

Supplementary Online Content

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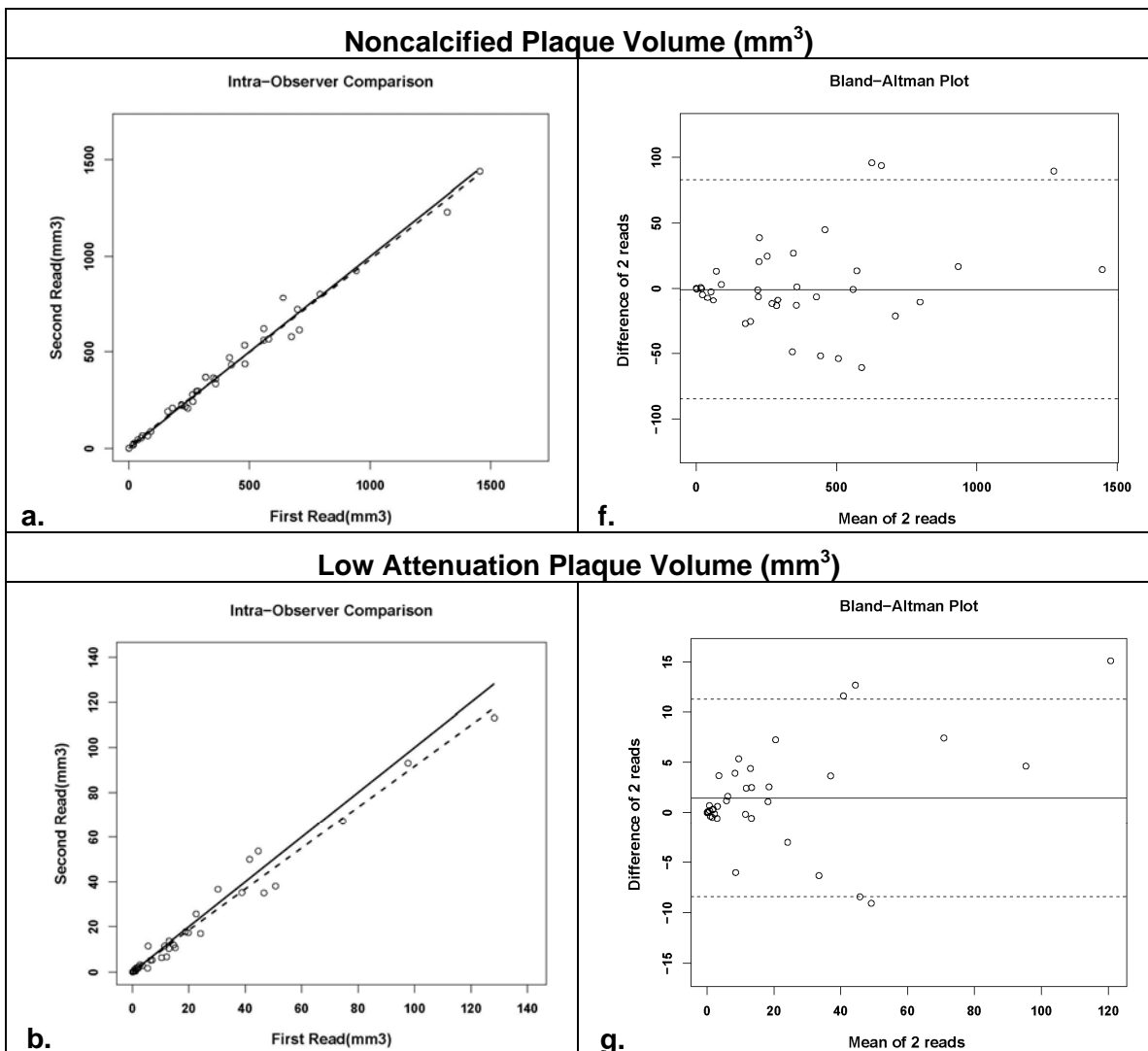
This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Study to Determine the Reproducibility of Assessing Coronary Artery Plaque Volume by Computerized Coronary Tomographic Angiography: Methods and Results

