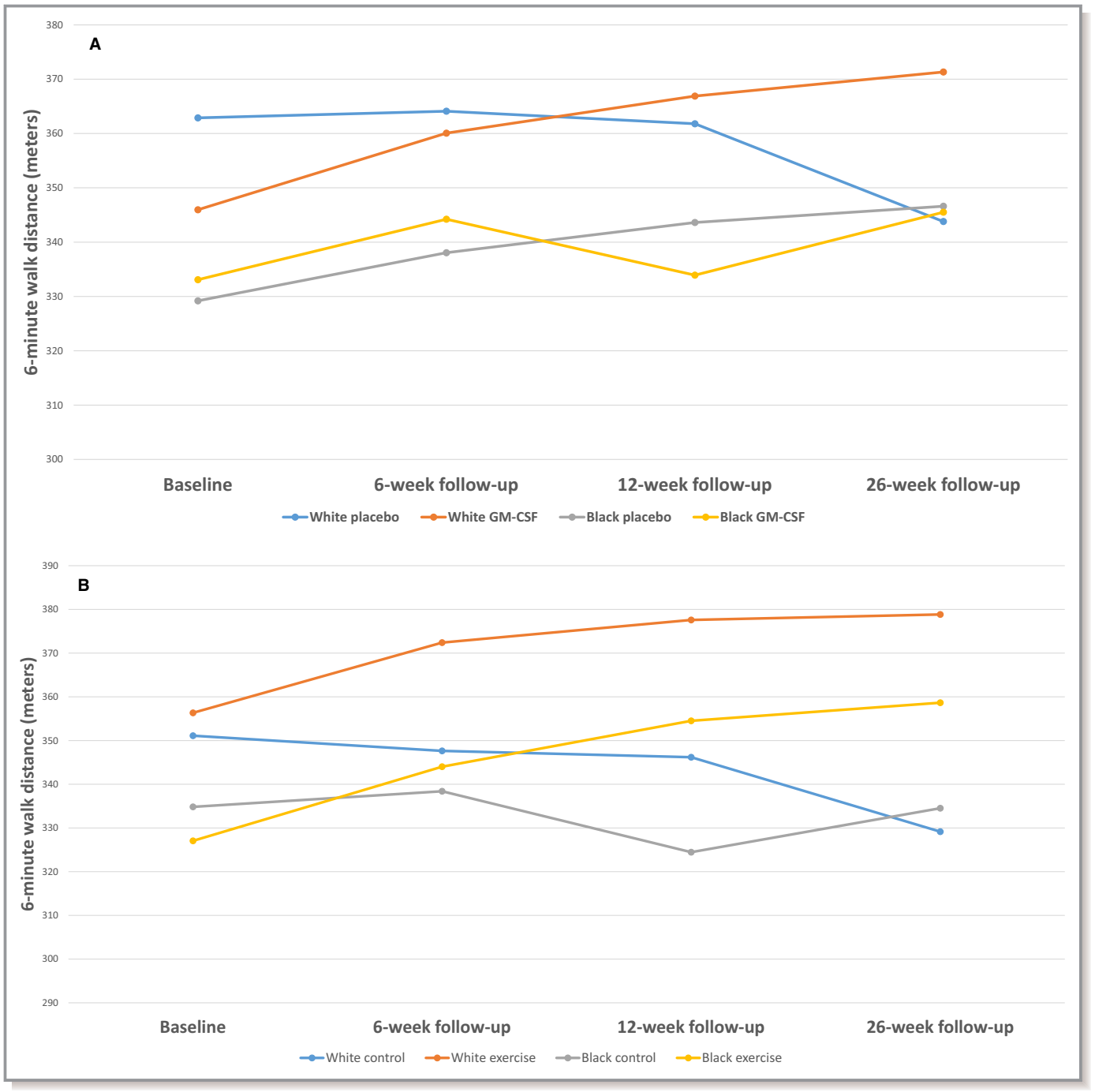

Figure 2. The effect of GM-CSF on change in 6-minute walk distance among black and white participants with PAD. A, Among white participants with peripheral artery disease (PAD), *P*=0.074 for the difference in overall change in 6-minute walk distance between (GMCSF) and placebo. Among black participants with PAD, *P*=0.70 for difference in overall change in 6-minute walk distance between GMCSF and placebo. B, The effect of exercise on change in 6-minute walk distance among black and white participants with PAD. Among white participants with PAD, *P*=0.034 for difference in overall change in 6-minute walk distance between exercise and control. Among black participants with PAD, *P*=0.006 for difference in overall change in 6-minute walk distance between exercise and control. GM-CSF indicates granulocyte-macrophage colony-stimulating factor; PAD, peripheral artery disease.

