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Plasma Amyloid-β, Neurofilament Light Chain, and Total Tau in the Systolic Blood Pressure Intervention Trial (SPRINT)

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Data Sharing Statement

De-identified participant data will be available in the BioLinCC repository (https://biolincc.nhlbi.nih.gov/studies/sprint).

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Abstract

Introduction: Blood pressure (BP) lowering reduces the risk for cognitive impairment and the progression of cerebral white matter lesions. It is unclear whether hypertension control also influences plasma biomarkers related to Alzheimer's disease and non-disease-specific neurodegeneration.

Methods: We examined the effect of intensive (<120 mm Hg) vs standard (<140 mm Hg) BP control on longitudinal changes in plasma $A\beta_{40}$ and $A\beta_{42}$, total tau, and neurofilament light chain (NfL) in a subgroup of participants from the Systolic Blood Pressure Intervention Trial (N=517).

Results: Over 3.8 years, there were no significant between-group differences for $A\beta_{40,}$ $A\beta_{42,}$ $A\beta_{42}$ / $A\beta_{40,}$ or total tau. Intensive treatment was associated with larger increases in NfL compared to standard treatment. Adjusting for kidney function, but not BP, attenuated the association between intensive treatment and NfL.

Discussion: Intensive BP treatment was associated with changes in NfL, which were correlated with changes in kidney function associated with intensive treatment.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01206062

1. INTRODUCTION

Meta-analyses of randomized trials have indicated that blood pressure (BP) lowering reduces the incidence of dementia [1,2]. Observational data [3,4], the Systolic Blood Pressure Intervention Trial (SPRINT) [5], and other randomized trials [6,7] have shown hypertension and its control are also associated with the presence and progression of white matter lesions. While cerebrovascular mechanisms are a likely explanation for the reduction in cognitive impairment observed in SPRINT [8], studies have also shown that vascular risk is associated the presence of brain amyloid deposition based on positron emission tomography [9] and that antihypertensive treatment is associated with a reduced risk of incident dementia and Alzheimer's disease (AD) [10]. It is, however, unknown whether intensive BP control may impact biomarkers of AD pathology, which frequently co-occurs with vascular contributors to dementia. There is considerable observational evidence that vascular damage may contribute to the progression of AD neuropathology [11,12], but causal experimental evidence to this effect is lacking [13]. Intensive BP control in SPRINT has also been associated with greater decreases in total brain and hippocampal volumes [5,14], but not with changes in other magnetic resonance imaging (MRI) markers that are sensitive, but not specific for, AD-related neurodegeneration [14].

The characterization of AD has transitioned to a biological definition of the disease, relying upon quantitative measurements of beta-amyloid, tau, and neurodegeneration via imaging or cerebrospinal fluid [15]. Given the expense of imaging, patient burden related to imaging and cerebrospinal fluid sampling, and resulting potential selection biases, there is a major effort to use and calibrate blood based protein biomarkers [16–18] to reduce both the burden

and cost of identifying pathologic AD. Using stored samples from a subgroup of SPRINT participants, here we examine the effect of intensive BP control on changes in plasma biomarkers related to AD and neurodegeneration more broadly (beta-amyloid, total tau, and neurofilament light chain). In addition, given the known effects of intensive treatment on kidney function [19,20], an important modulator of the composition of the blood proteome [21], we also explored the association of these biomarkers with changes in kidney function.

2. METHODS

2.1 Trial design

The trial design and methods have been published previously [22,23]. Briefly, we conducted a multicenter randomized clinical trial that compared two strategies for managing systolic BP (SBP) in older adults with hypertension who were at increased risk of cardiovascular disease. Participants were aged 50 years or older and had an SBP between 130 and 180 mm Hg at the screening visit, depending on the number of anti-hypertensive agents prescribed. Participants were considered to have an increased cardiovascular risk if they had clinical or subclinical cardiovascular disease, chronic kidney disease (defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2), or a Framingham Risk Score of 15% or greater or if they were aged 75 years or older. Individuals residing in a nursing home, persons with a diagnosis of dementia (based on medical record review), and those treated with medications primarily used for dementia therapy were excluded, as were persons with prevalent diabetes mellitus, history of stroke, proteinuria > 1 gram per day, or polycystic kidney disease. Individuals at 102 sites in the United States and Puerto Rico were randomized (1:1) to a SBP goal of less than 120 mm Hg (intensive treatment group, n = 4678) or a goal of less than 140 mm Hg (standard treatment group, n = 4683), using random permuted blocks with the randomization stratified by clinic site. The algorithms and formulary for the trial are listed in the published study protocol [8,23]. Trial enrollment began in November 2010 and ended in March 2013, with follow-up through July 1, 2016. The study was approved by the institutional review board at each participating site, and each participant provided written informed consent. The study is registered at ClinicalTrials.gov (NCT01206062).

2.2 Magnetic resonance imaging sub-study

A subset of participants (n = 2913) were recruited into a cognitive function sub-study to more extensively evaluate the effects of intensive SBP control on specific domains of cognitive function [24]. MRI scans were obtained in a further subset of these participants to evaluate brain structure [5]. All participants accessible to any one of 7 designated MRI sites (drawing from 27 clinic sites) were screened for the MRI sub-study, and eligible participants provided written informed consent. Exclusion criteria for the MRI sub-study included any implanted electrical medical device, such as a pacemaker, any MRI-incompatible or MRI compatibility unknown metallic foreign material, or claustrophobia. Structural MRI of the brain included 1-mm isotropic T1, T2, and fluid-attenuated inversion recovery imaging, and was processed using an automated pipeline [5].