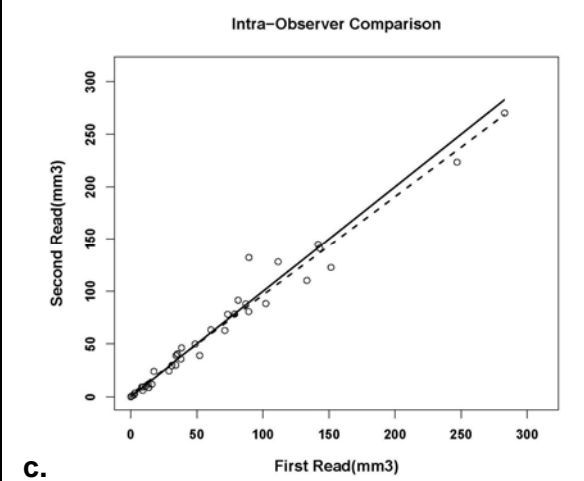
We assessed the reproducibility of the CCTA readings in a study involving 2 readers at the laboratory and a sample of 40 of the 276 scans performed for the study, selected to ensure representation of the full range of plaque volumes. One reader had read the scans originally, a little more than a year prior to the reproducibility evaluation. That reader (Reader 1) did one reading; the second reader (Reader 2) read the scans twice, at least one week apart, with the scans presented in a different order each time. We assessed intra-observer variability by comparing the 2 readings of Reader 2 and assessed inter-observer variability by comparing the current reading of Reader 1 with the second reading of Reader 2, for the primary outcome of noncalcified plaque and each of the 4 plaque components. eFigures 1a-e show the linear regression and Bland-Altman plots for the intra-observer comparisons; eFigures 2a-e show the plots for the inter-observer comparisons. We calculated the intraclass correlations and coefficients of variation for each comparison; these data are shown in eTable 1 and document excellent reproducibility for the primary endpoint of noncalcified plaque volume, with ICC values well above 90% for both intra- and inter-observer reliability. The intra- and inter-observer variability was greater for some of the individual plaque components, for which the ICC values dipped below 90% but remained above 60%, a value considered to represent good agreement [Cicchetti, *Psychological Assessment* 6:284-290, 1994.] We also compared Reader 1's first and second readings, which were done many months apart; these comparisons also showed good reproducibility for the primary outcome of noncalcified plaque, with an ICC for intra-observer variability above 90% and a CV under 20%, both generally accepted thresholds for acceptable reliability, but were more variable than the results of the second reader, whose readings were done closer in time.

eFigure 1. Intra-Observer Reliability

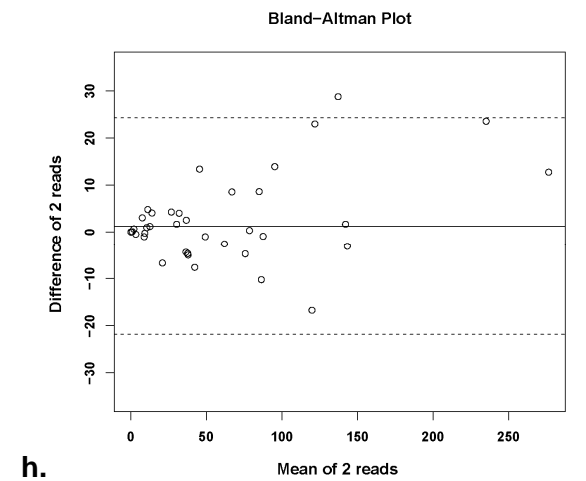
Figures a-e (left) show scatter plots of Reader 2's first and second reads for each of the 40 selected scans for fibrous, fibrous fatty, low attenuation, noncalcified (the sum of fibrous, fibrous fatty and low attenuation values), and dense calcium plaque volumes, respectively. The dashed lines indicate the best-fit regression lines, and the solid lines are the reference lines for exact agreement between the first and second reads. Figures f-j (right) similarly show the Bland-Altman plots of the differences of the two reads versus the means of the two reads for each plaque volume. The solid lines indicate the mean difference of the two reads, and the dashed lines show the Bland-Altman 95% limits of agreement. Randomly scattered points centered about 0 suggest no systematic difference between the two reads.