distance among white participants with PAD, compared with black participants with PAD. Among white participants, GM-CSF improved the 6-minute walk distance by 10.9 m at 6-week follow-up, 22.2 m at 12-week follow-up, and 45.3 m at 26-week follow-up, compared with placebo. This magnitude of effect was consistent with a clinically important difference at 12- and at 26-week follow-up.[25] However, GM-CSF had no effect on change in 6-minute walk distance among participants who were black. A statistically significant interaction was observed for white versus black race for the effect of

GM-CSF on change in 6-minute walk distance at 26-week follow-up. In contrast, supervised treadmill exercise improved the 6-minute walk in both black and white participants, and there was no significant interaction for race on the effect of supervised treadmill exercise on 6-minute walk.

The reason for the observed racial difference in response to GM-CSF is unclear. Since GM-CSF was administered subcutaneously by study staff, and rates of attendance at GM-CSF injection visits were similar between blacks and whites, adherence to GM-CSF should not explain the observed racial differences. In addition, there was no racial difference in the effect of GM-CSF on increases in circulating progenitor cells, suggesting that racial differences in the magnitude of increase in circulating progenitor cell increases do not explain the racial differences reported here. GM-CSF significantly increased brachial artery FMD at 6-week follow-up in white but not in black participants, suggesting a potential mechanism for racial differences. However, this difference was not observed at 12- or 26-week follow-up.

There are several potential explanations for results reported here of racial differences in responsiveness to GM-CSF. First, prior study showed lower quantities of circulating progenitor cells in blacks compared with whites.[31,32] In 1 study of 1747 people (including 457 [26%] black participants), black participants had significantly fewer circulating progenitor cells than whites and these findings were also observed in a second independent cohort.[31] Second, among 91 people presenting with an acute myocardial infarction, black patients had significantly lower circulating progenitor cell abundance compared with white patients (ie, 1316 versus 2231 $CD34^+$ cells/mL, P=0.01).[31] Third, in a study of umbilical cord blood, blacks had significantly lower umbilical blood progenitor cell counts compared with whites.[32] Fourth, the Framingham Heart Study demonstrated a heritable component of circulating $CD34^+$ progenitor cells.[33,34] Additional evidence demonstrated that blacks had poorer microvascular endothelial function compared with whites.[35] Although the PROPEL trial did not demonstrate racial differences in progenitor cell increases in response to GM-CSF, it is possible that findings reported here can be explained by racial differences in responsiveness to increased progenitor cells. It is also possible that there were racial differences in specific progenitor cells or responsiveness to progenitor cells that were not measured in the PROPEL Trial.

It is possible that racial differences in atherosclerosis location or severity might explain the racial differences reported here. Previous study demonstrated more severe infragenicular atherosclerosis in black patients compared with white patients.[3] Among patients presenting with critical limb ischemia, whites were more likely to present with isolated aortoiliac disease than blacks[36] and 5 years after infrainguinal bypass grafting, blacks had poorer graft patency than whites.[37]

Prior evidence regarding the effects of GM-CSF in patients with PAD was mixed.[10,16,38,39] The PROPEL trial included 210 participants, was the largest trial to study GM-CSF in people with PAD, and showed no overall benefit of GM-CSF on walking distance in PAD.[16] Poole et al randomized 159 participants with PAD and intermittent claudication to GM-CSF versus placebo.[38] There was no significant improvement in the primary outcome, 12-week change in maximal treadmill walking time, as compared with placebo (mean difference=53 s, P=0.08) and only 2 of 9 secondary outcomes—change in the Walking Impairment Questionnaire distance score and change in the 36-item short-form health survey physical functioning score—were significantly better in the GM-CSF group compared with placebo at 12-week follow-up. In this prior study, 78 (49.1%) PAD participants were white and 79 (49.7%) were black. A third study of 45 participants with PAD reported a significant benefit of GM-CSF on treadmill walking performance, but participant race was not reported.[10] A fourth study of 40 participants with PAD conducted in Europe demonstrated no effect of GM-CSF on treadmill walking distance.[39]

This study has limitations. First, results reported here were not prespecified, are considered exploratory, and require confirmation. Second, statistical power for the PROPEL trial was not calculated separately for black and white participants. Third, it is possible that there were racial differences in improvements of other types of endothelial progenitor cells, responsiveness to endothelial progenitor cells, or other unmeasured factors that explain these findings but were not measured in PROPEL.