2.3 Core laboratory measures

Participants were instructed to fast overnight for the randomization visit and for annual follow-up assessments. Blood was collected by venipuncture at the clinical sites into EDTA-plasma tubes, chilled for 20-30 minutes in a refrigerator, and then centrifuged for 10-15 minutes at 1800-1900 x g. Plasma was transferred into transport tubes, refrigerated, and shipped overnight on ice-cold gel packs the day of collection to the SPRINT Central Laboratory at the University of Minnesota. On receipt in the Laboratory, samples were aliquoted into 0.5 mL cryovials and stored at −70°C. Serum and urine creatinine were measured using a method traceable to isotope dilution mass spectrometry. Urine creatinine was measured with the Siemens ProSpec nephelometric analyzer. We calculated the estimated glomerular filtration rate (eGFR) with the Chronic Kidney Disease Epidemiology Collaboration equation [25]. Serum bicarbonate was measured at baseline using an enzymatic method with phosphoenolpyruvate carboxylase using Roche CO2-L reagent and Roche Cobas 6000 Chemistry Analyzers (Roche Diagnostics Corporation).

2.4 Plasma biomarkers

This work was intended as a pilot study. We included participants from the MRI sub-study that were 60 years or older at the time of randomization because biomarker changes would be most likely to be observed in older trial participants (Figure S1). We used stored plasma samples from the baseline visit, and then, if available, from a single follow-up visit for each participant (median follow-up of 3.8 years [interquartile range, 3.5 to 4.0 years]). For participants who completed the follow-up MRI assessment, we utilized the stored follow-up sample nearest to the date of the follow-up MRI. For participants who did not complete the follow-up MRI, we utilized their latest available stored follow-up sample (Table S1). Assays for plasma human beta-amyloid 40 ($A\beta_{40}$), beta-amyloid 42 ($A\beta_{42}$), total tau, and neurofilament light chain (NfL) were performed at the University of Kentucky on a single molecule-array (Simoa) HD-1 analyzer platform. NfL was measured using the Simoa Nf-light advantage kit. $A\beta_{40}$, $A\beta_{42}$, and total tau were assessed using the Simoa Human Neurology 3-Plex A assay. Frozen plasma samples from the SPRINT Central Laboratory were shipped on dry ice without thawing to the University of Kentucky where they were stored at −80°C. Samples were then thawed on ice and centrifuged at maximum speed for 10 minutes at 4°C. All samples were assayed in duplicate and were run with kits from the same lot for each analyte. Samples were randomly distributed across assay batches, with paired baseline and follow-up samples always performed within the same assay batch. While the median coefficients of variation by assay batch were generally <10% for $A\beta_{40}$, $A\beta_{42}$, and total tau, coefficients of variation were consistently higher for NfL (10-20%, Table S2).

2.5 Assessment of cognitive function

Methods for neuropsychological testing of cognitive function have been previously described [8,24]. All participants in the MRI sub-study were administered a comprehensive cognitive battery at baseline including the Montreal Cognitive Assessment, Logical Memory I and II, Digit Symbol Coding, Trail Making Test Parts A and B, Hopkins Verbal Learning Test-Revised, Modified Rey-Osterreith Complex Figure (Copy and Immediate Recall), Digit Span, Category Fluency – Animals, and the 15-item Boston Naming Test. Centrally trained

and certified examiners administered the cognitive tests. They were administered in either English or Spanish, depending on the participant's preferred language. Here we utilize composite cognitive domain scores at baseline representing memory, processing speed, executive function, language, and global cognitive function. Each composite domain score was calculated as the average of specific standardized test scores [24].

2.6 Statistical analyses

Because of skewed distributions for some of the biomarkers, Spearman rank correlations and partial correlation coefficients [26] adjusting for age (or age and eGFR) were used to describe correlations between measures at baseline. Robust linear mixed models, including random effects for participant and assay batch, were used to estimate the change in each plasma biomarker between the BP treatment groups, including time since randomization as a covariate [27]. Intuitively, robust mixed models address skewed outcome distributions by down-weighting observations with large residuals or random effects, reducing their influence on model estimates. We also conducted several sensitivity analyses. First, we fit models adjusting for baseline and follow-up SBP, diastolic BP, or eGFR measured at the same study visit as the biomarkers. Second, we examined treatment group differences as a function of the baseline level of each biomarker and white matter lesion volumes. All hypothesis tests were 2-sided, and P values less than .05 were considered statistically significant. No adjustments for multiple comparisons were made.