Fibrous Fatty Plaque Volume (mm³)

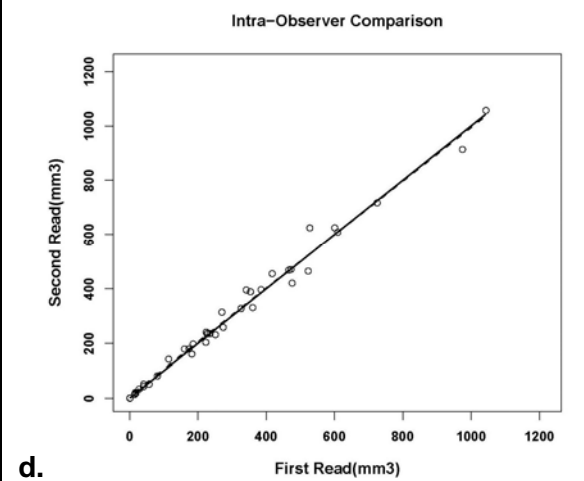


c.

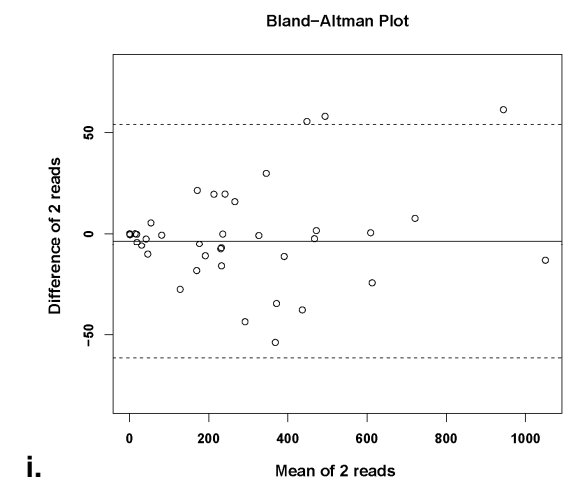


h.

Fibrous Plaque Volume (mm³)

