Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People

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Statistical Analysis Plan

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INFINITY Statistical Analysis Plan (modification)

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Amendment 1.1

The primary objective of the INFINITY Trial is to assess causality between 24-hour systolic BP levels and preservation of mobility, cognitive and urinary function associated with reduced accrual of small vessel disease of the subcortical white matter in people over the age of 75 years.

A key hypothesis of the trial is that intensive treatment of 24-hour systolic BP to levels of 130 mmHg or less will result in improved gait time, stair descent time, and maximal gait velocity compared to treatment of 24 hour systolic BP to levels of 145 mmHg or less. This separation of ambulatory BP goals should achieve at least a ≥10 mmHg differences between groups over time. Previously, this difference has been shown to be responsible for the mobility decrements associated with WMH in older patients with systolic hypertension in a prospective cohort study (Circulation. 2011;124 (21):2312-9. doi: 10.1161/CIRCULATIONAHA.111.037036).

Prior to database lock of this trial in October 2018, we have added several secondary analyses to be pre-specified with their rationale as needed.

1. Change in white matter hyperintensity (%) (WMH) from baseline to 3 years
    a. According to treatment group (primary analysis)

$$\begin{aligned} Y_{i1} &= \beta_0 + \beta_C x_i + \gamma_i + \varepsilon_{i1} \\ Y_{i2} &= \beta_0 + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i + \varepsilon_{i1} \end{aligned} \qquad (1.1)$$

Here, x_i is the treatment group indicator for participant i (one for intervention, zero for comparison); Y_{i1} is the WMH % for participant i at time 1 (baseline); Y_{i2} is the WMH % for participant i at time 2 (36 month follow-up); β_0 is interpreted as the average WMH % at baseline in the reference group; β_C is interpreted as the difference in the average WMH % at baseline between the intervention group and the reference group and will be zero if the two groups are exactly comparable in their baseline values; β_L is interpreted as the average change in WMH % between 36 month follow up and baseline in the reference group; β_T is interpreted as the difference average change in WMH % between 36 month follow up and baseline between the intervention group and the reference group and thus the parameter of primary interest; γ_i is a random intercept for participant i that addresses the correlation in WMH % across the two time points; and ε_{i1} and ε_{i2} are the residual error terms at baseline and follow-up, respectively. All analyses will be repeated as stratified analyses (b - e below).

    b. Stratified according to < or > median age
    c. Stratified according to gender
    d. Stratified according to median years of education
    e. Stratified according to a clinical diagnosis of minor or major depression
    f. Stratified according to presence or absence of statin therapy for hyperlipidemia
    g. Stratified according to presence of absence of anti-platelet therapies (aspirin, clopidigrel)
    h. Sensitivity analysis at 36 months by ambulatory systolic BP : rationale – for study patients who either never met the achieved BP for their group assignment or who shifted mid-trial to an ambulatory BP

value out of alignment with their assigned treatment group (e.g. a standard group patient whose 24 hour systolic BP was < 135 mmHg would be excluded from the sensitivity analysis; an intensive group patient whose 24 hour systolic BP was > 135 mmHg would be excluded from the sensitivity analysis).

2. Change in mobility, cognition and depression from baseline to 3 years
   a. According to treatment group (primary analysis)

$$Y_{i1} = \beta_0 + \beta_C x_i + \gamma_i + \varepsilon_{i1}$$
$$Y_{i2} = \beta_0 + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i + \varepsilon_{i1}$$

Here, x_i is the treatment group indicator for participant i as in (1); Y_{i1} is the mobility score for participant i at time 1 (baseline); Y_{i2} is the mobility score for participant i at time 2 (36 month follow-up); β_0 is interpreted as the average mobility score at baseline in the reference group; β_C is interpreted as the difference in the average mobility score at baseline between the intervention group and the reference group and will be zero if the two groups are exactly comparable in their baseline values; β_L is interpreted as the average change in mobility between 36 month follow up and baseline in the reference group; β_T is interpreted as the difference average change in mobility between 36 month follow up and baseline between the intervention group and the reference group and thus the parameter of primary interest; γ_i is a random intercept for participant i that addresses the correlation in mobility across the two time points; and ε_{i1} and ε_{i2} are the residual error terms at baseline and follow-up, respectively.

