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 1. Methods

Measures of Discrimination

We used the "roccomp" procedure in Stata 13.0 to compute and compare the AUC of the model-based predicted probability of dying during follow-up with the observed outcome (death vs. survival). The traditional Net Reclassification Improvement (NRI)[1] requires clinically meaningful risk strata, therefore we used four categories (low [10-year risk of CV events < 10%], low-intermediate [10-year risk of CV events between 10% and< 15%], high-intermediate [10-year risk of CV events between 15% and< 20%] or high [10-year risk of CV events ≥20%] cardiovascular risk). We also used a newer category-free version, continuous NRI(>0),[2] which quantifies the correct movement of model-based probabilities when additional markers are added to the model: downward for survivors and upward for decedents.[3] An alternative measure, the Integrated Discrimination Improvement (IDI), can be interpreted as the difference in discrimination slopes of models with and without the new markers, where the discrimination slope is the absolute difference in the average prediction between those who experienced the event and those who did not.[3] Although there are no established benchmarks, Pencina et al.[4] suggest ΔAUC>0.01 represents a meaningful improvement, while continuous NRI greater than 0.2 implies at least moderate improvement. Researchers do not provide a corresponding gauge for IDI.

eAppendix 2. Results

There were no major differences in distribution between gender, age and race especially taking into consideration the different age and systolic blood pressure (SBP) in each group (eFigure 1 and 2). As expected there was a correlation between estimated pulse wave velocity (ePWV) and SBP (r=0.497, p<0.001; eFigure 3A). Furthermore, the correlation between ΔSBP and ΔePWV was much higher (r=0.948, p<0.001; eFigure 3B).

Analysis of the predictive role of ePWV when adjusting for mean blood pressure (MBP)

ePWV predicted all-cause death, primary outcome, stroke, heart failure, cardiovascular death and non-cardiovascular death independently of FRS and other relevant confounders, even after adjustment for baseline MBP ($p \leq 0.01$ for all).

Furthermore, ePWV significantly modestly improved the Cox regression models for both all-cause death and primary outcome. Specifically, addition of ePWV modestly improved the C index from 0.67 (95 % CI: 0.64–0.70) of Model to 0.69 (95 % CI: 0.66–0.72) with p<0.05 for all-cause death. Correspondingly, the addition of ePWV modestly improved the C index from 0.676 (95 % CI: 0.652–0.699) of the Model to 0.683 (95 % CI: 0.660–0.706) with p<0.05 for the primary outcome. ePWV reclassified hypertensive patients for all-cause death with a statistically significant categorical NRI (catNRI) for Model categories (catNRI=0.113, p<0.001). Furthermore, the estimated IDI was 0.009 (p<0.001). Similarly, improvement of catNRI was statistically significant for the primary outcome (catNRI=0.045, p=0.007) Moreover, the estimated IDI was 0.002 (p=0.005).

Regarding the response to treatment, results were similar when adjusted for MBP and change in MBP instead of SBP. Specifically, in the standard treatment arm independently of change in MBP, responders had a lower risk compared to non-responders (HR=0.49 [95% CI: 0.29-0.82]; p=0.007).

eReferences

1. Pencina MJ, D'Agostino RB,Sr., D'Agostino RB,Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27(2):157,72; discussion 207-12.
2. Pencina MJ, D'Agostino RB S, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30(1):11-21.
3. Goldman N, Glei DA. Quantifying the value of biomarkers for predicting mortality. Ann Epidemiol 2015;25(12):901,906.e4.
4. Pencina MJ, D'Agostino RB, Pencina KM, Janssens ACW, Greenland P. Interpreting incremental value of markers added to risk prediction models. Am J Epidemiol 2012 Sep 15;176(6):473-81.

eTable 1. Cox Regression Models Predicting the Principal End Points in the SPRINT Trial and Adjusted for Model (Including Framingham Risk Score) Risk, With Estimated Pulse Wave Velocity (ePWV)