2.7 Role of the funding source

The National Institutes of Health and the US Department of Veterans Affairs had roles in the design and conduct of the trial; collection, management, analysis, and interpretation of the data; and in the preparation and review of the manuscript. Neither was involved in formal approval of the manuscript or the decision to submit the manuscript for publication. The Alzheimer's Association had a role in the design and conduct of the biomarker study; but not in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

3. RESULTS

3.1 Baseline characteristics

Table 1 contains baseline information for participants 60 years or older in this biomarker sub-study, with 283 randomized to intensive treatment and 234 to standard treatment. At baseline, participants had a mean age of 69.9 ± 7.1 years, 42.9% were female, and 28.2% were Black. Participants had a mean SBP of 138.3 ± 16.8 mm Hg, and mean eGFR of 70.6 ± 18.6 ml/min/1.73 m^2, with 29.8% having an eGFR <60 ml/min/1.73 m^2. In comparison to non-included trial participants who were 60 years or older at the time of randomization (Table S3), participants in the biomarker sub-study were younger, more likely to be female, were less likely to have a history of cardiovascular disease, had higher mean eGFR levels, and higher baseline cognitive test scores. Table S4 includes comparative data from the Rotterdam Study (mean age 71.9 ± 7.5 years, 58.0% female), where plasma biomarkers were measured using the same Simoa kits [28]. In comparison to that population,

participants in this sub-study had higher levels of $A\beta_{42}$ and total tau, lower levels of $A\beta_{40}$, with similar levels of NfL.

3.2 Cross-sectional associations with plasma biomarkers

Figure 1 displays baseline cross-sectional correlations between the plasma biomarkers and age, vital signs, and laboratory measures. All of the biomarkers were positively correlated with age, with the strongest associations observed for NfL (Spearman's rho = 0.43, p<0.001) and $A\beta_{40}$ (rho = 0.27, p <0.001). Adjusting for age, NfL (partial Spearman's correlation (PSC) = −0.30, p<0.001) and $A\beta_{40}$ (PSC = −0.32, p<0.001) were also negatively correlated with eGFR. Table S5 displays baseline levels for each biomarker stratified by eGFR. With the exception of the ratio $A\beta_{42}$ / $A\beta_{40}$, all of the biomarkers exhibited increasing levels with lower eGFR. Baseline correlations between the biomarkers, neuropsychological test scores, and structural MRI measures were generally much weaker, with no significant partial correlations after accounting for age and eGFR (Figure 1).

3.3 Association of intensive treatment with changes in plasma biomarkers

Figure 2 displays the association between changes in each biomarker with BP treatment group. For each of the biomarkers, with the exception of $A\beta_{42}$ / $A\beta_{40}$ [29], increases would generally be associated with a more pathogenic state and increased risk for dementia. The mean change per year (MCPY) for $A\beta_{40}$ was an increase of 11.8 pg/ml (95% CI: 9.2 to 14.4) with intensive treatment, as compared to 7.8 pg/ml (95% CI: 4.9 to 10.8) for standard treatment (p=0.05, Table S6). We observed larger mean increases in NfL with intensive treatment (between-group difference in MCPY = 0.8 pg/ml, 95% CI: 0.3 to 1.2, p=0.002). There were no significant differences for change in $A\beta_{42,}$ $A\beta_{42}$ / $A\beta_{40}$, or total tau between the treatment groups.

3.4 Sensitivity analyses

We also investigated how changes in eGFR might influence our results, given the early initial decline in eGFR associated with intensive BP treatment (Figure S2) [30]. During follow-up, 17 participants (6.0%) in the intensive treatment group experienced a ≥30% decline in eGFR on or before the collection of the follow-up blood sample used in this study, as compared to 2 (0.8%) in the standard treatment group. While based on a small number of participants, we found that the 19 participants that experienced a ≥30% decline in eGFR had significantly larger increases for all of the biomarkers with the exception of $A\beta_{42}$ / $A\beta_{40}$ (Table S7). For example, the MCPY for $A\beta_{40}$ was 30.0 pg/ml (95% CI: 19.8 to 40.1) for participants who experienced a ≥30% decline in eGFR, as compared to a MCPY of 9.3 pg/ml (95% CI: 7.4 to 11.3) for participants that did not (between-group difference = 20.6 pg/ml, 95% CI: 10.3 to 30.9, p<0.001). Experiencing a 30% decline in eGFR was similarly associated with larger increases in NfL (between-group difference in MCPY = 2.2 pg/ml, 95% CI: 0.9 to 2.4, 0.001). When we adjusted treatment group comparisons for both baseline and follow-up eGFR, the between-group difference for NfL was attenuated (Table 2). In comparison, the effect on NfL was not attenuated when we analogously adjusted for either SBP or diastolic BP (Table 2).

Figure 3 shows estimated mean differences between intensive and standard treatment on follow-up levels for each plasma biomarker as a function of baseline concentration. We did not observe evidence of statistical interactions with baseline levels for $A\beta_{40}$, $A\beta_{42}$, total tau, or NfL. While there was nominal evidence of heterogeneity with $A\beta_{42}$ / $A\beta_{40}$, estimates were consistent with a null effect of intensive treatment overall and were driven by a small number of participants with high values for $A\beta_{42}$ / $A\beta_{40}$. There were also no significant interactions in follow-up plasma concentrations as a function of baseline white matter lesion volume (Figure S3).