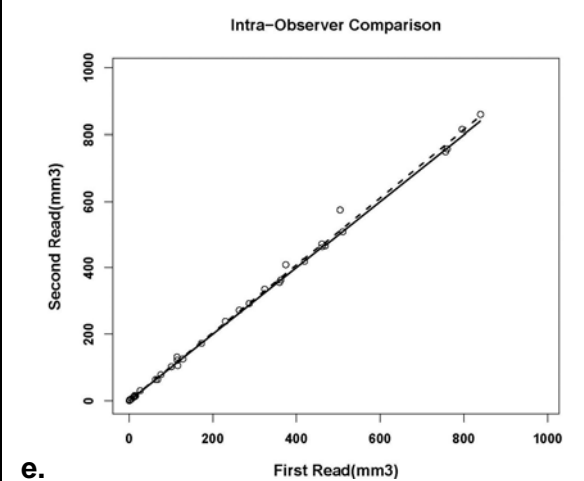


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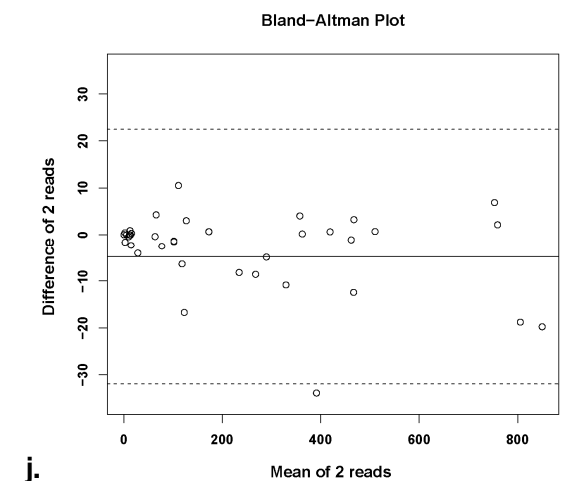


i.

Dense Calcium Plaque Volume (mm³)



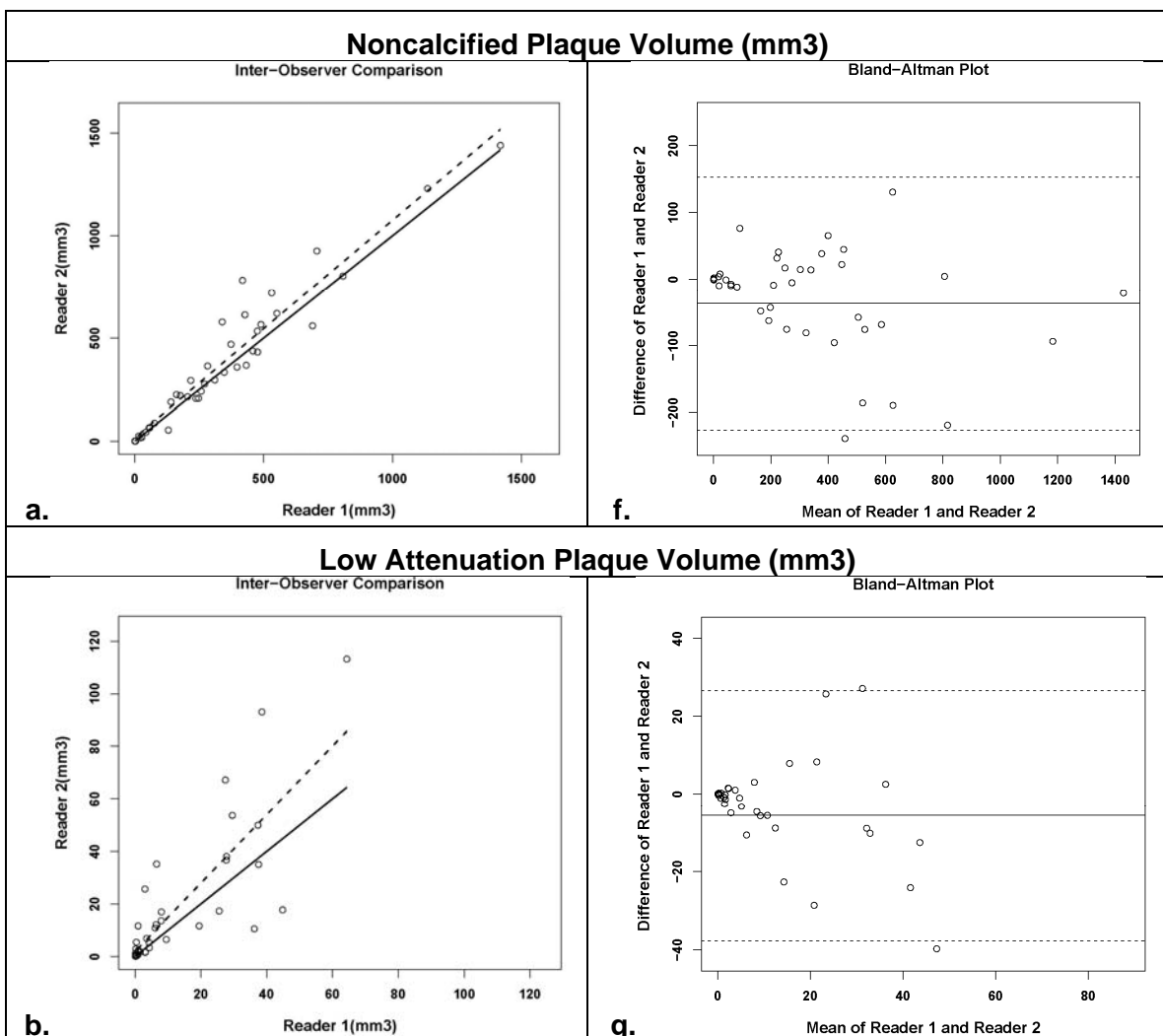
e.