Hazard ratios	Only Model with FRS	+ ePWV
Primary outcome		
ePWV per 1-SD (1.7 m/s)		1.30 (1.17–1.43)
Chi^2	275.0	322.2
-2LogLikelihood	13099	13052
C index	0.676 (0.65–0.70)	0.683 (0.66–0.71)*
All-cause death		
ePWV per 1-SD (1.7 m/s)		1.65 (1.46–1.86)
Chi^2	142.8	205.8
-2LogLikelihood	6273	6210
C index	0.67 (0.64–0.69)	0.69 (0.66–0.72)*
Primary outcome or death		
ePWV per 1-SD (1.7 m/s)		1.36 (1.25–1.48)
Chi^2	235.0	260.1
-2LogLikelihood	9737	9712
C index	0.67 (0.65–0.69)	0.68 (0.66–0.70)*

*p<0.05 for the comparison of the "Model that includes FRS" versus the Model "+ePWV"
The numbers in parenthesis represent the 95% confidence interval.

eTable 2. Reclassification of the Predicted Risk of Death by ePWV When Added to Model (Including FRS)

Based on the Model (including FRS)	**Risk Category for All-Cause Death for the Model with FRS Additionally Considering ePWV**				
	<10%	**10-15%**	**15-20%**	**>=20%**	**Total**
Events (n=362)					
<10%	280	33	5		318
10-15%	3	10	12	5	30
15-20%	1	3	1	2	7
≥20%	1		3	3	7
Total	285	46	21	10	362
Non-events (n=8,950)					
<10%	8,452	193	15		8,660
10-15%	80	83	38	12	213
15-20%	12	23	17	10	62
≥20%	1	3	7	4	15
Total	8,545	302	77	26	8,950

Reclassified Downward (%) 11/362 (events) and 126/8950 (non-events), Reclassified Upward (%) 57/362 (events) and 268/8950 (non-events)

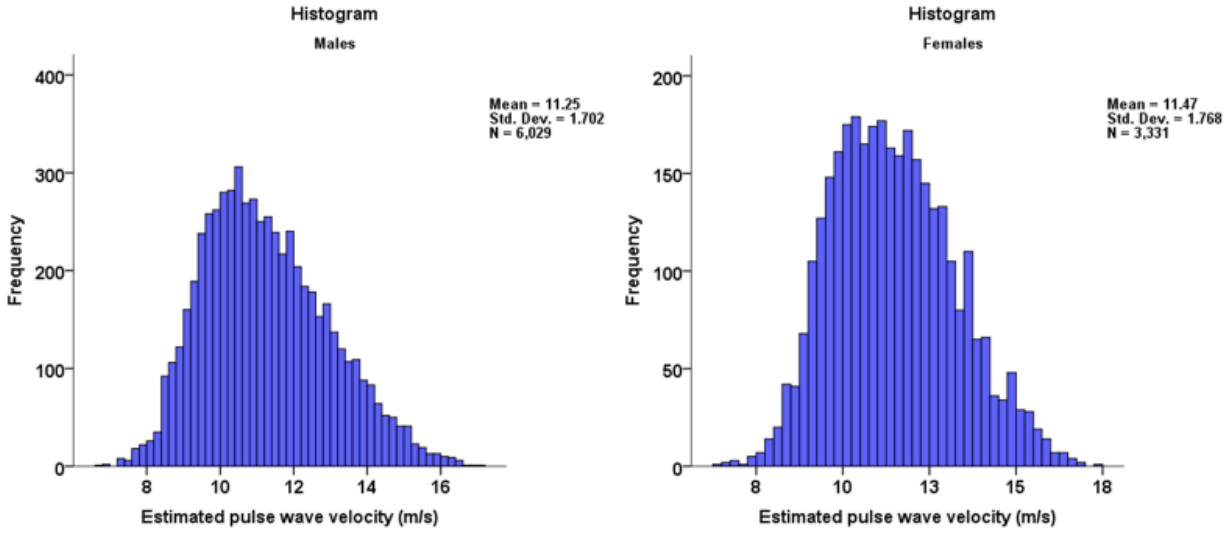
The bold values represent the percentages of predicted risk in the given population. The vertical values represent the risk with our initial Model that includes Framingham risk score and the horizontal values represent the risk with our initial Model plus ePWV. The non-bold figures in the upper events section represent subjects that suffered an event during follow-up categorized based on their predicted risk by each Model, while in the lower non-events section represent subjects that were free of events during follow-up categorized based on their predicted risk by each Model. Overall NRI=Pr(up|event) - Pr(down|event)] + [Pr(down|nonevent) - Pr(up|nonevent)] = event NRI - nonevent NRI = 46/362 - 162/8950=0.127-0.016=0.111