4. DISCUSSION

In this sub-study of a large randomized clinical trial, intensive SBP control resulted in greater increases in plasma NfL, which was attenuated by accounting for treatment-related changes in kidney function, as assessed by eGFR. There were not significant between-group differences for longitudinal change in $A\beta_{40}$, $A\beta_{42}$, $A\beta_{42}$ / $A\beta_{40}$, and total tau. SPRINT [5] and other randomized trials [6,7] have shown that intensive SBP control reduces the progression of cerebral white matter lesions measured via MRI. These results add to other observations that intensive BP treatment is associated with larger changes, albeit small, for several non-specific measures of atrophy and neurodegeneration, including TBV [5], hippocampal volume [14], and now plasma NfL. However, because all of these results emanate from the smaller and non-representative MRI sub-study in SPRINT, the implications of these biomarker results for the differences in adjudicated cognitive status observed in SPRINT remains unclear [8]. Several explanations are possible, though the most likely are selection biases due to sampling for the MRI sub-study and/or random variation. The lack of effect of intensive treatment on beta-amyloid and total tau is challenging to interpret with respect to effects on AD pathology. While plasma $A\beta_{42}$ / $A\beta_{40}$ is a sensitive marker for amyloid positivity measured by either positron emission tomography or cerebrospinal fluid, inference is limited by the somewhat lower accuracy of the Simoa platform relative to mass spectrometry [29] as well as the absence of a measure of phosphorylated tau, which is more specific for AD tauopathy [31–33].

A somewhat unexpected aspect of our results was the strength of the association between the plasma biomarkers and kidney function. Previous cross-sectional studies have noted associations between serum creatinine and plasma amyloid and NfL [34–39]. However, to our knowledge, this is the first study to demonstrate changes in these biomarkers within the context of an intervention known to affect kidney function [19,20] and also slow the development of cognitive impairment [8]. Declines in eGFR occurred more frequently with intensive treatment, though this effect is thought to reflect acute hemodynamic effects with BP lowering, as it did not lead to increases in urinary kidney injury markers or kidney failure [19,20,40]. The majority of studies to date investigating the potential diagnostic utility of plasma and serum AD biomarkers have largely ignored kidney function [16–18]. Chronic kidney disease has a high prevalence in older adults, estimated to affect one in five adults 65 to 79 years and half of those 80 years or older in the United States [41], and is a known risk factor for mild cognitive impairment and dementia [42]. With movement towards the amyloid, tau, and neurodegeneration (AT[N]) research framework as part of diagnostic screening and future clinical trials [15], these findings suggest a need to clarify

the diagnostic interpretation of plasma and serum biomarkers and dementia more broadly within the context of impaired kidney function as well as populations with generally normal cognitive function. Similar to the use of brain natriuretic peptide in the diagnosis of heart failure, appropriate clinical thresholds for dementia biomarkers may differ in the context of chronic kidney disease [43].

Another non-intuitive result was that none of the plasma biomarkers, after accounting for age and eGFR, were associated with neuropsychological test scores or structural brain MRI measures at baseline. One explanation is that cognitive heterogeneity at baseline was limited given that dementia was a specific exclusion criterion. Other cohorts primarily comprised of individuals with normal cognition have generally shown rather weak cross-sectional correlations between cognitive test scores, white matter lesions, and amyloid biomarkers [44,45]. In addition, weak cross-sectional associations would certainly be expected viewing the plasma biomarkers as risk factors for subsequent cognitive decline. Unfortunately, very few participants included in this sub-study were adjudicated with cognitive impairment during the course of follow-up, precluding meaningful analyses correlating the plasma biomarkers with subsequent changes in cognitive function.

This study has several additional limitations that should be considered. First, there are several differences between participants included in this sub-study versus the much larger group of trial participants that were not. As such, our results should be considered preliminary, with a future need to study plasma biomarkers related to AD and vascular contributors to dementia in a larger, more representative group of participants both in SPRINT and in other populations. Second, the population in SPRINT was free of diagnosed dementia at baseline, follow-up was limited to a median of roughly 4 years, and the intensive blood pressure intervention was stopped early, all of which may have limited power to detect differential changes in these biomarkers. Third, the prevalence of AD pathology, indicated by amyloid positivity, in this cohort was likely low at baseline (<10-15%) on the basis of plasma $A\beta_{42}/A\beta_{40}$ levels [18].

In summary, within a subgroup of SPRINT participants, intensive treatment did not lead to significant changes in several plasma biomarkers of AD and neurodegeneration. Intensive treatment did, however, lead to larger increases in NfL, but this effect was explained by changes in kidney function. Future studies of blood-based dementia biomarkers should consider kidney function and distinguish between elevated biomarker levels due to increased production versus reduced clearance, especially within the context of chronic kidney disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

1. **Systematic review:** The PubMed database was searched to review literature concerning the relationship between vascular mechanisms and Alzheimer's disease pathology, and whether the treatment of hypertension influences biomarkers of Alzheimer's disease and neurodegeneration.
2. **Interpretation:** Findings from a sub-study of a randomized trial indicate that intensive treatment of hypertension (target systolic blood pressure <120 mm Hg), as compared to less aggressive treatment (<140 mm Hg), is not associated with changes in plasma biomarkers of plasma beta-amyloid and total tau. Intensive treatment was associated with greater increases in plasma neurofilament light chain, though this difference was attenuated after accounting for changes in kidney function.
3. **Future directions:** Future studies addressing the interpretation of blood-based biomarkers should evaluate populations prior to the onset of symptomatic cognitive impairment, and examine the role that kidney function plays in circulating levels of these biomarkers.

