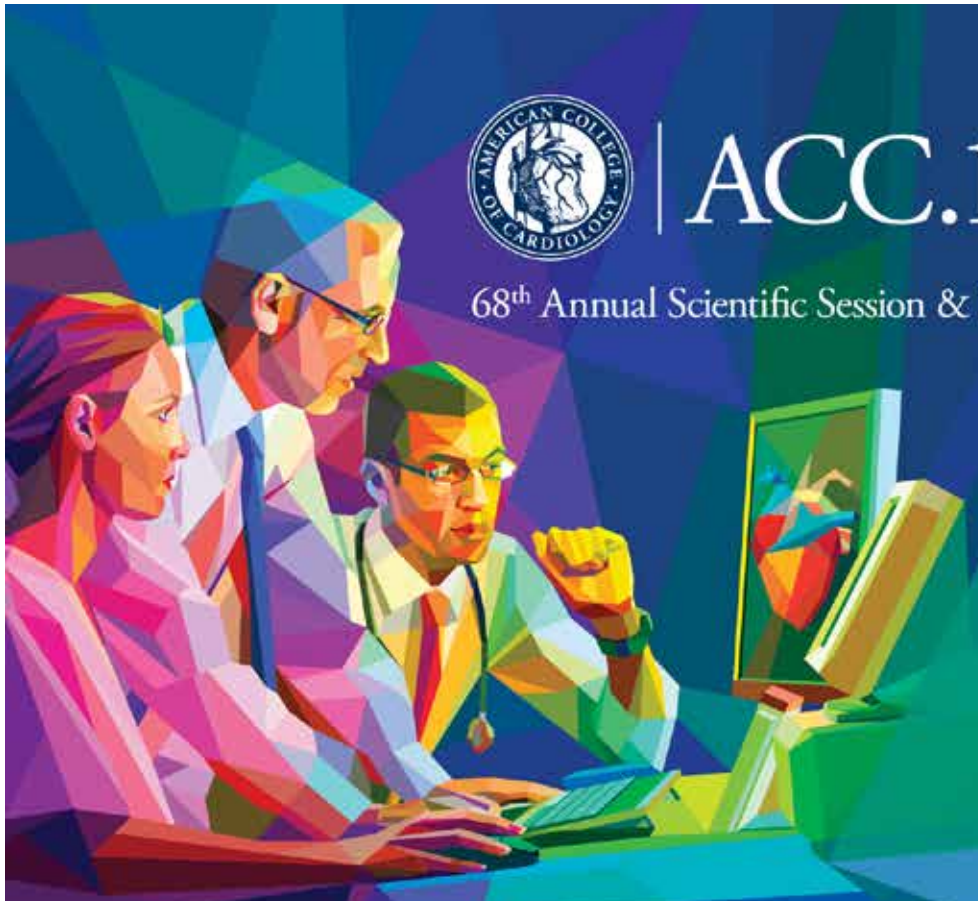

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Primary Results of the Intensive versus Standard Ambulatory Blood Pressure Lowering to Lessen Functional Decline in the Elderly Trial (INFINITY)

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Investigators

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- Neuropsychology: Richard Kaplan, Ph.D.
- Biostatistics: Charles Hall, Ph.D. and Dorothy Wakefield

Sponsored by the National Institute of Aging, National Institutes of Health and the Lowell Weicker Clinical Research Center at the University of Connecticut Health Center, Farmington

Background

- Subcortical microvascular disease of the brain, represented by white matter hyperintensity on magnetic resonance images, is associated with functional decline in older people with hypertension.
- The use of ambulatory blood pressure to guide longitudinal therapy is novel in clinical research and practice, despite its superiority to predict target organ involvement in patients with hypertension.
- Based on our prior findings that 24-hour systolic blood pressure was a better predictor of progression of microvascular disease of the brain than blood pressure measured in the clinic setting (*Circulation* 2011;124:2312-9), we conducted the INFINITY trial to evaluate 2 levels of ambulatory systolic blood pressure on cerebrovascular disease and functional outcomes in older people.