eTable 3. Hazard Ratios and 95% CI for the Comparison Between Responses to Treatment Groups in the Cox Regression Survival Analysis

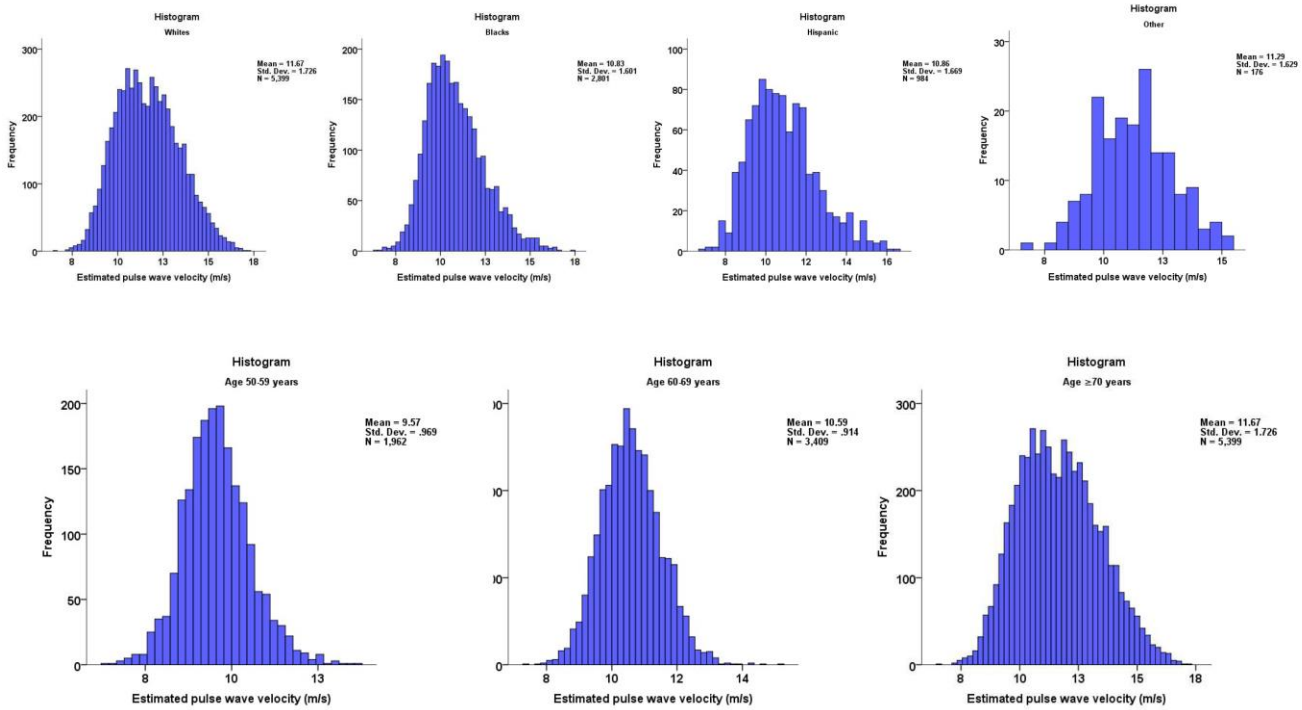
All-cause death / Primary outcome	**Group 1*** Standard treatment /ePWV non-responders		**Group 2** Standard treatment /ePWV responders		**Group 3** Intensive treatment /ePWV non-responders		**Group 4** Intensive treatment /ePWV responders	
Group 1 Standard treatment/ePWV non-responders			HR=0.72 [95% CI: 0.47-1.09]	p=0.12	HR=0.54 [95% CI: 0.30-0.97]	**p=0.04**	HR=0.49 [95% CI: 0.30-0.78]	**p=0.003**
Group 2 Standard treatment/ePWV responders	HR=0.93 [95% CI: 0.66-1.32]	p=0.69			HR=0.75 [95% CI: 0.41-1.40]	p=0.37	HR=0.68 [95% CI: 0.48-0.94]	**p=0.02**
Group 3 Intensive treatment/ePWV non-responders	HR=0.79 [95% CI: 0.51-1.23]	p=0.30	HR=0.85 [95% CI: 0.53-1.36]	p=0.50			HR=0.90 [95% CI: 0.47-1.71]	p=0.74
Group 4 Intensive treatment/ePWV responders	HR=0.59 [95% CI: 0.39-0.88]	**p=0.009**	HR=0.63 [95% CI: 0.48-0.83]	**p=0.001**	HR=0.74 [95% CI: 0.45-1.21]	p=0.23		