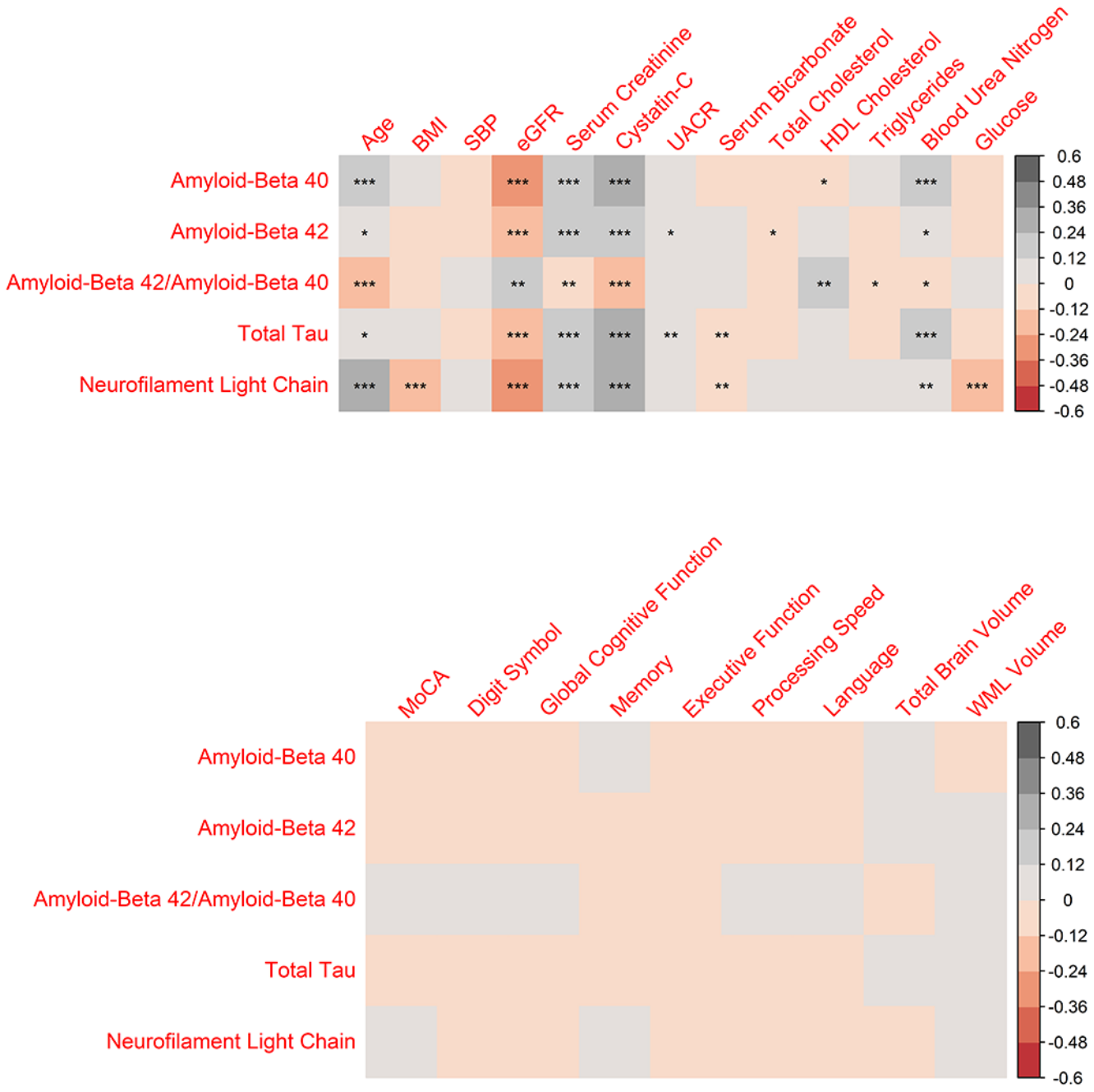

Figure 1.

Baseline correlations between plasma biomarkers and age, vital signs, laboratory measures, cognitive test scores, and structural MRI measures

For age, values represent Spearman's rank correlation for each biomarker. For all other variables, values represent a partial Spearman's correlation adjusting for age (top panel), or adjusting for age and eGFR (bottom panel). BMI denotes body mass index, eGFR estimated glomerular filtration rate based on the CKD-EPI equation, HDL high density lipoprotein, UACR urine albumin to creatinine ratio, MoCA Montreal Cognitive Assessment, and

WML white matter lesion. The memory composite domain score consisted of scores from the HVLT-R immediate and delayed recall, the ROCFm immediate recall, and Logical Memory I and II; Processing speed included the TMT-Parts A and B and Digit Symbol Coding; Executive function included the TMT – Part B minus Part A and Digit Span; Language included the Boston Naming and Category Fluency; and global cognitive function consisted of all tests included in the above domain scores. *** denotes P value<0.001, ** P value<0.01, and * P value<0.05.