Objectives and Study Endpoints in INFINITY

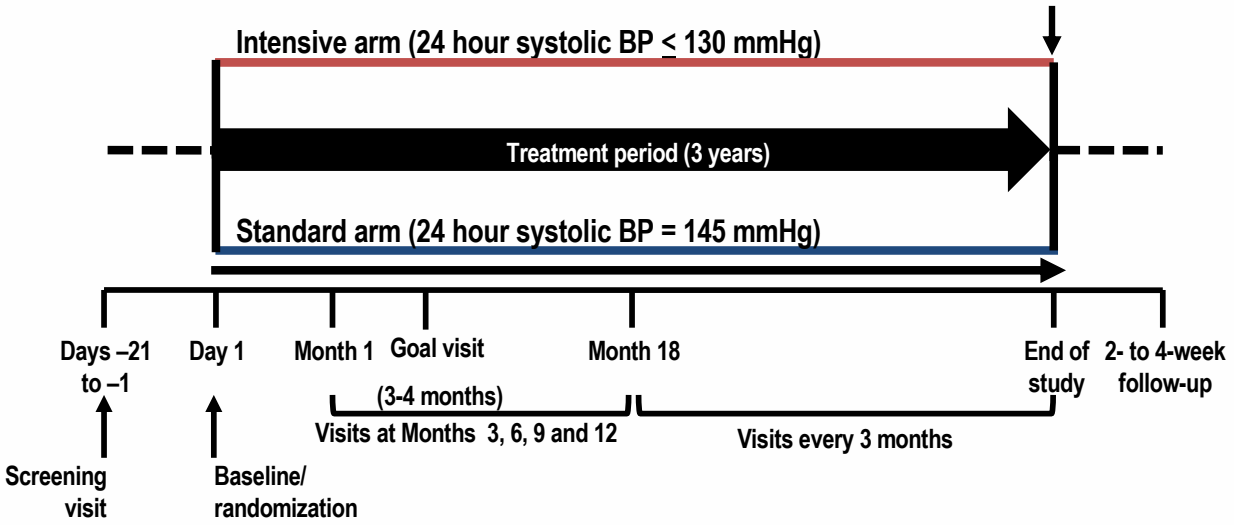
- **Primary objective:** To demonstrate that maintaining 24-hour ambulatory systolic blood pressure at 130 mmHg is superior to values of 145 mmHg in preventing functional decline (mobility) due to less accrual of microvascular disease of the brain.
  - **Primary endpoint:** Changes from baseline in mobility parameters (e.g., gait speed) and accrual of white matter hyperintensity (WMH) lesions on brain MRI
  - **Secondary endpoints:** Changes from baseline in cognitive functional parameters, serious adverse events (cardiovascular, falls with injury, syncope associated with orthostatic hypotension)

White WB et al. *Am Heart J*. 2013;165:258-265.e1.

Study Design

- Randomized, open-label, blinded endpoints single center study of intensive versus standard ambulatory blood pressure in patients with hypertension and cerebrovascular disease in Connecticut

Drug classes used: ACEi or ARB, diuretics, calcium channel blockers, MRAs, beta-blockers