This analysis will be repeated for each mobility parameter (gait speed, four stair ascent and descent time, supine to sit time), cognition scores (Trailmaking A and B, Stroop Color & Word score, and simple reaction time), and the Geriatric Depression Scale. The timed measures – Trailmaking A and B, and simple reaction time – will be inverse-transformed so that they have a speed interpretation; this will also reduce the influence of outliers. Similarly, all analyses will be repeated as stratified analyses (b - e below).

   b. Stratified according to < or > median age
   c. Stratified according to gender
   d. Stratified according to median years of education
   e. Stratified according to a clinical diagnosis of minor or major depression (for mobility and cognition)

3. Change in urinary severity index and depression category (based on the Geriatric Depression Scale) from baseline to 3 years. These analyses will be similar to the analyses for white matter hyperintensities in (1) and for mobility and cognition in (2), but using ordinal logistic regression.
   a. According to treatment group (primary analysis)

$$\log\left(Y_{i1} > k \,/\, Y_{i1} \le k\right) = \beta_{0k} + \beta_C x_i + \gamma_i$$
$$\log\left(Y_{i2} > k \,/\, Y_{i2} \le k\right) = \beta_{0k} + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i$$
$$k = 1, \ldots, m-1$$

Here, x_i is the treatment group indicator for participant i as in (1) and (2); Y_{i1} is the ordinal urinary severity index score for participant i at time 1 (baseline), which takes values from 1 to m; Y_{i2} is the ordinal urinary severity index score for participant i at time 2 (36 month follow-up); β_{0k} is interpreted as the log odds of having ordinal urinary severity index score k at baseline in the reference group; β_C is interpreted as the log odds ratio for a one unit higher urinary severity index score at baseline between the intervention group and

the reference group, and will be zero if the two groups are exactly comparable in their baseline values; β_L is interpreted as the log odds ratio for a one unit higher urinary severity index score between the 36 month follow up and baseline in the reference group; β_T is interpreted as an interaction, the difference in log odds ratios for a one unit higher urinary severity index score between between the 36 month follow up and baseline and between the intervention group and the reference group and thus the parameter of primary interest; and γ_i is a random intercept for participant i that addresses the correlation in mobility across the two time points.

This analysis makes the proportional odds assumption which will be checked by software.

b. Stratified according to < or > median age
c. Stratified according to gender
d. Stratified according to median years of education
e. Stratified according to a clinical diagnosis of minor or major depression

4. Change in markers of tissue damage associated with microvascular disease of the brain (via diffusion tensor imaging (DTI)) from baseline to 3 years. Change in DTI will be evaluated as it relates to:
   a. Treatment group (primary analysis)

$$\begin{aligned} Y_{i1} &= \beta_0 + \beta_C x_i + \gamma_i + \varepsilon_{i1} \\ Y_{i2} &= \beta_0 + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i + \varepsilon_{i1} \end{aligned} \qquad (1.1)$$

Here, x_i is the treatment group indicator for participant i (one for intervention, zero for comparison); Y_{i1} is the DTI for participant i at time 1 (baseline); Y_{i2} is the DTI for participant i at time 2 (36 month follow-up); β_0 is interpreted as the average DTI at baseline in the reference group; β_C is interpreted as the difference in the average DTI at baseline between the intervention group and the reference group and will be zero if the two groups are exactly comparable in their baseline values; β_L is interpreted as the average change in DTI between 36 month follow up and baseline in the reference group; β_T is interpreted as the difference average change in DTI between 36 month follow up and baseline between the intervention group and the reference group and thus the parameter of primary interest; γ_i is a random intercept for participant i that addresses the correlation in DTI across the two time points; and ε_{i1} and ε_{i2} are the residual error terms at baseline and follow-up, respectively. All analyses will be repeated as stratified analyses (b - e below).

   b. Stratified according to < or > median age
   c. Stratified according to gender
   d. Stratified according to median years of education
   e. Stratified according to a clinical diagnosis of minor or major depression
   f. Change from baseline in cognitive variables
   g. Changes from baseline in mobility parameters
   h. Changes from baseline in urinary function

5. Change in sleep scales (Pittsburgh Sleep Quality Index, and Epworth Sleep scale) and the SF-36 survey (QOL). Quality of sleep and quality of life will be evaluated as it relates to:

   a. Treatment assignment

$$Y_{i1} = \beta_0 + \beta_C x_i + \gamma_i + \varepsilon_{i1}$$
$$Y_{i2} = \beta_0 + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i + \varepsilon_{i1}$$