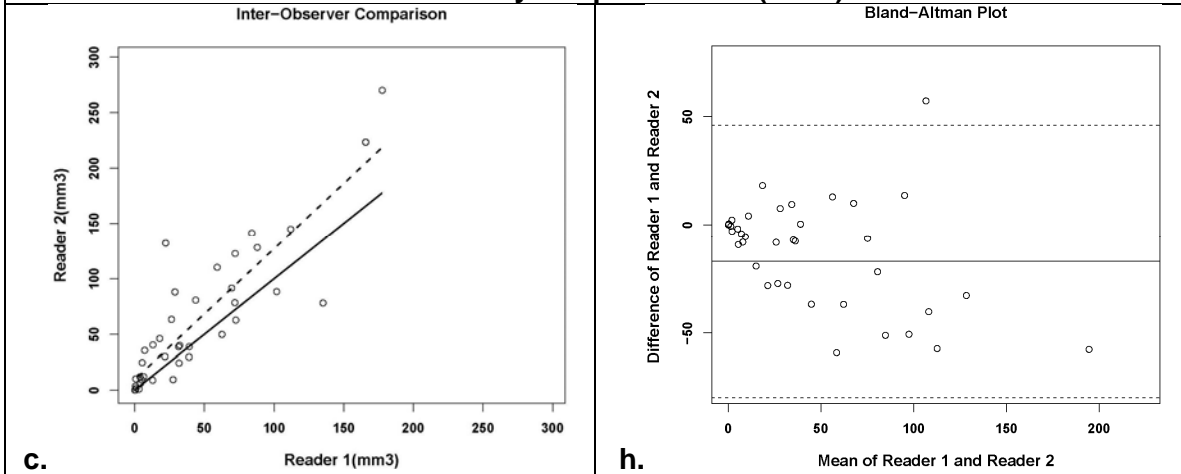
j.