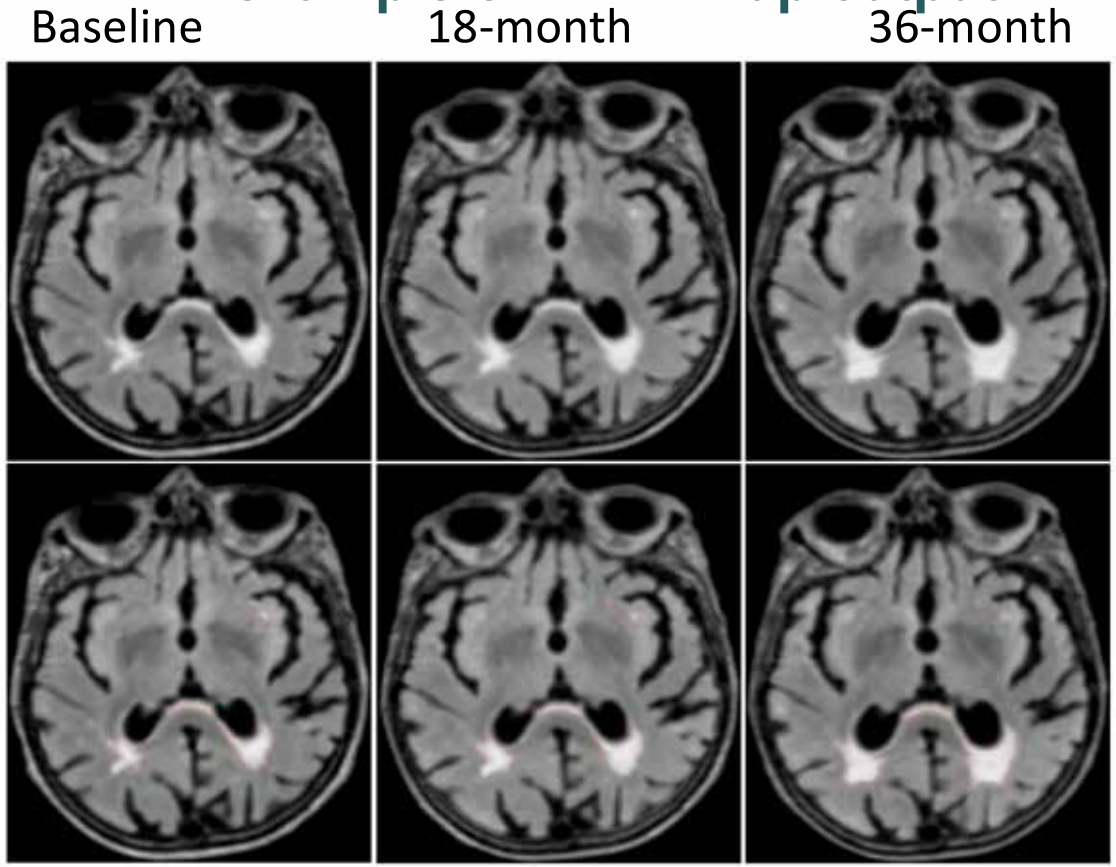
*Neuroimaging, ambulatory blood pressure and functional tests were performed prior to baseline, at 18 months and the end of study (36 months)

White WB et al. *Am Heart J*. 2013;165:258-265.e1.

Study Patients

- Age ≥75 years old ; no upper age limit
- Diagnosis of hypertension based on clinic systolic blood pressures of 150 to 170 mmHg if taking 1 or more antihypertensive drugs or > 170 mmHg on 0 to 1 antihypertensive drug; confirmed by 24-hour ambulatory systolic blood pressure ≥ 140 mmHg
- Visual evidence of white matter hyperintensity (WMH) lesions on MRI (> 0.5% corrected by intracranial chamber size)
- Patients with unstable cardiovascular conditions or chronic neurologic conditions, such as stroke, Parkinson's disease or dementia, clinically impaired gait were excluded