*In every box the Group where two Groups are compared the one with the smaller number is used as reference Group.

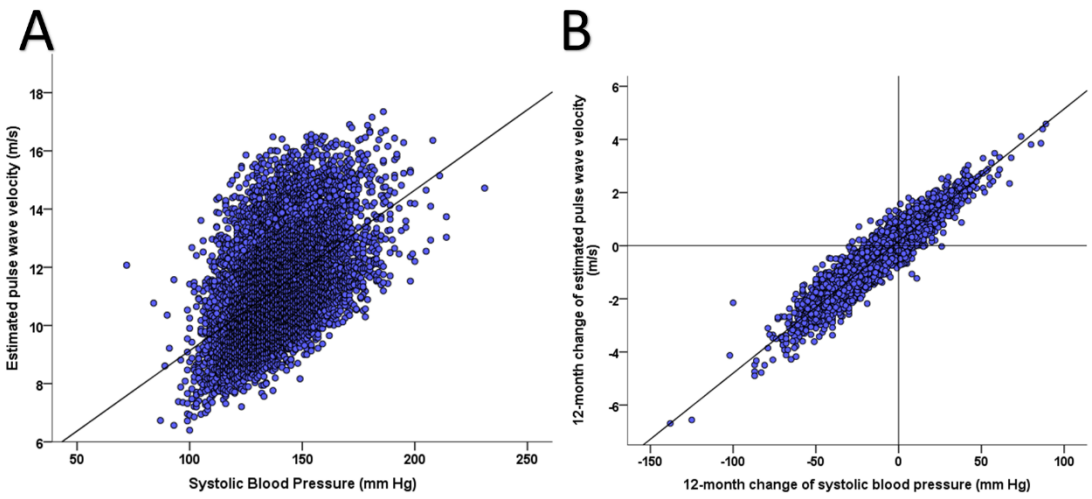
eFigure 1. Histograms of Estimated Pulse Wave Velocity Based on Sex