eFigure 2. Inter-Observer Reliability

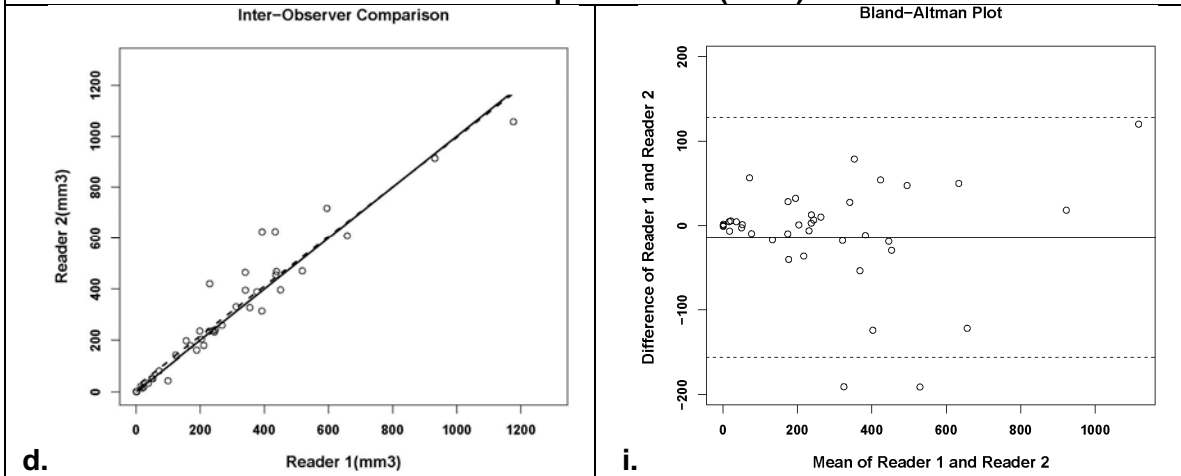
Figures a-e (left) show scatter plots of Reader 1 and Reader 2's second reads for each of the 40 selected scans for fibrous, fibrous fatty, low attenuation, noncalcified (the sum of fibrous, fibrous fatty and low attenuation values), and dense calcium plaque volumes, respectively. The dashed lines indicate the best-fit regression lines, and the solid lines are the reference lines for exact agreement between each reader's second read. Figures f-j (right) similarly show the Bland-Altman plots of the differences of the two reads versus the means of the two reads for each plaque volume. The solid lines indicate the mean difference of the two reads, and the dashed lines show the Bland-Altman 95% limits of agreement. Randomly scattered points centered about 0 suggest no systematic difference between the two reads.



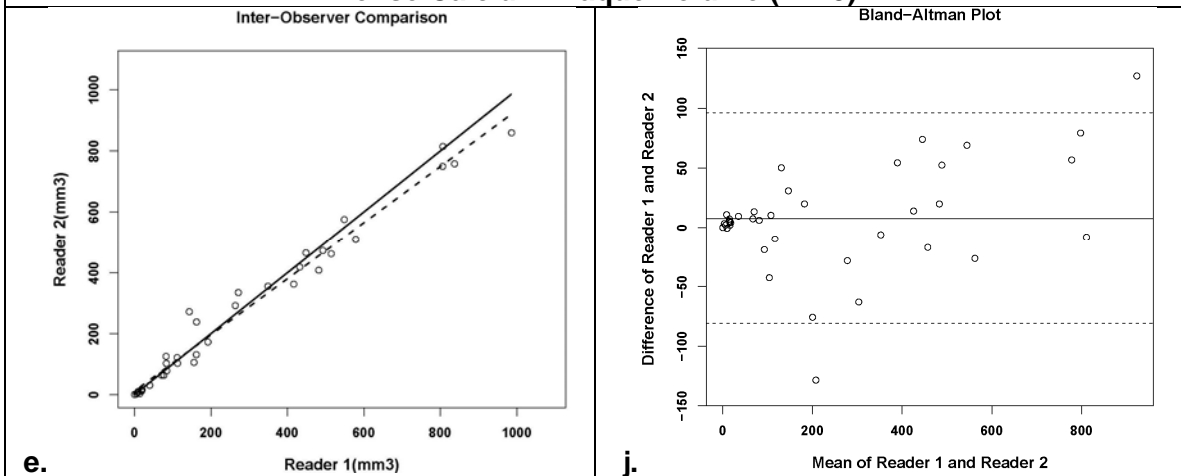
Fibrous Fatty Plaque Volume (mm³)



Fibrous Plaque Volume (mm³)