White Matter Hyperintensity Lesion Segmentation: example of WMH map output

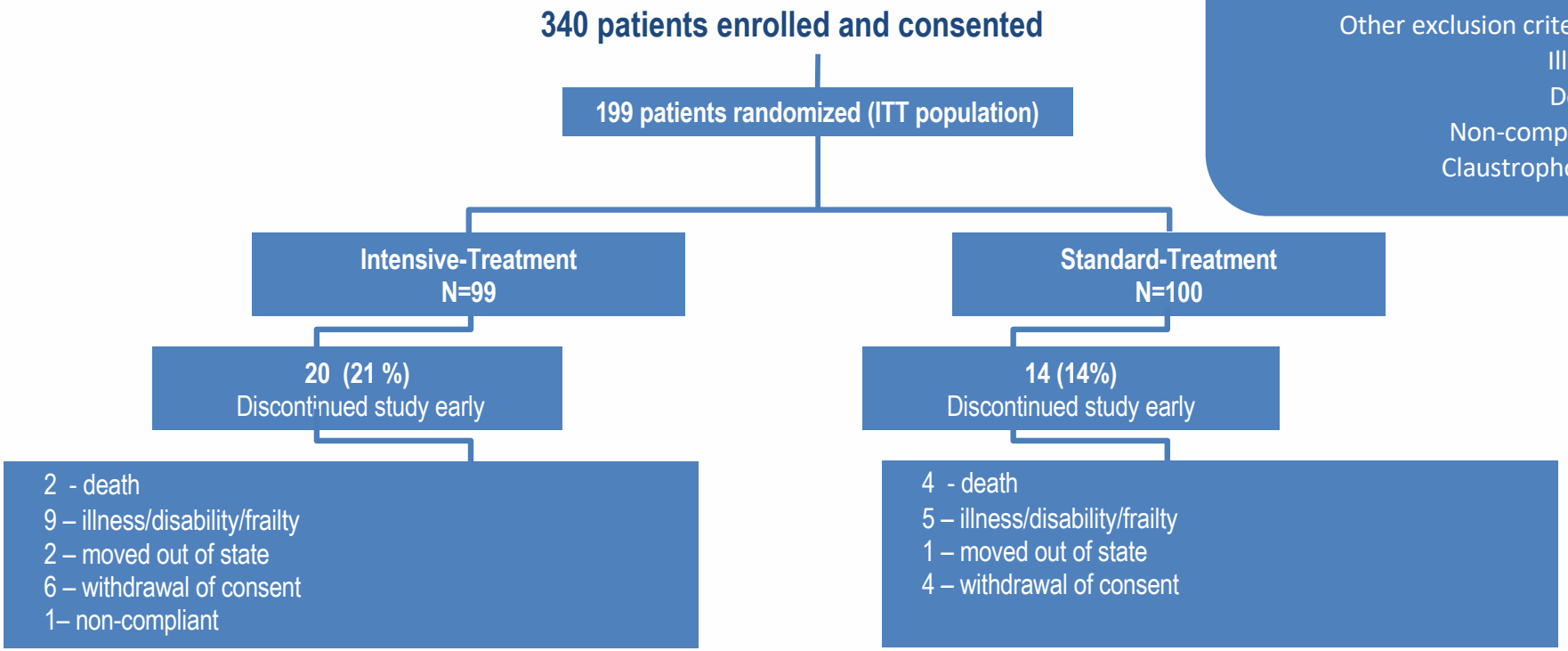


Meier DS, et al. J Neuroimaging 2018 ;28:36-47.

Statistical Analyses

- **Primary endpoint**
  - Linear mixed model to compare changes from baseline in white matter hyperintensity lesion volume after 36 months in the intensive-treatment and standard-treatment ITT population. The model included time, treatment group, and the time x treatment group interaction. Similar models compared changes in mobility parameters.
  - A sensitivity analysis, using the same statistical methods, was pre-specified to evaluate the outcomes in those patients who met and remained at goal ambulatory BP throughout the trial (for intensive-treatment defined as 24- hour systolic BP values of < 135 mmHg and for the standard group, 24-hour BP values of > 140 mmHg).
- **Secondary endpoints**
  - Similar analyses to above were performed for cognitive measures; safety endpoints were also categorized and evaluated.

Disposition of Patients



Excluded after Consent (N=141)

Ineligible based on MRI: 92
Ineligible based on systolic BP: 20
Withdrew consent: 12
Other exclusion criteria: 10
Illness: 3
Death: 1
Non-compliant: 2
Claustrophobic: 1