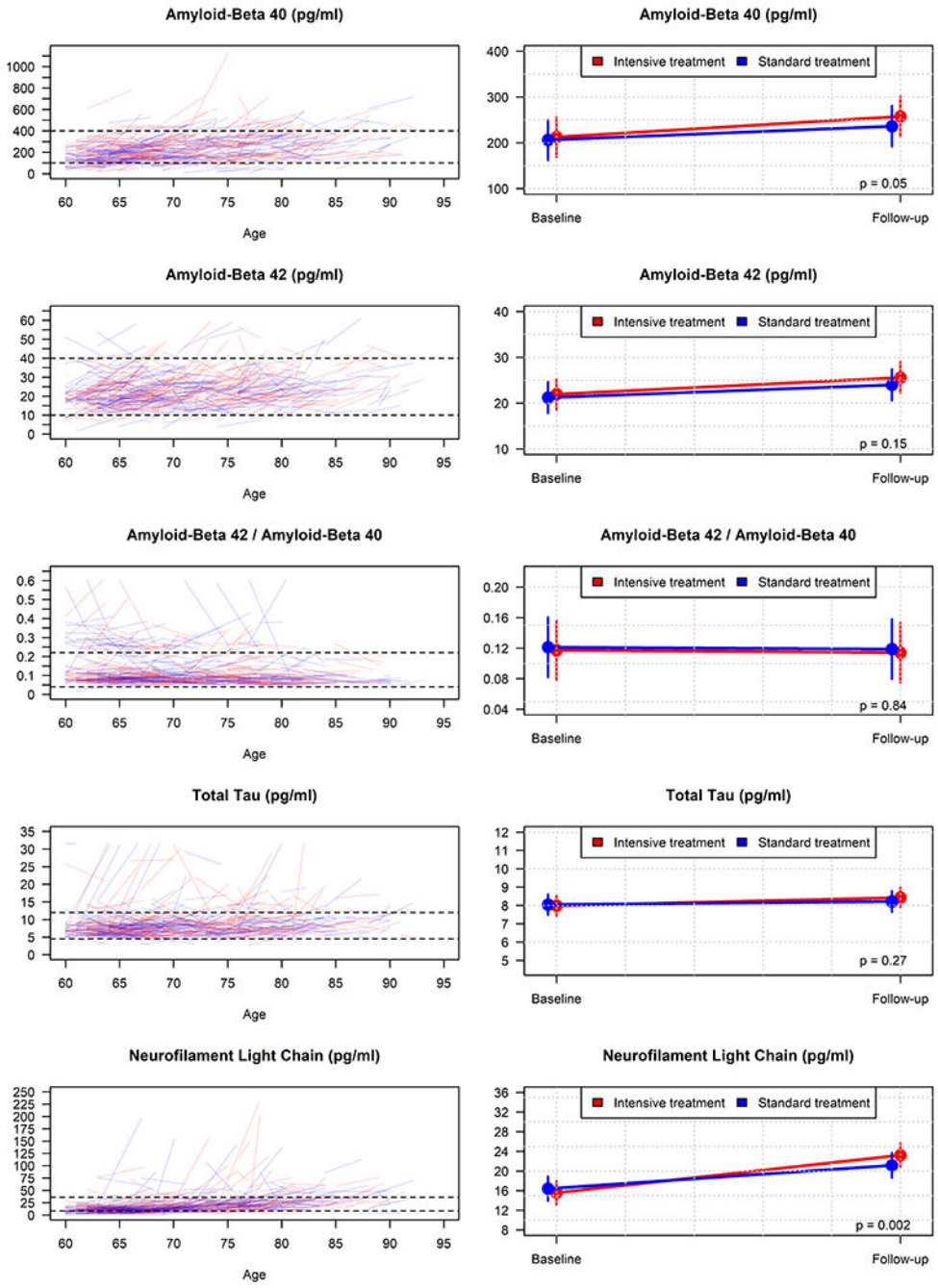

Figure 2.

Change in plasma biomarkers comparing intensive treatment to standard treatment

Left panels display raw trajectories for each biomarker by participant as a function of baseline age. Dashed horizontal lines correspond to the y-axis limits for the right panel figures. Right panels display mean estimates from a robust linear mixed model with follow-up values computed at 3.81 years since randomization.