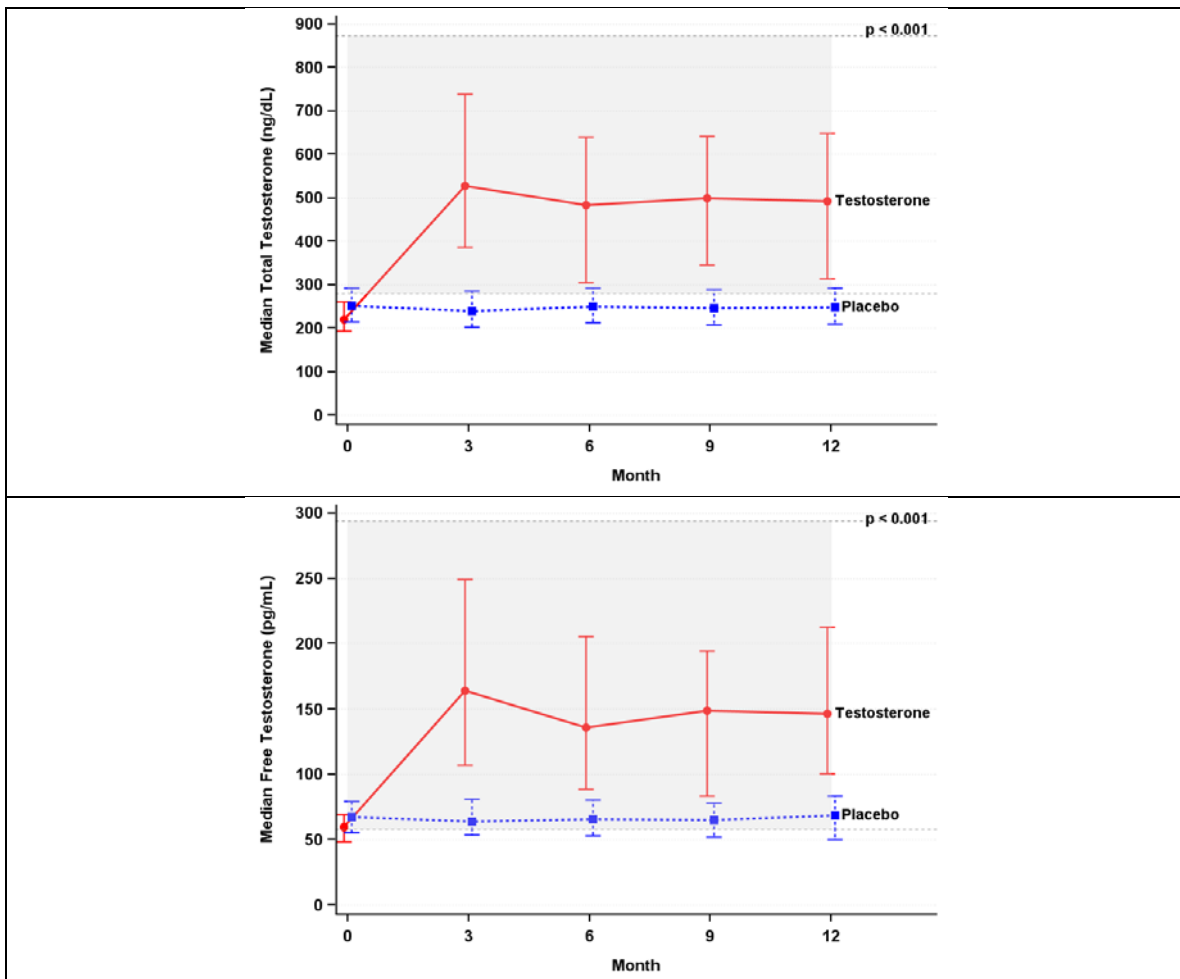


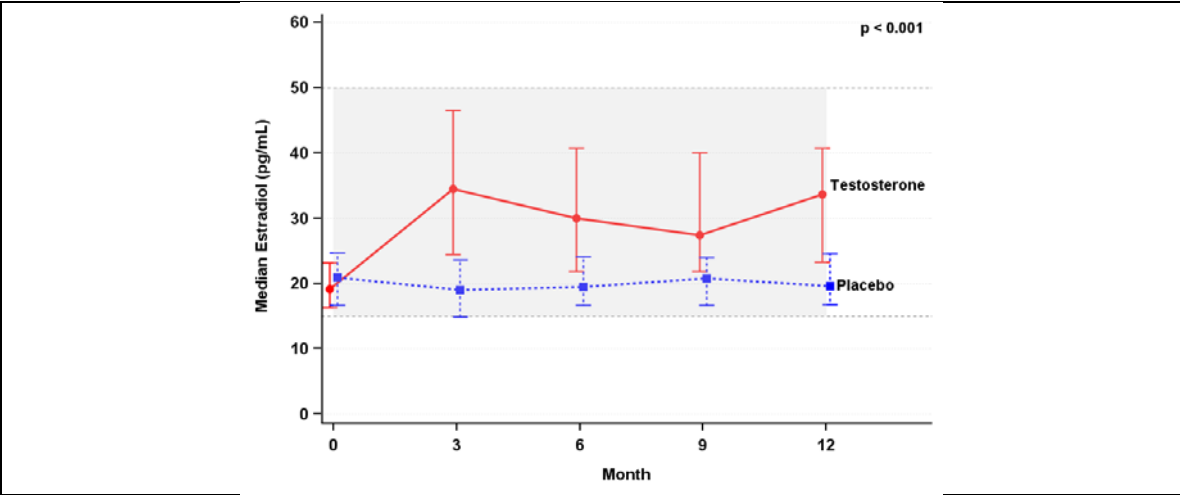
Dense Calcium Plaque Volume (mm³)



eFigure 3. Median (Interquartile Ranges) Serum Concentrations of Testosterone, Free Testosterone and Estradiol From Months 0 to 12 in Men Treated With Testosterone or Placebo in the Cardiovascular Trial

The p-values indicate the significance of the difference in serum concentrations in men in the testosterone arm compared to men in the placebo arm from baseline to month 12. For each plot, 73 men in the testosterone group and 65 men in the placebo group were evaluated, except for Month 3 when there are values for 64 men in the placebo group. The shaded areas represent the normal ranges for healthy young men. To convert the values for testosterone to nmol/L, multiply by 0.0347; to convert the values for free testosterone to pmol/L, multiply by 3.47; to convert the values for estradiol to pmol/L, multiply by 3.67.





eTable 1. Reproducibility of Plaque Volume Measurements

Plaque Type	Intra-reader				Inter-reader	
	Reader 1		Reader 2		Coefficient of Variation (%)	Intracluster Correlation Coefficient