Vital status known in all study patients

Baseline Patient Characteristics

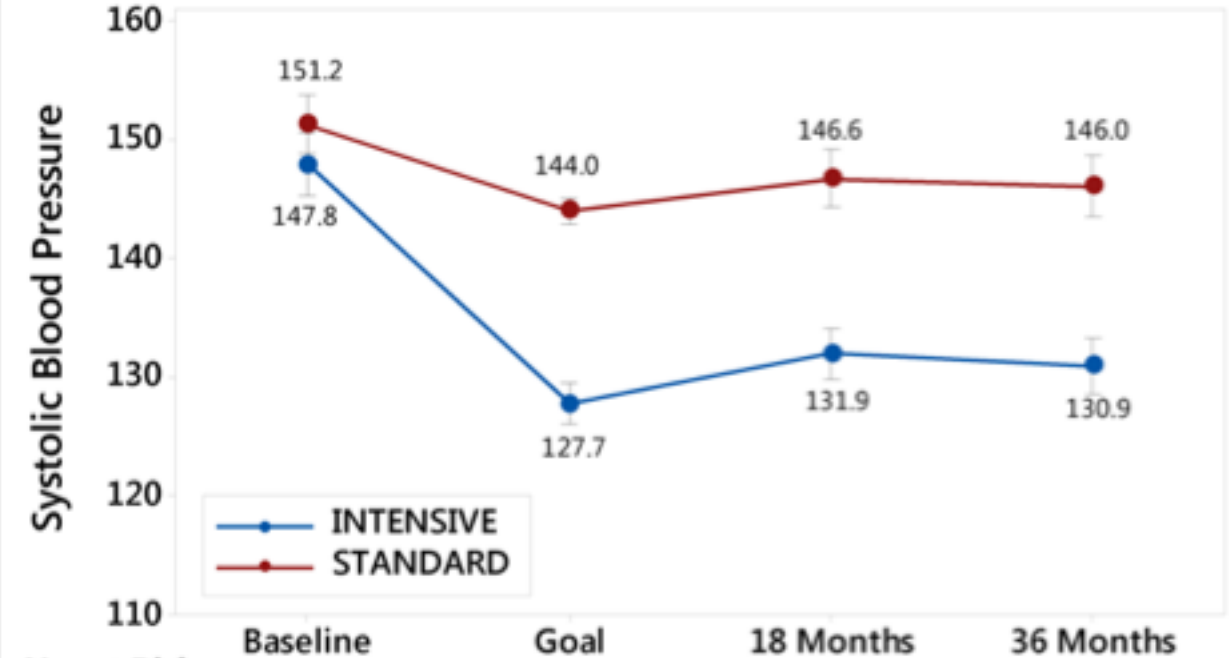
	Intensive-Treatment (N=99)	Standard-Treatment (N=100)
Age		
Median, years	80.0	80.0
Patients ≥80 years, n (%)	46(46.5)	38 (38.0)
Sex		
Female, n (%)	57 (57.6)	51 (51.0)
Race or Ethnic group, n (%)		
White	85 (85.9)	89 (89.0)
African-American	7 (7.6))	7 (7.0)
Asian	2 (2.0)	2 (2.0)
Hispanic/Latino	5 (5.1)	4 (4.0)
Short Physical Performance Battery for mobility	10.8 ± 1.1	10.7 ± 1.1
Mini-mental status exam score	28.1 ± 1.5	28.3 ± 1.5
Education (years)	14.7 ± 3.0	15.6 ± 3.0

Baseline Patient Characteristics (2)

	Intensive-Treatment (N=99)	Standard-Treatment (N= 100)
Magnetic resonance imaging (MRI)		
WMH/total brain volume (%)	1.45 ± 1.2	1.35 ± 1.1
BMI		
Mean, kg/m^2	27.5 ± 4.8	28.2 ± 5.2
Lipids (mean ± SD)		
LDL cholesterol, mg/dl	107.8 ± 32.4	101.8 ± 31.4
HDL cholesterol, mg/dl	57.8 ± 17.5	57.1 ± 16.0
Blood Pressure (mmHg), mean ± SD		
Clinic systolic	149.7 ± 15.4	152.0 ± 17.5
24-hour systolic	147.8 ± 13.4	150.3 ± 13.4
Awake systolic	150.2 ± 12.4	152.1 ± 13.6
Sleep systolic	140.4 ± 21.1	143.9 ± 18.1

BMI, body mass index; SD, standard deviation.

Ambulatory (24-hour) Systolic Blood Pressure over 3 years by Treatment Group



No. at Risk

	Baseline	Goal	18 Months	36 Months
Standard Group	100	88	89	85
Intensive Group	99	91	85	78

White Matter Hyperintensity Lesion Accrual

Baseline	Intensive (n=99)	Standard (n=100)	P-Value
Intracranial Cavity Volume (milliliters)	1452 ± 145	1503 ± 161	0.02
White Matter Hyperintensity (milliliters)	21 ± 17	20 ± 16	0.70
White Matter Hyperintensity (%), mean ± SD	1. 5 ± 1.2	1.4 ± 1.1	0.54
Change from Baseline to End of Study			
White Matter Hyperintensity (%), mean ± SE	0.29 ± 0.06	0.48 ± 0.06	0.03