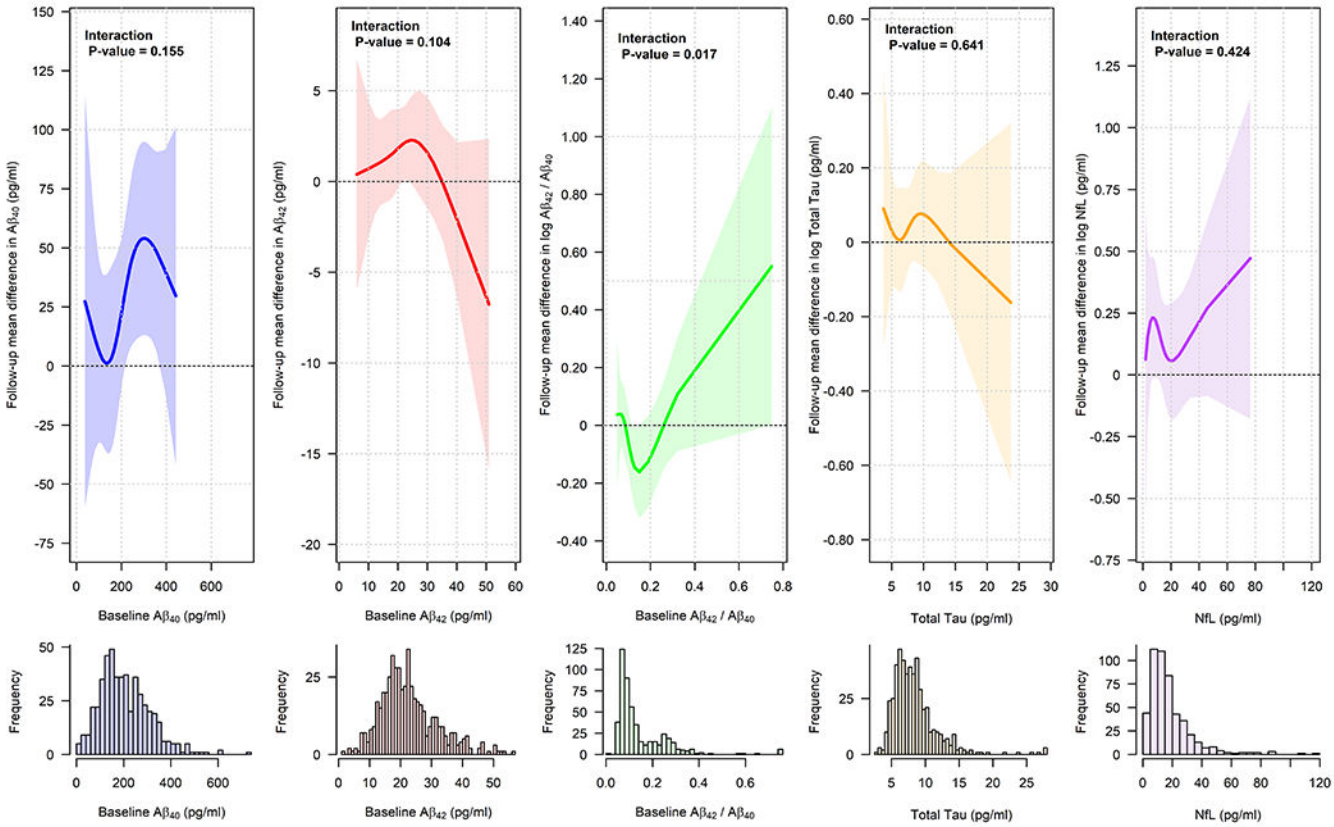

Figure 3.

Association of intensive treatment versus standard treatment on follow-up plasma biomarkers as a function of baseline levels

Estimates based on linear model for follow-up plasma biomarker levels, adjusted for time since randomization, including an interaction between baseline levels and treatment group, with the effect of baseline levels modeled using cubic splines. Lines represent estimated treatment group difference at 3.81 years post-randomization (intensive treatment minus standard treatment) with associated 95% simultaneous confidence bands.

Table 1.

Baseline characteristics of participants in the blood biomarker sub-study by treatment group

Characteristic	Intensive Treatment N = 283	Standard Treatment N = 234
Age, years, mean (SD)	69.8 (6.9)	69.9 (7.4)
Age ≥ 75 years, No. (%)	82 (29.0)	65 (27.8)
Female sex, No. (%)	126 (44.5)	96 (41.0)
Race/Ethnicity, No. (%)		
White	192 (67.8)	152 (65.0)
Black	81 (28.6)	65 (27.8)
Hispanic	6 (2.1)	14 (6.0)
Other	4 (1.4)	3 (1.3)
History of Cardiovascular Disease, No. (%)	42 (14.8)	37 (15.8)
Systolic Blood Pressure, mm Hg, mean (SD)	138.0 (17.6)	138.7 (15.9)
Diastolic Blood Pressure, mm Hg, mean (SD)	75.7 (10.5)	77.0 (12.3)
eGFR, ml/min/1.73 m^2, mean (SD)	71.1 (19.0)	70.1 (18.0)
eGFR<60 ml/min/1.73 m^2	77 (27.9)	74 (32.0)
Urine Albumin to Creatinine Ratio, mg/g, median [IQR]	9.4 [5.3 to 21.3]	9.9 [6.2 to 20.4]
Use of Statin, No. (%)	125 (44.3)	109 (47.2)
Use of Aspirin, No. (%)	156 (55.1)	131 (56.0)
Montreal Cognitive Assessment, median [IQR][a]	24 [21 to 26]	24 [21 to 27]
Logical Memory II, median [IQR][b]	9 [6.5 to 12]	8 [6 to 11]
Digit Symbol Coding, median [IQR][c]	52 [43. to 60]	52 [41 to 62]
Total Brain Volume, cm^3, mean (SD)	1124.7 (116.8)	1133.4 (114.4)
WML Volume, cm^3, median [IQR]	3.6 [1.7 to 7.5]	3.9 [2.0 to 6.8]
$A\beta_{40}$, pg/ml, median [IQR]	194.9 [133.9 to 277.5]	186.0 [123.1 to 267.5]
$A\beta_{42}$, pg/ml, median [IQR]	21.0 [16.2 to 26.4]	21.6 [16.5 to 28.8]
$A\beta_{42}$ / $A\beta_{40}$, median [IQR]	0.10 [0.07 to 0.15]	0.10 [0.08 to 0.22]
Total Tau, pg/ml, median [IQR]	7.7 [6.3 to 9.3]	8.1 [6.1 to 9.7]
Neurofilament Light Chain, pg/ml, median [IQR]	13.7 [9.3 to 20.1]	14.9 [8.6 to 23.4]

eGFR denotes estimated glomerular filtration rate based on the CKD-EPI equation, IQR Interquartile Range, SD Standard Deviation, and WML White Matter Lesion.