Conclusion

GM-CSF significantly improved the 6-minute walk at 26-week follow-up among people with PAD who were white, but had no effect on people with PAD who were black. Further study is needed to confirm the racial differences reported here in response to GM-CSF among people with PAD.

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Supplemental Material

Table S1. Two-week change in progenitor cell abundance by receipt of GM-CSF vs. placebo among blacks and whites with peripheral artery disease.

Race		No.	Mean (SD)		Mean (95% CI)			P interact
			Baseline	2-week follow-up	Within-group Change	Difference in Changes	P value	
CD34_CD45lo								
Black	**GM-CSF**	56	0.026 (0.014)	0.050 (0.045)	+0.025 (+0.016, +0.033)	+0.022 (+0.010, +0.034)	.0003	0.8277
	Placebo	62	0.026 (0.017)	0.028 (0.020)	+0.003 (-0.005, +0.011)	Reference	-	
White	**GM-CSF**	28	0.030 (0.014)	0.055 (0.052)	+0.025 (+0.013, +0.038)	+0.024 (+0.007, +0.042)	.0076	
	Placebo	28	0.027 (0.011)	0.028 (0.014)	+0.001 (-0.011, +0.014)	Reference	-	
CD34_CD45loCD133_								
Black	**GM-CSF**	56	0.016 (0.009)	0.032 (0.031)	+0.016 (+0.010, +0.022)	+0.014 (+0.005, +0.022)	.0015	0.7257
	Placebo	62	0.016 (0.011)	0.019 (0.014)	+0.003 (-0.003, +0.008)	Reference	-	
White	**GM-CSF**	28	0.018 (0.010)	0.036 (0.034)	+0.018 (+0.010, +0.026)	+0.016 (+0.005, +0.028)	.0069	
	Placebo	28	0.017 (0.009)	0.019 (0.011)	+0.002 (-0.006, +0.010)	Reference	-	
CD34_CD45lo_CD31_								
Black	**GM-CSF**	43	0.022 (0.013)	0.041 (0.032)	+0.019 (+0.011, +0.026)	+0.017 (+0.007, +0.027)	.0009	0.2429
	Placebo	47	0.023 (0.016)	0.024 (0.020)	+0.001 (-0.005, +0.008)	Reference	-	
White	**GM-CSF**	19	0.031 (0.014)	0.063 (0.053)	+0.032 (+0.016, +0.048)	+0.030 (+0.007, +0.053)	0.0131	
	Placebo	18	0.022 (0.011)	0.025 (0.014)	+0.003 (-0.014, +0.019)	Reference	-	
CD34_CD45lo_CD31_CD133_								
Black	**GM-CSF**	43	0.015 (0.009)	0.029 (0.023)	+0.014 (+0.008, +0.019)	+0.013 (+0.005, +0.021)	.0009	0.3032
	Placebo	47	0.017 (0.013)	0.017 (0.014)	+0.001 (-0.005, +0.006)	Reference	-	
White	**GM-CSF**	19	0.021 (0.009)	0.044 (0.036)	+0.024 (+0.013, +0.035)	+0.021 (+0.005, +0.037)	0.0109	
	Placebo	18	0.016 (0.010)	0.019 (0.012)	+0.003 (-0.009, +0.014)	Reference	-	

Table S2. Effects of GM-CSF on changes in six-minute walk distance over time among black and white participants who do not have diabetes (data are shown in meters).