Here, x_i is the treatment group indicator for participant i (one for intervention, zero for comparison); Y_{i1} is the SF-36 score for participant i at time 1 (baseline); Y_{i2} is the SF-36 score for participant i at time 2 (36 month follow-up); β_0 is interpreted as the average SF-36 score at baseline in the reference group; β_C is interpreted as the difference in the average SF-36 score at baseline between the intervention group and the reference group and will be zero if the two groups are exactly comparable in their baseline values; β_L is interpreted as the average change in SF-36 between 36 month follow up and baseline in the reference group; β_T is interpreted as the difference average change in SF-36 between 36 month follow up and baseline between the intervention group and the reference group and thus the parameter of primary interest; γ_i is a random intercept for participant i that addresses the correlation in SF-36 across the two time points; and ε_{i1} and ε_{i2} are the residual error terms at baseline and follow-up, respectively. Above analysis will be repeated for Sleep Scales (Pittsburgh Sleep Quality Index, and Epworth Sleep scale), and then as stratified analyses (b - e below) for both Sleep and SF-36 scales.

b. Stratified according to < or > median age
c. Stratified according to gender
d. Stratified according to years of education
e. Stratified according to a clinical diagnosis of minor or major depression
f. Change from baseline in cognitive variables
g. Changes from baseline in mobility parameters
h. Changes from baseline in urinary function
i. Change from baseline in WMH (%)

6. Regression of changes from baseline in WMH as a mediator of changes from baseline in mobility, cognition, urinary function and depressive symptoms. These analyses will be based on the analyses in (2) and (3), but with the addition of mediation by and interaction with WMH using the methods of Vanderweele (REF below).

$$Y_{i1} = \beta_0 + \beta_C x_i + \gamma_i + \varepsilon_{i1}$$
$$Y_{i2} = \beta_0 + \beta_C x_i + \beta_L + \beta_T x_i + \gamma_i + \theta_M \left(m_{i2} - m_{i1}\right) + \theta_{INT} x_i \left(m_{i2} - m_{i1}\right) + \varepsilon_{i1}$$
$$m_{i2} - m_{i1} = \alpha_0 + \alpha_1 x_i + \delta_i$$

For mobility, cognition, and depression, variables are defined as in (1) with the following additions: δ_i is residual error in the model for change in WMH, and m_{i1} and m_{i2} are the values of WMH at baseline and follow-up, respectively. Some mediation measures of interest are as follows:

$$CDE = \beta_T$$
$$INT_{REF} = \theta_{INT}\alpha_0$$
$$INT_{MED} = \theta_{INT}\alpha_1$$
$$PIE = \theta_M \alpha_1$$

The controlled direct effect $CDE = \beta_T$ is the effect of treatment assignment in the absence of any WMH, $INT_{REF} = \theta_{INT}\alpha_0$ is the reference interaction between treatment assignment and WMH, $INT_{MED} = \theta_{INT}\alpha_1$ is the mediated interaction, and $PIE = \theta_M \alpha_1 x_i$ is the pure indirect effect. Combinations of these derived measures will be used to assess the degree of mediation, as described in VanderWeele. T.J. (2015). Explanation in Causal Inference: Methods for Mediation and Interaction, Oxford University Press. In particular, the proportion mediated is $\frac{INT_{REF} + INT_{MED} + PIE}{CDE + INT_{REF} + INT_{MED} + PIE}$.

Bootstrap standard errors and confidence intervals will be used for statistical inference, including estimation of standard errors and confidence intervals.

In secondary analyses, age, sex, and resultant ambulatory systolic BP at 36 months regardless of treatment assignment will be considered as mediators through similar methods. Specifically, age, sex, and systolic BP will replace $m_{i2} - m_{i1}$ in the model above and similar measures of interaction and mediation will be estimated.

7. Special Interest adverse events (falls, nervous system and vascular disorders) as related to numerous predictors of interest.

   These outcomes are all count variables, so we use Poisson regression with each of the following predictors.

$$\log(\mu_i) = \log(n_i) + \beta_0 + \beta_1 x_i$$

   Here μ_i is the count, n_i is the number of months in study, β_0 is the intercept with $\exp(\beta_0)$ interpeted as the rate of AE with mobility scale is zero, x_i is the predictor of interest, mobility scale and β_1 is the log rate ratio between groups and $\exp(\beta_1)$ is interpreted as the estimated ratio of rates for two subjects differing by one in their predictors of interest scale. This analysis will be repeated for the following predictors predictors described below:

   a. Mobility variables
   b. Cognitive variables
   c. Treatment assignment
   d. Blood pressure
   e. Age
   f. Gender
   g. Number of classes of antihypertensive medications
   h. A clinical diagnosis of minor or major depression
   i. Sleep scales and SF-36 (QOL)

   A final multivariate model will include all significant predictors.