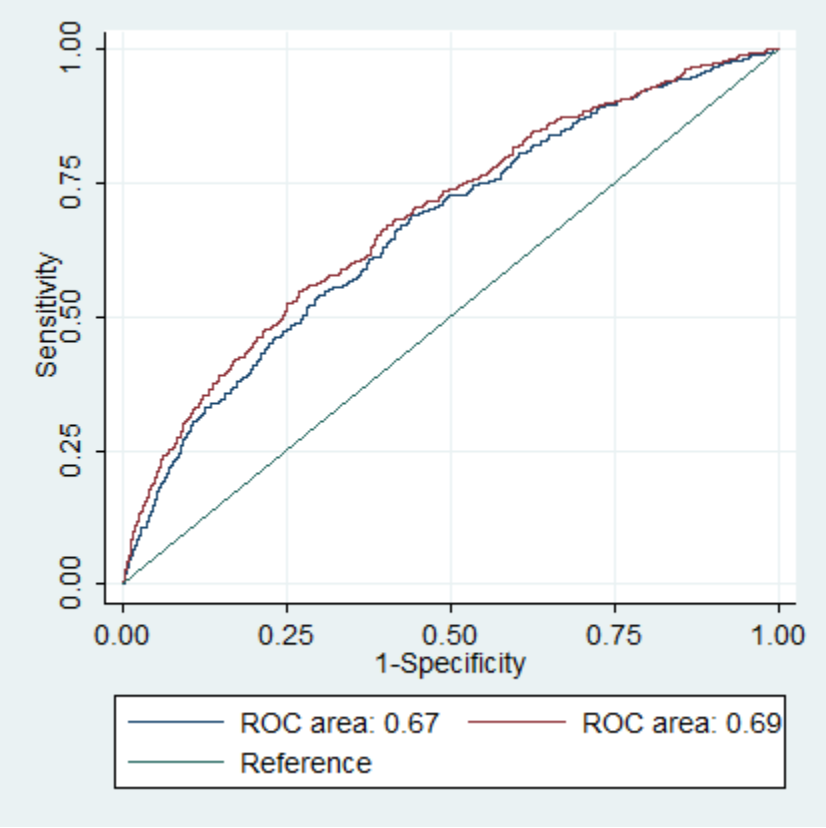
eFigure 2. Histograms of Estimated Pulse Wave Velocity Based on Race and Age Groups



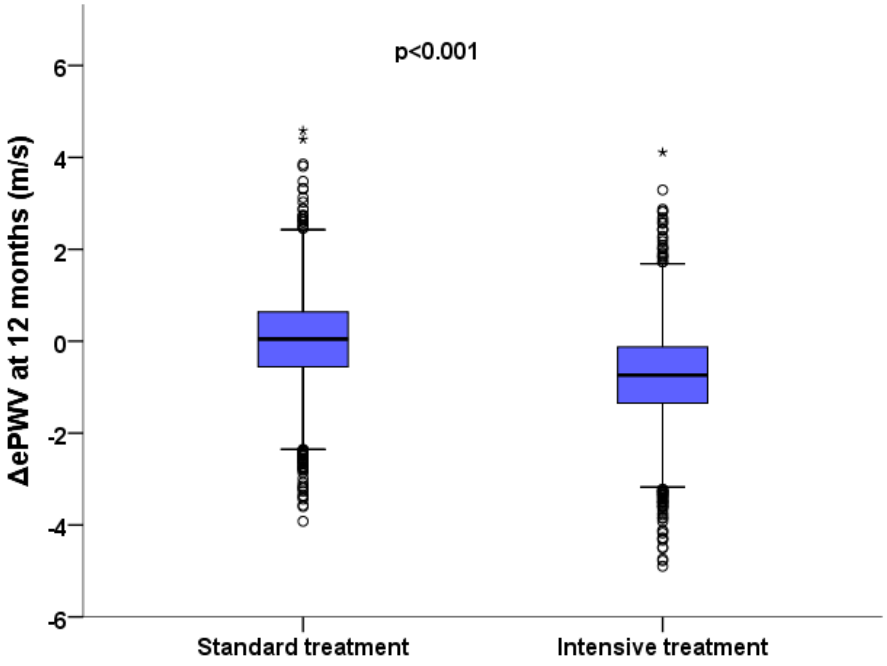
eFigure 3. Correlation Between (A) Estimated Pulse Wave Velocity and Systolic Blood Pressure and (B) Between Their 12-Month Changes