	Black participants without diabetes		White participants without diabetes	
	GM-CSF N=45	**Placebo N=47**	**GM-CSF N=18**	**Placebo N=16**
Baseline	351 (91)	342 (98)	337 (141)	367 (74)
6-week follow-up	365 (88)	352 (85)	355 (127)	371 (75)
12-week follow-up	349 (96)	356 (90)	377 (119)	366 (86)
26-week follow-up	362 (97)	355 (90)	376 (125)	342 (126)
Within group change at 6-week follow-up	+14.1 (+0.7, +27.6)	+9.6 (-3.8, +22.9)	+18.0 (-6.1, +42.1)	+4.1 (-21.5, +29.7)
Between group change at 6-week follow-up (mean difference in change, 95% CI)	+4.6 (-14.4, +23.6) P=0.64		+13.9 (-22.4, +50.1) P=0.45	
Interaction at 6-week follow-up	-9.3 (-46.6, +28.0) P=0.62			
Within group change at 12-week follow-up	-1.5 (-19.5, +16.5)	+14.0 (-4.0, +31.9)	+39.6 (+14.1, +65.2)	-0.4 (-27.5, +26.7)
Between group change at 12-week follow-up	-15.4 (-41.2, +10.3) P=0.24		+40.0 (+1.6, +78.5) P=0.041	
Interaction at 12-week follow-up	-55.5 (-101.9, -9.0) P=0.019			
Within group change at 26-week follow-up	+11.4 (-5.5, +28.3)	+13.3 (-3.6, +30.2)	+38.4 (-2.1, +78.9)	-24.5 (-67.5, +18.4)
Between group change at 26-week follow-up	-1.9 (-26.5, +22.7) P=0.88		+62.9 (+2.1, +123.8) P=0.043	
Interaction at 26-week follow-up	-64.8 (-116.6, -13.0) P=0.014			

Table S3. Effects of GM-CSF on changes in six-minute walk distance over time among black and white participants with diabetes (data are shown in meters).

	Black participants with diabetes		**White participants with diabetes**	
	GM-CSF N=24	**Placebo N=24**	**GM-CSF N=14**	**Placebo N=14**
Baseline	300 (103)	304 (91)	357 (72)	359 (98)
6-week follow-up	306 (94)	312 (105)	366 (87)	357 (95)
12-week follow-up	305 (101)	319 (106)	354 (86)	357 (109)
26-week follow-up	314 (108)	330 (90)	365 (105)	346 (101)
Within group change at 6-week follow-up	+5.5 (-20.5, +31.5)	+7.5 (-19.1, +34.1)	+9.1 (-13.2, +31.3)	-2.1 (-24.0, +19.8)
Between group change at 6-week follow-up (mean difference in change, 95% CI)	-2.0 (-39.5, +35.6) P=0.92		+11.2 (-20.3, +42.7) P=0.49	
Interaction at 6-week follow-up	-13.1 (-66.3, +40.0) P=0.63			
Within group change at 12-week follow-up	+5.2 (-29.5, +39.9)	+15.3 (-20.2, +50.8)	-3.1 (-26.0, +19.8)	-1.9 (-26.1, +22.3)
Between group change at 12-week follow-up	-10.1 (-60.4, +40.1) P=0.69		-1.2 (-35.8, +33.3) P=0.94	
Interaction at 12-week follow-up	-8.9 (-78.4, +60.6) P=0.80			
Within group change at 26- week follow-up	+14.3 (-18.6, +47.3)	+25.5 (-9.0, +60.0)	+8.6 (-19.7, +36.9)	-12.9 (-41.9, +16.2)
Between group change at 26-week follow-up	-11.2 (-59.5, +37.1) P=0.65		+21.4 (-20.8, +63.6) P=0.32	
Interaction at 26-week follow-up	-32.6 (-101.5, +36.2) P=0.35			

Table S4. Effects of GM-CSF on brachial artery flow-mediated dilation according to black vs. white race*.