	Coefficient of Variation (%)	Intracluster Correlation Coefficient	Coefficient of Variation (%)	Intracluster Correlation Coefficient		
Noncalcified Plaque ¹	28.69	0.9123	7.8	0.9927	19.93	0.952
Total Plaque ²	16.12	0.9724	5.14	0.997	12.04	0.9828
Fibrous	19.82	0.9536	6.86	0.9938	17.41	0.9606
Fibrous Fatty	72.26	0.6531	13.35	0.9841	48.77	0.7987
Low Attenuation	125.28	0.4344	19.21	0.9829	78.71	0.7109
Dense Calcium	14.86	0.9821	6.86	0.9985	12.82	0.9864

- 1 Noncalcified plaque volume is the sum of the fibrous, fibrous fatty and low attenuation plaque volumes.
- 2 Total plaque volume is the sum of the noncalcified and dense calcium plaque volumes.

eTable 2. Overlap of Participation in the 3 Main Trials (Sexual Function, Physical Function, and Vitality) With Participation in the Cardiovascular Trial, by Treatment Group

Allocation	Testosterone	Placebo	All
Enrolled in Cardiovascular Trial	n=88	n=82	N=170
Main Trials Participation			
Physical Function Trial Only	9	8	17
Sexual Function Trial Only	12	16	28
Vitality Trial Only	11	12	23
Physical Function and Vitality Trial	14	10	24
Physical Function and Sexual Function Trial	8	11	19
Sexual Function and Vitality Trial	19	14	33
All 3 Trials (Physical Function, Sexual Function and Vitality)	15	11	26