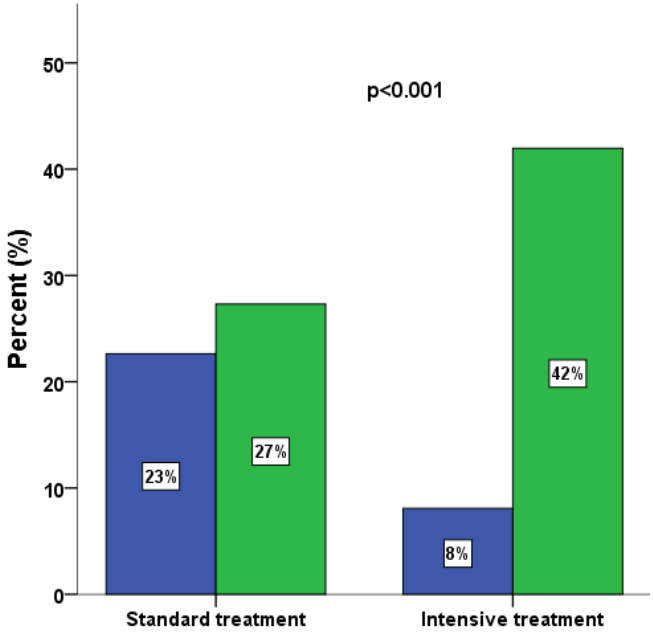
eFigure 4. Receiver Operating Curves for the Primary Outcome and All-Cause Death



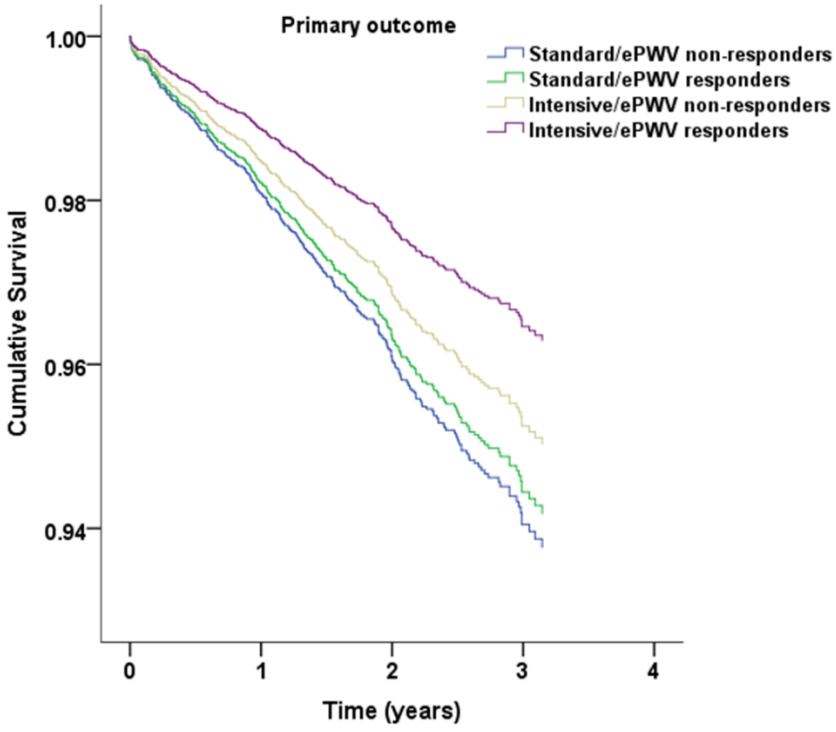
eFigure 5. The Change of Estimated Pulse Wave Velocity at 12 Months in the Two Treatment Arms



eFigure 6. Proportion of Estimated Pulse Wave Velocity (ePWV) Responders (Green Bars) Compared to Nonresponders (Blue Bars) in the Two Treatment Arms



eFigure 7. The Combined Effect of Treatment Allocation and Response of Estimated Pulse Wave Velocity (ePWV) to Treatment on the Primary Outcome
Time zero is 12 months post-randomization



Number at risk				
Standard/ePWV non-responders	1884	1798	1183	296
Standard/ePWV responders	2256	2172	1490	396
Intensive/ePWV non-responders	669	644	426	102
Intensive/ePWV responders	3486	3372	2334	649