White Matter Hyperintensity Lesion Accrual
Sensitivity analysis for those whose BP stayed in assigned group

	Intensive (n=49)	**Standard (n=54)**	**P-Value**
Baseline, mean ± SD	1.26 ± 1.13	1.35 ± 1.18	0.70
End of Study (36 months), mean ± SD	1.48 ± 1.10	1.93 ± 1.66	0.11
Change from Baseline to End of Study, mean± SE	0.23 ± 0.08	0.58 ± 0.08	<0.01

SD – Standard deviation; SE – Standard error of estimate

Mobility Endpoints

Mobility Parameters	Baseline		Change from Baseline to End of Study		
	Intensive Mean ± SD	**Standard** Mean ± SD	**Intensive** Mean ± SE	**Standard** Mean ± SE	P-Value
Gait (8 m) Time (s)	8 ± 2	8 ± 2	0.4 ± 0.3	0.4 ± 0.3	0.91
Four Stair Descent Time (s)	4 ± 1	3 ± 2	0.6 ± 0.2	0.7 ± 0.3	0.72
Four Stair Ascent Time (s)	4 ± 1	4 ± 1	0.4 ± 0.1	0.4 ± 0.1	0.88
Sit to Stand Time (s)	11 ± 4	10 ± 10	1.9 ± 0.5	3.0 ± 0.5	0.12
Supine to Sit Time (s)	3 ± 2	3 ± 1	0.1 ± 0.2	0.2 ± 0.2	0.58
Unipedal Balance (s)	12 ± 10	13 ± 11	-3.1 ± 1.1	-4.0 ± 1.3	0.56

Cognitive Endpoints

Cognitive Parameters	Baseline		Change from Baseline to End of Study		
	Intensive Mean ± SD	**Standard** Mean ± SD	**Intensive** Mean ± SE	**Standard** Mean ± SE	P-Value
Symbol Digit Modalities Test, (no. correct in 90 s)	34 ± 10	36 ± 10	-2 ± 1	-1 ± 1	0.29
Trail Making Test Part A (s)	46 ± 18	48 ± 23	7 ± 4	3 ± 4	0.45
Trail Making Test Part B (s)	150 ± 76	125 ± 68	22 ± 7	17 ± 7	0.59
Stroop Color and Word Test, (no. correct in 45 s)	26 ± 9	27 ± 9	-2 ± 1	-1.0 ± 6.4	0.07
Simple Reaction Time (ms)	431 ± 175	404 ± 124	-25 ± 19	6 ± 18	0.25
Sequential Reaction Time (ms)	661 ± 156	619 ± 155	-23 ± 16	33 ± 15	**<0.01**

Serious Adverse Events

Number (%)	Intensive-Treatment (N=99)	Standard-Treatment (N=100)
Deaths	2 (2.1)	4 (4)
Nonfatal CV events	4 (4.1)	17 (17)*
Falls with injury	4 (4.1)	5 (5)
Falls without injury	31 (31.3)	32 (32)
Syncope/near syncope	4	4

*risk ratio = 0.24 (95% confidence intervals, 0.08, 0.68), p<0.01

Summary

- Patients randomized to intensive treatment had a 24 hour systolic BP 14-16 mmHg lower than the standard.
- Intensive lowering of ambulatory blood pressure in older patients with hypertension reduced the accrual of subcortical white matter disease.
- This observation was not accompanied by differences in mobility or cognitive function.
- There were significantly fewer major CV events (myocardial infarction, stroke, hospitalization for heart failure, and arrhythmias) in the intensive-treatment group.
- There were no differences in falls or syncope between treatment groups.
- It is probable that 3 years was too short in duration to observe functional differences between the intensive- and standard-treatment groups.

CV, cardiovascular.

Special Thanks to our Clinical Research Staff (2011 to 2018)

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Thanks to our INFINITY Study Patients

Fred's age at study start: 97 years
Age at study completion: 100 years
White matter hyperintensity progression – 0.1%

With permission from the family