	Black		White	
	GM-CSF N=69	**Placebo N=71**	**GM-CSF N=32**	**Placebo N=30**
Baseline	5.8% (3.7, 7.6)	4.7% (2.9, 6.3)	4.8% (2.9, 5.6)	6.8% (4.2, 9.5)
6-week follow-up	5.5% (2.8, 8.7)	4.3% (2.8, 7.5)	5.1% (3.6, 7.2)	5.9% (3.6, 8.7)
12-week follow-up	5.3% (3.2, 8.0)	3.9% (2.2, 6.4)	4.2% (2.6, 6.4)	6.9% (3.7, 9.8)
26-week follow-up	5.8% (3.7, 7.8)	4.0% (2.5, 7.2)	3.9% (2.2, 6.1)	5.3% (2.3, 7.3)
Within group change at 6-week follow-up	+0.10% (-1.42, +1.88)	-0.07% (-1.33, +1.91)	+0.65% (-0.89, +1.96)	-1.00% (-3.26, +1.85)
Between group change at 6-week follow-up	-0.07% (-0.92, +0.79) P=0.88		+1.96% (+0.51, +3.42) P=0.008	
Interaction at 6-week follow-up	-2.03% (-3.72, -0.34) P=0.019			
Within group change at 12-week follow-up	+0.10% (-1.77, +1.18)	-0.17% (-1.73, +2.04)	-1.09% (-2.46, +1.81)	-0.18% (-1.63, +1.40)
Between group change at 12-week follow-up	-0.03% (-0.99, +0.93) P=0.95		-0.24% (-1.78, +1.29) P=0.76	
Interaction at 12-week follow-up	+0.21% (-1.60, +2.02) P=0.82			
Within group change at 26-week follow-up	+0.16% (-1.57, +1.82)	-0.08% (-2.04, +1.65)	-0.73% (-1.71, +0.08)	-1.37% (-4.16, -0.01)
Between group change at 26-week follow-up	+0.22% (-0.73, +1.18) P=0.65		+0.75% (-0.67, +2.16) P=0.30	
Interaction at 26-week follow-up	-0.53% (-2.23, +1.18) P=0.54			

*Median (Interquartile range) is shown for the outcome at each time point, as well as for the within-group change. Estimate (95% CI). P values for between-group changes are from the combined results for Hodges-Lehmann Estimation. Data were imputed for individuals who did not die but missed the outcome measure at each visit.

Table S5. Effects of exercise on brachial artery flow-mediated dilation according to black vs. white race .

	Black		**White**	
	Exercise N=67	**Attention Control N=73**	**Exercise N=36**	**Attention Control N=26**
Baseline	4.9% (2.9, 7.4)	5.5% (3.8, 7.2)	5.0% (2.9, 9.5)	5.3% (3.5, 7.3)
6-week follow-up	4.8% (2.4, 7.0)	5.5% (3.3, 9.0)	6.3% (4.1, 8.7)	5.1% (3.0, 6.6)
12-week follow-up	4.4% (2.3, 6.4)	5.3% (3.0, 8.2)	4.7% (3.2, 8.7)	6.0% (3.4, 8.3)
26-week follow-up	5.2% (2.5, 7.6)	5.0% (3.3, 7.8)	4.8% (2.2, 7.2)	3.8% (2.3, 5.5)
Within group change: 6-week follow-up	-0.20% (-1.45, +1.91)	+0.28% (-1.26, +1.89)	+0.25% (-1.72, +2.39)	+0.15% (-1.89, +0.87)
Between group change: 6-week follow-up	-0.36% (-1.30, +0.57) P=0.44		+0.88% (-0.73, +2.49) P=0.28	
Interaction at 6-week follow-up	-1.24% (-3.10, +0.62) P=0.19			
Within-group change: 12-week follow-up	-0.03% (-1.90, +1.24)	-0.39% (-1.58, +1.80)	-0.45% (-2.50, +1.40)	-0.44% (-1.49, +1.64)
Between group change: 12 week	-0.16% (-1.12, +0.81) P=0.75		-0.48% (-1.98, +1.02) P=0.53	
Interaction at 12-week follow-up	+0.32% (-1.46, +2.10) P=0.73			
Change between baseline and 26-week follow-up	+0.33% (-1.48, +2.16)	-0.27% (-2.04, +1.49)	-0.73% (-1.95, +0.28)	-1.13% (-3.69, -0.50)
Between group change: 26 week	+0.63% (-0.32, +1.57) P=0.19		+0.47% (-0.66, +1.59) P=0.42	
Interaction at 26-week follow-up	+0.16% (-1.31, +1.63) P=0.83			

*Median (interquartile range) is shown for the outcome at each time point, as well as for the within-group change. Estimate (95% CI). P values for between-group changes are from the combined results for Hodges-Lehmann Estimation. Data were imputed for individuals who did not die but missed the outcome measure at each visit.

Figure S1. Changes in six minute walk distance by group assignment among black and white participants in the PROPEL Trial.