[a] Scores range from 0 to 30, with higher scores denoting better cognitive function.

[b] Subtest of the Wechsler Memory Scale. Scores range from 0 to 14, with higher scores denoting better cognitive function.

[c] Subtest of the Wechsler Adult Intelligence Scale. Scores range from 0 to 135, with higher scores denoting higher cognitive function.

Table 2.

Association of intensive treatment versus standard treatment on plasma biomarkers adjusted for kidney function and blood pressure

Adjusted for eGFR	**Intensive Treatment**		**Standard Treatment**			
Biomarker	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Difference (95% CI)**	**P value**
$A\beta_{40}$ (pg/ml)	216.7 (173.8, 259.5)	7.6 (4.8, 10.3)	208.7 (165.6, 251.7)	6.6 (3.6, 9.7)	1.0 (−3.1, 5.0)	0.65
$A\beta_{42}$ (pg/ml)	22.1 (18.6, 25.6)	0.7 (0.5, 0.9)	21.2 (17.7, 24.7)	0.7 (0.4, 0.9)	0.0 (−0.3, 0.3)	0.89
$A\beta_{42}$ / $A\beta_{40}$	0.118 (0.079, 0.156)	0.000 (−0.001, 0.001)	0.122 (0.083, 0.161)	0.000 (−0.002, 0.001)	0.001 (−0.001, 0.002)	0.43
Total Tau (pg/ml)	8.1 (7.5, 8.6)	0.0 (−0.1, 0.1)	8.0 (7.5, 8.5)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.1)	0.96
NfL (pg/ml)	16.8 (14.1, 19.6)	1.1 (0.6, 1.7)	16.8 (14, 19.5)	1.1 (0.5, 1.7)	0.0 (−0.8, 0.8)	0.92
Adjusted for SBP	**Intensive Treatment**		**Standard Treatment**			
Biomarker	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Difference (95% CI)**	**P value**
$A\beta_{40}$ (pg/ml)	212.4 (168.8, 256.0)	11.2 (8.3, 14.0)	206.3 (162.4, 250.1)	7.7 (4.7, 10.7)	3.5 (−0.6, 7.5)	0.09
$A\beta_{42}$ (pg/ml)	21.9 (18.6, 25.3)	0.9 (0.7, 1.1)	21.2 (17.8, 24.6)	0.7 (0.5, 0.9)	0.2 (−0.1, 0.5)	0.27
$A\beta_{42}$ / $A\beta_{40}$	0.12 (0.08, 0.16)	−0.001 (−0.002, 0.001)	0.12 (0.08, 0.16)	−0.001 (−0.002, 0.001)	0.000 (−0.002, 0.002)	0.97
Total Tau (pg/ml)	8.0 (7.5, 8.5)	0.1 (0.0, 0.2)	8.0 (7.5, 8.6)	0.0 (0.0, 0.1)	0.1 (−0.1, 0.2)	0.23
NfL (pg/ml)	15.6 (13.2, 18.0)	2.1 (1.7, 2.4)	16.4 (13.9, 18.9)	1.3 (0.9, 1.6)	0.8 (0.3, 1.3)	0.001
Adjusted for DBP	**Intensive Treatment**		**Standard Treatment**			
Biomarker	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Difference (95% CI)**	**P value**
$A\beta_{40}$ (pg/ml)	211.4 (168.4, 254.4)	9.5 (6.7, 12.3)	206.6 (163.4, 249.9)	7.1 (4, 10.1)	2.4 (−1.6, 6.5)	0.24

Adjusted for eGFR	Intensive Treatment		Standard Treatment			
Biomarker	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Baseline Mean (95% CI)**	**Change / Year (95% CI)**	**Difference (95% CI)**	**P value**
$A\beta_{42}$ (pg/ml)	21.9 (18.5, 25.3)	0.8 (0.6, 1.0)	21.3 (17.9, 24.6)	0.7 (0.4, 0.9)	0.1 (−0.2, 0.4)	0.45
$A\beta_{42}$ / $A\beta_{40}$	0.12 (0.08, 0.16)	0.000 (−0.001, 0.001)	0.12 (0.08, 0.16)	0.000 (−0.002, 0.001)	0.000 (−0.001, 0.002)	0.68
Total Tau (pg/ml)	8.0 (7.4, 8.5)	0.1 (0.0, 0.2)	8.1 (7.5, 8.6)	0.0 (−0.1, 0.1)	0.0 (−0.1, 0.2)	0.45
NfL (pg/ml)	15.5 (13.2, 17.9)	1.7 (1.4, 2.1)	16.6 (14.1, 19.0)	1.1 (0.8, 1.5)	0.6 (0.1, 1.1)	0.03

CI denotes confidence interval, DBP diastolic blood pressure, eGFR denotes estimated glomerular filtration rate based on the CKD-EPI equation, NfL neurofilament light chain, and SBP systolic blood pressure. Estimates are from a robust linear mixed model with random effects for participant and batch, adjusting for time since randomization.